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Nicolas Marion
ISBN:978-84-691-9871-1/DL:T-1264-2008

N-Heterocyclic Carbenes as Supporting Ligands in Homogeneous Catalysis

Nicolas MARION

Tesis Doctoral 2008

Under the supervision of Prof. Steven P. NOLAN

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ABSTRACT

In the last ten years, N-heterocyclic carbenes (NHCs) have gained tremendous popularity, notably as highly versatile ligands for transition metals. Their strong σ-donating properties, associated with high steric hindrance, often impart enhanced stability *and* activity to a given metallic center. Two main successes of the NHCs in homogeneous catalysis are arguably the ruthenium-mediated olefin metathesis and the palladium-promoted cross-coupling reactions.

In this work, we have studied the effect of N-heterocyclic carbenes as supporting ligands in well-defined complexes of palladium(II), gallium(III), and gold(I) that we used in homogeneous catalysis.

Notably, we have synthesized, in very straightforward manners, two families of palladium compounds of formulae [(NHC)Pd(L)Cl], where L, which is a R-allyl or R-acac moiety, acts as a protecting shell for the catalytically active [(NHC)Pd^0] species. Hence, upon activation under the reaction conditions, these new Pd complexes were found extremely active in the Suzuki-Miyaura, the Buchwald-Hartwig, and the α-ketone arylation cross-coupling reactions. More precisely, the more active "R-allyl family" allowed for reactions to be performed with as low as 10 ppm of palladium.

A series of [(NHC)$GaCl_3$] complexes was synthesized *via* a simple one-step procedure. The resulting unprecedented NHC–Ga^{III} compounds were found extremely stable but showed only moderate activity in isomerization reactions.

Demonstrating further the versatile application of NHCs in metal-based catalysis, we developed several new catalytic transformations using [(NHC)AuCl] complexes. Hence, these pre-catalysts, activated *in situ* with a silver salt, proved to be excellent activators of alkynes, allenes, and alkenes. This led to the development of efficient synthetically useful protocols, encompassing enyne cycloisomerization, indene cyclization, formation of conjugated enone, and allylic rearrangement.

KEYWORDS

gallium – gold – homogeneous catalysis – N-heterocyclic carbene – palladium

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RESUMEN

En los últimos diez años, los carbenos N-heterocíclicos (NHCs) han ganado una gran popularidad, especialmente como ligandos versátiles de metales de transición. Su fuerte carácter σ–donor, asociado con su gran impedimento estérico, confieren a menudo una mayor estabilidad *y* actividad al centro metálico en cuestión. Los dos mayores éxitos de los NHCs en catálisis homogénea se encuentran, sin duda, en la metátesis de olefinas catalizada por rutenio y en las reacciones de acoplamiento cruzado promovidas por paladio.

En este trabajo, hemos estudiado el efecto de los carbenos N-heterocíclicos como ligandos en complejos bien definidos de paladio(II), galio(III) y oro(I), que hemos empleado en catálisis homogénea.

En particular, hemos sintetizado, de forma directa, dos familias de compuestos de paladio de fórmula general [(NHC)Pd(L)Cl] donde L, grupo R-alilo o R-acac, actúa como protector para las especies catalíticamente activas [(NHC)Pd^0]. De hecho, tras la activación en las condiciones de reacción, estos nuevos complejos de paladio se mostraron extremadamente activos en las reacciones de Suzuki-Miyaura, de Buchwald-Hartwig y en la α-arilación de cetonas. Más concretamente, la 'familia R-arilo', más activa, permitió llevar a cabo estas reacciones con tan sólo 10 ppm de paladio.

Una serie de complejos [(NHC)$GaCl_3$] fue preparada en una simple etapa. Los compuestos resultantes NHC–Ga^{III}, sin precedentes en la literatura, se mostraron extremadamente estables pero sólo moderadamente activos en reacciones de isomerización.

Con el fin seguir ampliando la gran aplicabilidad de los NHCs en catálisis con metales, estudiamos varias nuevas transformaciones utilizando los complejos [(NHC)AuCl]. De hecho, estos pre-catalizadores, activados *in situ* con una sal de plata, demostraron ser excelente activadores de alquinos, alenos y alquenos. Esto llevó al desarrollo de protocolos eficientes, y sintéticamente útiles, tales como la cicloisomerización de eninos, la ciclación de indenos, la formación de enonas conjugadas, y reordenamientos arílicos.

PALABRAS CLAVES

galio – oro – catálisis homogénea – carbeno N-heterocíclico – paladio

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ABBREVIATIONS

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ABBREVIATIONS

Ac	acyl
acac	acetylacetonato
Ad	adamantyl (tricyclo[3.3.1.1^{3,7}]decyl)
Am	amyl
Ar	aryl
BAr'$_4$	tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BDE	bond-dissociation energy
Bu	butyl
CAAC	cyclic alkyl amino carbene
cin	cinnamyl [allylbenzene]
^{Cl}IPr	1,3-bis(2,6-diisopropylphenyl)-4,5-dichloro-imidazol-2-ylidene
COD	cyclooctadiene
COE	cyclooctene
conv.	conversion
Cp	cyclopentadiene
Cp*	pentamethylcyclopentadiene
cro	crotyl [but-1-ene]
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density functional theory
DMAc	dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane

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DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDA	energy decomposition analysis
Eq	equation
equiv	equivalent
Et	ethyl
GC	gas chromatography
gem	geminal
Hex	hexyl
HRMS	high-resolution mass spectrometry
i	iso
IA MALDI-TOF MS	inert atmosphere matrix-assisted laser desorption/ionisation-time of flight mass spectrometry
IAd	*N,N*'-diadamantylimidazol-2-ylidene
ICy	*N,N*'-dicyclohexylimidazol-2-ylidene
IDD	*N,N*'-dicyclododecylimidazol-2-ylidene
IDM	*N,N*'-dimethylimidazol-2-ylidene
IiBu	*N,N*'-diisobutylimidazol-2-ylidene
Im	imidazole
IMes	*N,N*'-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IMesPr	*N*-(2,4,6-trimethylphenyl)-*N'*-propyl-imidazol-2-ylidene
IPr	*N,N*'-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IPrMe	1,3-diisopropyl-4,5-dimethyl-imidazol-2-ylidene
IR	infrared
ItBu	*N,N*'-di-*tert*-butylimidazol-2-ylidene
ITM	1,3,4,5-tetramethyl-imidazol-2-ylidene
KHMDS	potassium hexamethyldisilazide

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m	multiplet
m	*meta*
Me	methyl
Mes	mesityl [1,3,5-trimethylphenyl]
MW	molecular weight
mol %	molar percentage
MTBE	*tert*-butylmethyl ether
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
NR	no reaction
o	*ortho*
Oct	octyl
p	*para*
PCC	pyridinium chlorochromate
Ph	phenyl
PNB	*para*-nitrobenzoate
Pr	propyl
pre	prenyl [3-methylbut-1-ene]
q	quartet
quint	quintet
rac	racemic
RCM	ring-closing metathesis
ROMP	ring-opening metathesis polymerization
rt	room temperature
s	singlet
s	*sec*

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sept	septet
SIBiphen	*N*,*N*'-bis(*o*-biphenylyl)imidazolidin-2-ylidene
SIMes	*N*,*N*'-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene
SIPr	*N*,*N*'-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene
t	triplet
t	*tert*
tech.	technical
Tf	triflyl [trifluoromethylsulfonyl]
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilane
TMSA	trimethylsilylacetylene
TOF	turnover frequency
tol	toluene
TON	turnover number
TPh	2-phenyl-6,7-dihydro-5*H*-pyrrolo-[2,1-c]-[1,2,3]triazol-2-ylidene
Ts	tosyl [(4-methylphenyl)sulfonyl]
TS	transition state
V_{Bur}	buried volume
μW	microwave

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INTRODUCTION

Generalities About N-Heterocyclic Carbenes

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I. Historical Background

A. Breakthroughs in carbene chemistry

Carbenes are electron-deficient two-coordinate carbon compounds that have two non-bonding electrons on that carbon (Figure 1). In the ground state, the two unshared electrons may be either in the same orbital with antiparallel spins (singlet state), or in two different orbitals with parallel spins (triplet state).

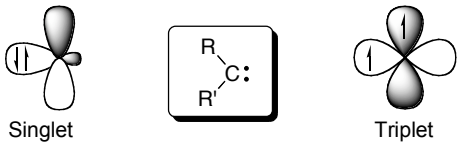
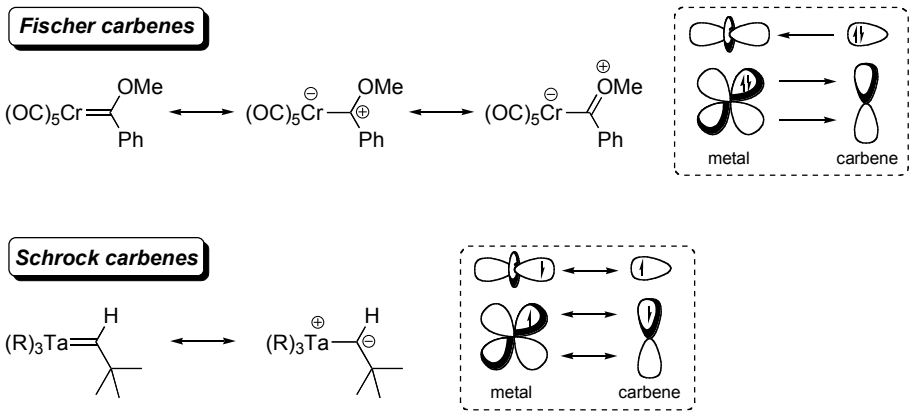


Figure 1. Schematic representation of a carbene and its electronic configurations

The quest for a stable carbene was long considered an unreasonable target, until Wanzlick showed that the stability of carbenes could be dramatically increased by vicinal amino substituents.[1] However, no isolation of a 'monomeric' carbene was achieved at that time. In 1964, Fischer eventually reported the first stable transition metal complexes bearing carbene ligands.[2] The so-called Fischer carbene complexes were characterized as having an electrophilic carbenic carbon (Scheme 1).



Scheme 1. Fischer and Schrock carbenes

Ten years later, Schrock isolated a different type of carbenic complex in which the polarization of the metal–carbon bond is inverted and the carbenic carbon is nucleophilic (Scheme 1).[3]

[1] (a) Wanzlick, H. W.; Kleiner, H. J. *Angew. Chem.* **1961**, *73*, 493. (b) Wanzlick, H. W. *Angew. Chem.* **1962**, *74*, 129–134. (c) Wanzlick, H. W.; Kleiner, H. J. *Chem. Ber.* **1963**, *96*, 3024–3027.
[2] Fischer, E. O.; Maasböl, A. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 580–581.
[3] Schrock, R. R. *J. Am. Chem. Soc.* **1974**, *96*, 6796–6797.

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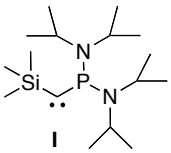
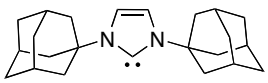
In 1988, Bertrand and co-workers succeeded in isolating the first stable carbene.[4] Unfortunately, the reported (phosphino)(silyl)carbene **I** did not show any ability as a ligand for transition metals.

The isolation of the free imidazol-2-ylidene **II** by Arduengo et al. in 1991 provided access to numerous transition metal carbene complexes by simple complexation of a stable carbene acting as a two-electron donor.[5] The dogma that carbenes were only transient species disappeared and a new field of research unfolded for synthetic chemists.



I



II

B. Development of N-heterocyclic carbenes

The unexpected stability of the N-heterocyclic carbenes (NHCs) has prompted several groups to carry out studies in order to better understand these unusual species. The nature and strength of the NHC–metal bond are key information to rational catalyst design. Indeed, studies aimed at quantifying tertiary phosphines steric and electronic effects have had a major impact on the development of new and improved ligands for catalysis,[6] and a parallel can easily be made with the development of NHCs.

First considered as simple tertiary phosphine mimics,[7] there is increasing experimental evidence that NHC–metal catalysts can surpass their phosphine-based counterparts in both activity and scope.[8] Despite the existence of several families of stable carbenes, only the five-membered cyclic diaminocarbenes have found numerous applications so far. Even if exceptions have been reported,[9] free acyclic carbenes including diamino carbenes[10] are far more fragile than these NHCs and are poorer ligands for transition metal complexes.[11] Structures for the most commonly employed carbene ligands are shown in

[4] Igau, A.; Grutzmacher, H.; Baceiredo, A.; Bertrand, G. *J. Am. Chem. Soc.* **1988**, *110*, 6463–6466.
[5] (a) Arduengo, A. J., III; Harlow, R. L.; Kline, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 361–363. (b) Arduengo, A. J., III *Acc. Chem. Res.* **1999**, *32*, 913–921.
[6] Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313–324.
[7] Green, J. C.; Scur, R. G.; Arnold, P. L.; Cloke, G. N. *Chem. Commun.* **1997**, 1963–1964.
[8] (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290–1309. (b) Cavallo, L.; Correa, A.; Costabile, C,; Jacobsen, H. *J. Organomet. Chem.* **2005**, *690*, 5407–5413.
[9] Teuma, E.; Lyon-Saunier, C.; Gornitzka, H.; Mignani, G.; Baceiredo, A.; Bertrand, G. *J. Organomet. Chem.* **2005**, *690*, 5541–5545.
[10] (a) Alder, R. W.; Allen, P. R.; Murray, M.; Orpen, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1121–1123. (b) Alder, R. W.; Blake, M. E. *Chem. Commun.* **1997**, 1513–1514. (c) Alder, R. W.; Blake, M. E.; Chaker, I.; Harvey, J. N.; Paolini, F.; Schutz, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5896–5911.
[11] Herrmann, W. A.; Öfele, K.; Preysing, D. v.; Herdtweck, E. *J. Organomet. Chem.* **2003**, *684*, 235–248.

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Figure 2. In the following sections, we will discuss the synthesis, properties and coordination chemistry of NHCs as well as their applications in catalysis, with a strong focus on five-membered ring diaminocarbenes.

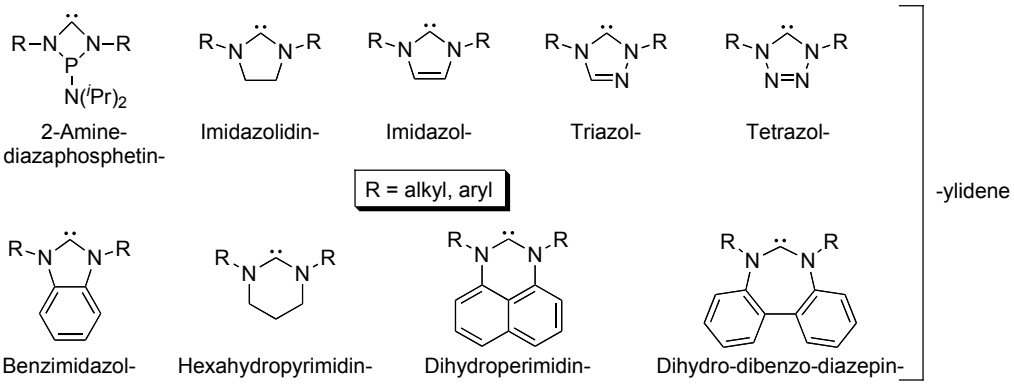

Figure 2. Structures of most common N-heterocyclic carbene ligands

II. Synthesis of NHCs

Numerous synthetic routes can be found in the literature for the preparation of *N*-containing ring systems that can be used as precursors of N-heterocyclic carbenes. These procedures, not necessarily designed for the synthesis of NHC ligands, can be one-pot, multi-components or stepwise syntheses and encompass tedious to extremely easy protocols.

In this section, we will only present the most commonly employed synthetic routes for the formation of five-membered ring imidazol-2-ylidene and imidazolidin-2-ylidene, which represent the two classes of NHCs used during this Ph.D. work.

A. Imidazol-2-ylidenes

1. Imidazol-2-ylidenes via imidazoliums

Symmetrical imidazolium salts

Various reliable routes are available to prepare imidazolium salts, which are the immediate precursors of imidazol-2-ylidenes. One of the most straightforward is the one-pot synthesis described in Scheme 2, using a primary amine, glyoxal and formaldehyde.[12] Under acidic conditions, the reaction proceeds through a coupling between the amine and the

[12] (a) Arduengo, A. J., III Patent: WO 9114678, **1992**. (b) Gridnev, A. A.; Mihaltseva, I. M. *Synth. Commun.* **1994**, *24*, 1547–1555.

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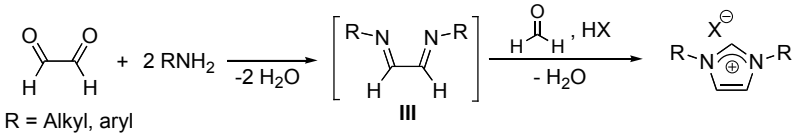
glyoxal, forming, upon dehydration, the corresponding Schiff base **III**. Condensation with formaldehyde leads to the imidazolium salt (Scheme 2).



Scheme 2. One-pot synthesis of imidazolium salts

Alternatively, the reaction can be split in two distinct steps, with the isolation of diimine **III**.[13] This very general procedure allows for the synthesis of symmetrically *N,N'*-substituted imidazolium salts with various aryl and alkyl groups such as the commercially available IPr·HCl and IMes·HCl (Figure 3).

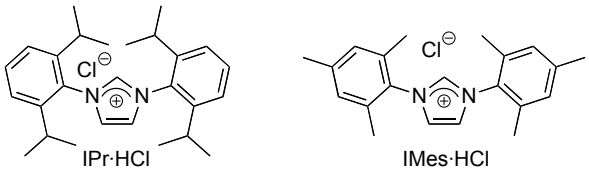
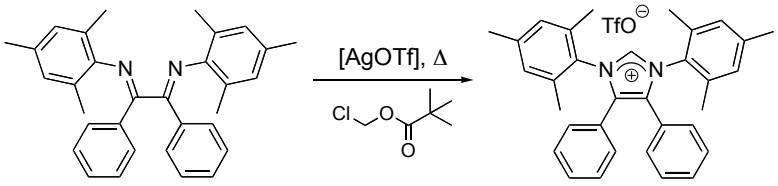


Figure 3. Structure of IPr·HCl and IMes·HCl used as NHC precursors.

Nevertheless, this synthetic approach is not always applicable. Notably, when the C4 and C5 positions are substituted, the cyclization step becomes disfavored.[14] Recently, Glorius proposed an alternative approach for the general synthesis of imidazolium salts from diimines.[15] The reaction of silver triflate with chloromethyl pivalate generates, *in situ*, a one-carbon alkylating agent that efficiently cyclizes hindered and non-hindered diimines (Eq 1).



(1)

Unsymmetrical imidazolium salts

The one-pot reaction between glyoxal, ammonium chloride, paraformaldehyde, and only one equivalent of primary amine leads to the mono *N*-substituted imidazole. This

[13] (a) Arduengo, A. J., III; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523–14534. (b) Jafarpour, L.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2000**, *606*, 49–54. (c) Hintermann, L. *Beilstein J. Org. Chem.* **2007**, *3*:22.
[14] Dove, A. P.; Li, H.; Pratt, R. C.; Lohmeijer, B. G. G.; Culkin, D. A.; Waymouth, R. M.; Hedrick, J. L. *Chem. Commun.* **2006**, 2881–2883.
[15] Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. W. *Chem. Commun.* **2002**, 2704–2705.

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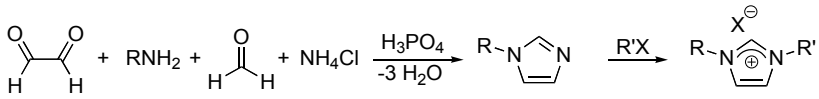
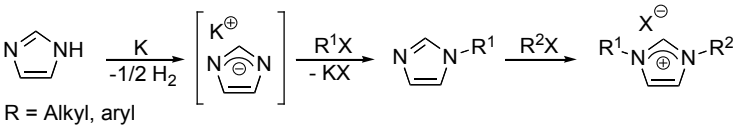
compound can be further *N*-alkylated by reaction with an alkyl halide to form an unsymmetrical *N,N'*-substituted imidazolium salt (Scheme 3).[12]



Scheme 3. Stepwise synthesis of imidazolium salts

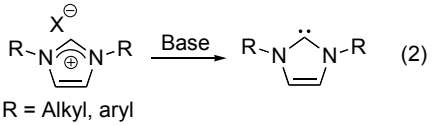
Another route to synthesize unsymmetrical imidazolium salts is the stepwise alkylations of an imidazolide anion generated from the reaction of imidazole with elemental potassium (Scheme 4).[12] Completion of the synthesis follows a classical imidazole alkylation procedure with a halide derivative.



Scheme 4. Stepwise alkylations of imidazole through imidazolide

Deprotonation of imidazoliums and formation of imidazol-2-ylidenes

The reaction of deprotonation of imidazoliums is usually carried out in ammonia or in non-protic solvents such as THF or ethers. The deprotonation requires anhydrous conditions and the use of strong bases, with pK_a values above 14 (Eq 2).



(2)

Generally, potassium or sodium hydride with a catalytic amount of *tert*-butoxide are employed, but *tert*-butoxide itself, lithium aluminium hydride, butyllithium, potassium hexamethyldisilazide (KHMDS) and DBU are also efficient alternatives.[13,16]

2. Imidazol-2-ylidenes via imidazole-2-thiones

Symmetrical imidazole-2-thiones

The condensation reaction of thioureas with 3-hydroxy-2-butanone in refluxing hexanol leads to 4,5-dimethyl-1,3-dialkylimidazole-2-thiones (Eq 3).[17] The reaction requires

[16] (a) Douthwaite, R. E.; Haüssinger, D.; Green, M. L. H.; Silcock, P. J.; Gomes, P. T.; Martius, A. M.; Danapoulos, A. A. *Organometallics* **1999**, *18*, 4584–4590. (b) Amyes, T. L.; Diver, S. T.; Richard, J. P.; Rivas, F. M.; Toth, K. *J. Am. Chem. Soc*. **2004**, *126*, 4366–4374. (c) Waltman, A. W.; Ritter, T.; Grubbs, R. H. *Organometallics* **2006**, *25*, 4238–4239.
[17] Kuhn, N.; Kratz, T. *Synthesis* **1993**, 561–562.

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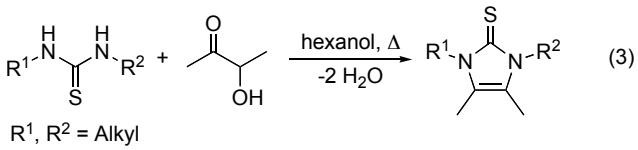
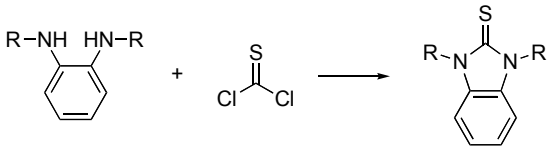
harsh conditions, but it represents a fairly general route producing, in one step, tetraalkylimidazole-2-thiones in good yields.



(3)

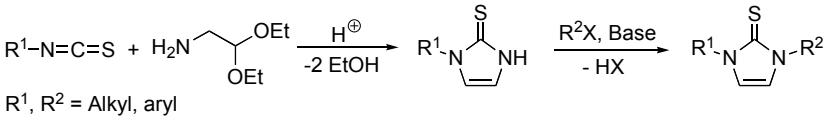
Alternatively, thiophosgene can be used as thiocarbonyl fragment. This allows notably for the high yield synthesis of benzimidazole-2-thiones, from 1,2-diaminobenzenes (Eq 4).[18]



(4)

Unsymmetrical imidazole-2-thiones

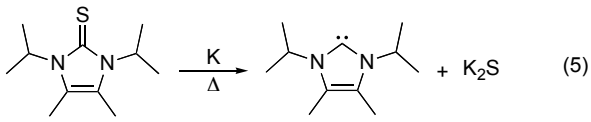
Under acidic conditions, aryl- or alkyl isothiocyanates react with amino-2,2-diethoxyethane to form mono *N*-substituted imidazole-2-thiones, which can react further with an alkyl halide to form *N,N'*-disubstituted imidazole-2-thiones (Scheme 5).[19]



Scheme 5. Stepwise synthesis of imidazole-2-thione

Desulfurization and formation of imidazol-2-ylidenes

Imidazole-2-thiones lead to imidazol-2-ylidenes by desulfurization. The reaction is carried out in boiling THF with excess potassium and yields the corresponding NHC upon formation of K_2S (Eq 5). Despite the drastic conditions required, the yields are generally almost quantitative.[17,18,20]



(5)

3. Imidazol-2-ylidenes via carboxylate adducts

Imidazolium salts react with carbon dioxide or alkyl chloroformates to yield, under

[18] Hahn, F. E.; Wittenbecher, L.; Boese, R.; Bläster, D. *Chem.–Eur. J.* **1999**, *5*, 1931–1935.
[19] Matsuda, K.; Yanagisawa, I.; Isomura, Y.; Mase, T.; Shibanuma, T. *Synth. Commun.* **1997**, *27*, 3565–3571.
[20] Denk, M. K.; Thadani, A.; Hatano, K.; Lough, A. J. *Angew. Chem., Int. Ed.* **1997**, *36*, 2607–2609.

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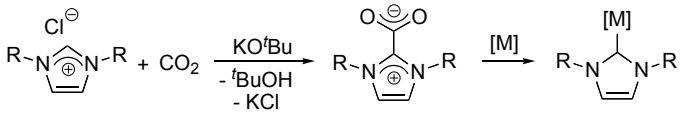
basic conditions, 2-carboxylate- or 2-ester-imidazoles (Scheme 6).[21] First reported by Louie and co-workers,[22] these adducts are air stable and can generate NHCs upon loss of CO_2. In the presence of transition metals, they are excellent NHC surrogates and can deliver carbene ligands to a variety of metal salts without the need for base.[23]



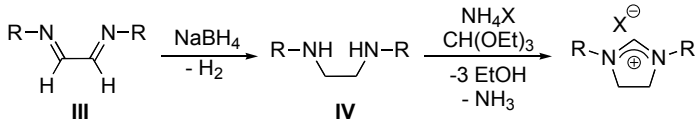
Scheme 6. Formation of NHC–CO_2 adducts

B. Imidazolidin-2-ylidenes

1. Imidazolidin-2-ylidenes via imidazoliniums

Symmetrical imidazolinium salts

Diazabutadienes **III**, obtained as intermediates in the synthesis of imidazol-2-ylidenes (see Scheme 2), can be reduced to 1,2-diaminoethane **IV** by treatment with sodium borohydride. The reduced diamines further react with triethyl orthoformate under acidic conditions to form imidazolinium salts (Scheme 7).[13] The cyclization is actually an equilibrium that can be driven towards the salt by removal (distillation) of ethanol. The reaction time can be reduced from hours to a few minutes using microwave heating.[24] This methodology allows for the synthesis of symmetrically *N,N'*-disubstituted imidazolinium salts with various aryl groups.



Scheme 7. Synthesis of symmetrical imidazolinium salts

Unsymmetrical imidazolinium salts

Ethyl-2-chloro-2-oxoacetate **V** can react, in a stepwise fashion, with two different amines, forming oxalamide **VI** (Scheme 8). Its reduction with borane·THF or lithium

[21] (a) Chianese, A. R.; Zeglis, B. M.; Crabtree, R. H. *Chem. Commun.* **2004**, 2176–2177. (b) Voutchkova, A. M.; Appelhans, L. N.; Chianese, A. R.; Crabtree, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17624–17625. (c) Tommasi, I.; Sorrentino, F. *Tetrahedron Lett.* **2006**, *47*, 6453–6456.
[22] Duong, H. A.; Tekavec, T. N.; Arif, A. M.; Louie, J. *Chem. Commun.* **2004**, 112–113.
[23] (a) Tudose, A.; Demonceau, A.; Delaude, L. *J. Organomet. Chem.* **2006**, *691*, 5356–5365. (b) Tudose, A.; Delaude, L.; Andre, B.; Demonceau, A. *Tetrahedron Lett.* **2006**, *47*, 8529–8533. (c) Voutchkova, A. M.; Feliz, M.; Clot, E.; Eisenstein, O.; Crabtree, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 12834–12846.
[24] Aidouni, A.; Demonceau, A.; Delaude, L. *Synlett* **2006**, 493–495.

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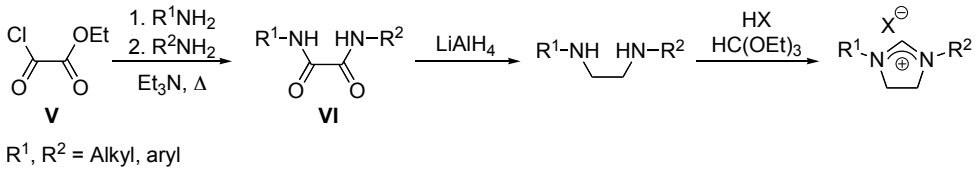
aluminium hydride yields 1,2-diaminoethanes, which can be cyclized to form unsymmetrically *N,N'*-substituted imidazolinium salts.[25]



Scheme 8. Synthesis of unsymmetrical imidazolinium salts

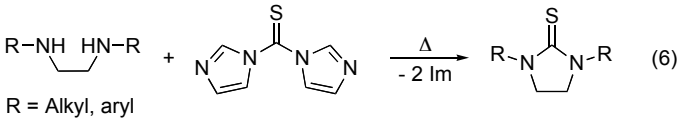
Deprotonation and formation of imidazolin-2-ylidenes

Similarly to their unsaturated counterparts (see Eq 2), imidazolinium salts are deprotonated by strong bases. Nevertheless, it should be noted that ammonia, alkoxides and any other nucleophilic base have to be avoided since their use would result in the formation of an adduct with the imidazolidin-2-ylidene.[26]

2. Imidazolidin-2-ylidenes via imidazolidine-2-thiones

Symmetrical imidazolidine-2-thiones

The cyclization reaction of ethane-1,2-diamines with thiophosgene or 1,1'-thiocarbonyldiimidazole (Eq 6) represent two viable synthetic routes for the formation of symmetrical imidazolidine-2-thiones in high yields.[27]



(6)

Unsymmetrical imidazolidine-2-thiones

In a one-pot reaction, secondary alkylamines can be deprotonated with *n*-butyllithium and treated with carbon disulfide to yield lithium dithiocarbamates **VII**. A second lithiation with *sec*-butyllithium yields lithium *N*-lithiomethyldithiocarbamate compounds **VIII**. Finally, addition of an aldimine yields imidazolidine-2-thiones (Scheme 9).[28] Even if this route leads to poor yields of thiones (around 50%), it remains a rapid synthesis for unsym-

[25] (a) Clavier, H.; Coutable, L.; Guillemin, J.-C.; Mauduit, M. *Tetrahedron: Asymmetry* **2005**, *17*, 921–924. (b) Paczal, A.; Bényei, A. C.; Kotschy, A. *J. Org. Chem.* **2006**, *71*, 5969–5979.
[26] (a) Hocker, J.; Merten, R. *Chem. Ber.* **1972**, *105*, 1651–1653. (b) Taton, T. A.; Chen. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1011–1013. (c) Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Chem.–Eur. J.* **1996**, *2*, 772–780.
[27] Yang, D.; Chen, Y.-C.; Zhu, N.-Y. *Org. Lett.* **2004**, *6*, 1577–1580.
[28] (a) Hahn, F. E.; Paas, M.; Le Van, D.; Lügger, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 5243–5246. (b) Hahn, F. E.; Le Van, D.; Paas, M.; Fröhlich, R. *Dalton Trans.* **2006**, 860–864.

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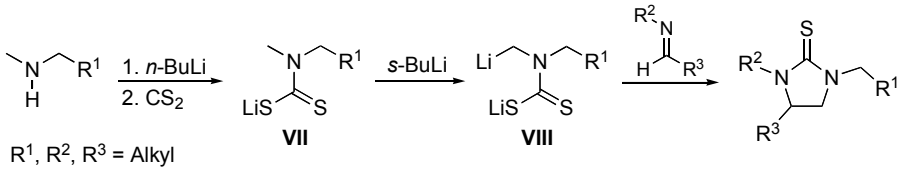
metrically *N,N'*-substituted imidazolidin-2-ylidene precursors.



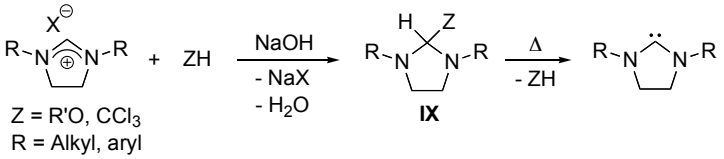
Scheme 9. Synthesis of imidazolidine-2-thiones via condensation of aldimines

Desulfurization and formation of imidazolidin-2-ylidenes

Similarly to imidazole-2-thiones (see Eq 5), imidazolidine-2-thiones are reduced with excess potassium in boiling THF, leading to imidazolidinylidenes in high yields.

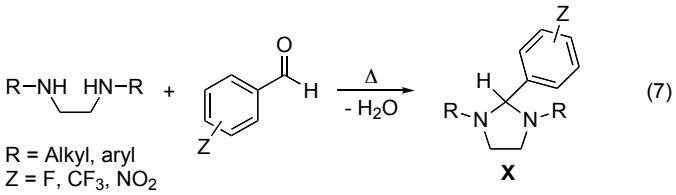
3. Imidazolidin-2-ylidenes via imidazolidine adducts

Under basic conditions, methanol, *tert*-butanol, and chloroform react with imidazolinium halides to yield imidazolidine adduct **IX** substituted at the C2 position[29,30,31] (Scheme 10). These adducts act as masked NHCs and can be chemically manipulated in air. Interestingly, they generate imidazolidinylidenes by thermolysis without the need for a strong base (Scheme 10).



Scheme 10. Synthesis of imidazolidine adducts and thermal generation of NHCs

Another possible route for the synthesis of masked NHCs is the condensation-cyclization of 1,2-diaminoethanes onto benzaldehydes leading to diaminoketals **X** (Eq 7).[32]



(7)

[29] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
[30] Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546–2558.
[31] (a) Cetinkaya B.; Cetinkaya, E.; Chamizo, J. A.; Hitchcock, P. B.; Jasim, H. A.; Kücükbay, H.; Lappert, M. F. *J. Chem. Soc., Faraday Trans.* **1998**, 2047–2054. (b) Blum, A. P.; Ritter, T.; Grubbs, R. H. *Organometallics* **2007**, *26*, 2122–2124.
[32] (a) Nyce, G. W.; Csihony, S.; Waymouth, R. M.; Hedrick, J. L. *Chem.–Eur. J.* **2004**, *10*, 4073–4079. (b) Bedford, R. B.; Betham, M.; Bruce, D. W.; Danopoulos, A. A.; Frost, R. M.; Hird, M. *J. Org. Chem.* **2006**, *71*, 1104–1110.

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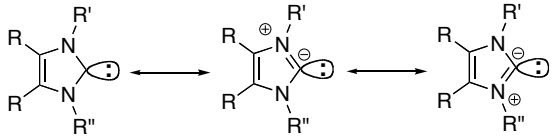
These diaminoketals can be viewed as aryl adduct of imidazolidine and can be used as NHC surrogates for the formation of NHC-containing transition metal complexes.[33]

III. Stereoelectronic Parameters of NHCs

A. Electronic structure of NHCs: The aromaticity question

1. σ-Stabilization

To date, all theoretical and experimental evidence indicates that, in order to form a stable carbene, the carbenic carbon needs to be bonded to strong π-donor atoms.[34] However, the remarkable stability of the first isolated carbene, IAd, was totally unexpected at the time. *Ab initio* studies led Dixon and Arduengo to postulate that p(π)–p(π) delocalization is not extensive and that the bonding in these ligands should be considered carbenic since ylidic resonance structures are not dominant contributors (Scheme 11).[35] Similar conclusions have been reached using diverse techniques:[36] the unexpected stability of free NHC would arise mainly from substantial σ-charge transfer from the carbenic carbon to the more electronegative neighboring nitrogen atoms. Therefore, the additional synergistic effect of π-donation would only play a minor role.



Scheme 11. Resonance structures of NHCs

Additional steric protection from the *N*-substituents may enhance the stability of the carbenes and it might compensate for less electronic stabilization, but it is not a decisive factor since sterically less demanding substituents also lead to isolable carbenes.[37]

[33] Bedford, R. B.; Betham, M.; Blake, M. E.; Frost, R. M.; Horton, P. N.; Hursthouse, M. B.; López-Nicolás, R.-M. *Dalton Trans*. **2005**, 2774–2779.
[34] Recently Bertrand showed that the presence of a tertiary carbon center next to the carbene center allowed for the isolation of stable carbenes that could coordinate transition metals: (a) Lavallo, V.; Canac, Y.; Präsang, C.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 5705–5709. (b) Lavallo, V.; Canac, Y.; DeHope, A. ; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed*. **2005**, *44*, 7236–7239.
[35] Dixon, D. A.; Arduengo, A. J., III *J. Phys. Chem.* **1991**, *95*, 4180–4182.
[36] (a) Cioslowski, J. *Int. J. Quantum Chem., Quantum Chem. Symp*. **1993**, *27*, 309–319. (b) Arduengo, A. J., III; Bock, H.; Chen, H.; Denk, M.; Dixon, D. A.; Green, J. C.; Herrmann, W. A.; Jones, N. L.; Wagner, M.; West, R. *J. Am. Chem. Soc*. **1994**, *116*, 6641–6649. (c) Arduengo, A. J., III; Dias, H. V. R.; Dixon, D. A.; Harlow, R. L.; Klooster, W. T.; Koetzle, T. F. *J. Am. Chem. Soc*. **1994**, *116*, 6812–6822.
[37] Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc*. **1992**, *114*, 5530–5534.

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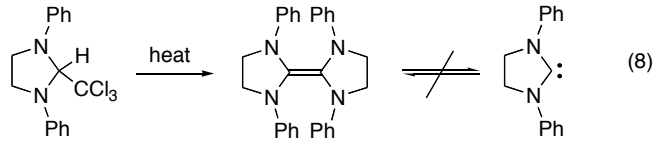
2. π-Stabilization

It has been argued that the dominant factor stabilizing the carbenes is the donation from the nitrogen lone pairs into the formally empty p(π) orbital of the carbene carbon atom.[38] It was also showed that the method of density mapping employed by Arduengo was not suitable for analyzing electron delocalization. Related theoretical and experimental reports have also suggested that there is a cyclic electron stabilization, conferring the imidazol-2-ylidenes a certain aromatic character.[39] This aromaticity would be appreciably smaller than in 'standard' systems such as benzene or imidazolium salts but still significant from magnetic and thermodynamic perspectives. At this point, it is important to note that there is no direct way to correlate the degree of conjugation with the resulting thermodynamic stabilization.[40]

Intuitively, the essential stabilizing role of the C=C bond in imidazol-2-ylidenes has been evoked for a long time. Wanzlick's pioneer work on saturated carbenes, where only the corresponding dimeric enetetramines could be isolated,[41] seemed to also point in this direction (Eq 8). The classical explanation invoking a thermodynamic stabilization of carbenes via cyclic 6π-electron delocalization had to be revised after the isolation of the first imidazolidin-2-ylidene in 1995 (Eq 9).[42]



It was then clear that such a delocalization would only be an additional stabilizing factor, and that the electron donation of the nitrogen atoms would be sufficient for stabilizing the free carbene. Arduengo alternatively suggested a kinetic stabilization provided by the double bond, which was stated as critical for achieving an electron repulsion strong enough to prevent any electrophilic reactivity of the carbene.[16c]

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[38] (a) Heinemann, C.; Müller, T.; Apeloig, Y.; Schwarz, H. *J. Am. Chem. Soc.* **1996**, *118*, 2023–2038. (b) Boehme, C.; Frenking, G. *J. Am. Chem. Soc.* **1996**, *118*, 2039–2046.

[39] Lehmann, J. F.; Urquhart, S. G.; Ennios, L. E.; Hitchcock, A. P.; Hatano, K.; Gupta, S.; Denk, M. K. *Organometallics* **1999**, *18*, 1862–1872.

[40] Minkin, V. I.; Glukhovtsev, M. N.; Simkin, B. Y. *Aromacity and Antiaromacity*, J. Wiley & Sons: New York, 1994.

[41] (a) Wanzlick, H. W. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 75–80. (b) Schönherr, H.-J.; Wanzlick, H. W. *Chem. Ber.* **1970**, *103*, 1037–1040.

[42] Arduengo, A. J., III; Goerlich, J. R.; Marshall, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11027–11028.

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B. Electronic and steric factors affecting the NHC–metal bond

1. Electronic factors

An interesting approach to assess the binding strength of a ligand is to determine its basicity. However, there are only a few reports in the literature dealing with the experimental pK_b[43] of imidazol-2-ylidenes.[44] Recent theoretical calculations have allowed for a classification of a number of carbenes according to their basicity (Figure 4).[45] This study showed that electron delocalization is not key in determining basicity. The most influential factors would be the substitution on the backbone and mainly the NCN bond angle.

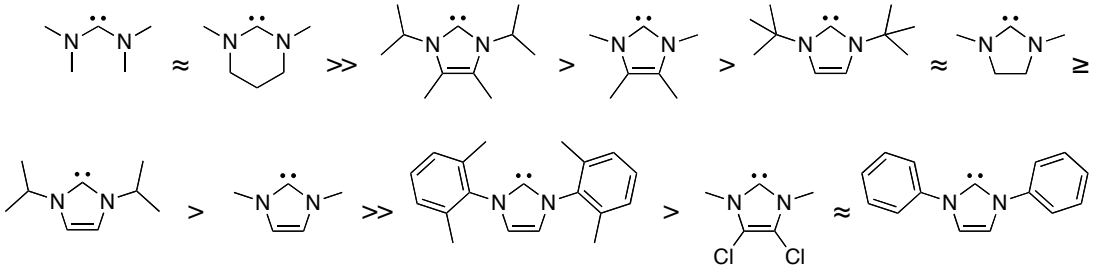

Figure 4. Classification of carbenes according to their theoretical pK_b values

These results support the experimental suggestion that the bis(diisopropylamine)carbene[10a] is probably the most basic carbene ligand known to date.[46] Moreover, the very basic phosphine P(*t*-Bu)$_3$ is still 10 pK_b units less basic than the least basic carbene.[47] However, it should be taken into account that no studies on the basicity of late generation phosphines, that have shown enhanced catalytic activities, have been reported to date.[48] Another empirical approach to the understanding of the electronic properties of these ligands is based on the study of the carbonyl stretching frequencies of NHC-containing carbonyl transition metal complexes. To date, all reports point to the fact that NHCs are more electron-donating than tertiary phosphines.[49] Notably, the substitution

[43] Since ligand basicity is an important concept in organometallic chemistry, pK_a is usually used when refering to the conjugated base. However, we prefer using the more formally correct pK_b. See ref. 10a.
[44] (a) Alder, R. W.; Allen, P. R.; Williams, S. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1267–1268. (b) Kim, Y.-J.; Streitwieser, A. *J. Am. Chem. Soc.* **2002**, *124*, 5757–5761. For a study on the basicity of phosphino(silyl)carbenes see: (c) Martin, D.; Illa, O.; Baceiredo, A.; Bertrand, G.; Ortuño, R. M.; Branchadell, V. *J. Org. Chem.* **2005**, *70*, 5671–5677.
[45] Magill, A. M.; Cavell, K. J.; Yates, B. F. *J. Am. Chem. Soc.* **2004**, *126*, 8717–8724.
[46] Denk, K.; Sirsch, P.; Herrmann, W. A. *J. Organomet. Chem.* **2002**, *649*, 219–224.
[47] Rahman, M. M.; Liu, H.-Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1–7.
[48] For representative examples see: (a) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028–13032. (b) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180–2181.
[49] (a) Huang, J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2000**, *19*, 1194–1197. (b) Perrin, L.; Clot, E.; Eisenstein, O.; Loch, J.; Crabtree, R. H. *Inorg. Chem.* **2001**, *40*, 5806–5811. (c) Chianese, A. R.; Li, X.; Jarzen, M. C.; Faller, J. W.; Crabtree R. H. *Organometallics* **2003**, *22*, 1663–1667.

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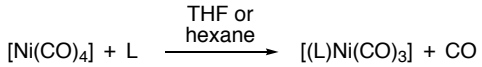
reactions involving [Ni(CO)$_4$] and NHC ligands have been studied to some extent.[50] When reacted with this nickel precursor, most carbene ligands form the saturated [(NHC)Ni(CO)$_3$] complexes (Table 1).[51] Direct comparison of the electronic properties of NHCs with tertiary phosphines[52] could be done measuring the carbonyl stretching frequencies of these complexes. These data clearly showed that NHCs are better σ-donor than even the very basic phosphine P(*t*-Bu)$_3$. Of note, IR data have also suggested that abnormal C5-bound NHCs, which are called NHCs simply by extension, would be substantially stronger electron-donor than normal C2-bound carbenes.[53]

Table 1. Preparation and IR values of [(NHC)Ni(CO)$_3$] complexes



Ligand	Yield (%)	υ_{CO} (A_1)[a]	υ_{CO} (E)[a]
IPr	86	2051.5	1970.0
SIPr	84	2052.2	1971.3
IMes	95	2050.7	1969.8
SIMes	91	2051.5	1970.6
ICy	88	2049.6	1964.6
P(*t*-Bu)$_3$		2056.1	1971
PPh$_3$		2068.9	1990

[a] In cm^{-1}, mesured in CH_2Cl_2

These results suggest notably that the saturated NHC ligands would be slightly less electron-donating than their unsaturated analogues and that alkyl-substituted NHCs are only marginally more electron-donating than their aryl-substituted counterparts, which contradicts again the accepted dogma.

Finally, stable NHCs with a diboron backbone[54] and six-membered ring carbenes derivatives of borazines have recently been reported (Figure 5).[55] Variation of the boron substituents would notably allow tuning the electronic properties without changing the steric

[50] (a) Öfele, K.; Herrmann, W. A.; Mihalios, D.; Elison, M.; Herdtweck, E.; Scherer, W.; Mink, J. *J. Organomet. Chem.* **1993**, *459*, 177–184. (b) Herrmann, W. A.; Goossen, L. J.; Artus, G. R. J.; Köcher, C. *Organometallics* **1997**, *16*, 2472–2477.
[51] (a) Dorta, R.; Stevens, E. D.; Hoff, C. D.; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 10490–10491. (b) Dorta, R.; Stevens, E. D.; Scott, N. M.; Costabile, C.; Cavallo, L.; Hoff, C. D.; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 2485–2495.
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[53] Chianese, A. R.; Kovacevic, A.; Zeglis, B. M.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2004**, *23*, 2461–2468.
[54] Krahulic, K. E.; Enright, G. D.; Parvez, M.; Roesler, R. *J. Am. Chem. Soc.* **2005**, *127*, 4142–4143.
[55] Präsang, C.; Donnadieu, B.; Bertrand, G. *J. Am. Chem. Soc.* **2005**, *127*, 10182–10183.

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demands and therefore might permit a better understanding of the factors governing the catalytic activity of organometallic complexes.

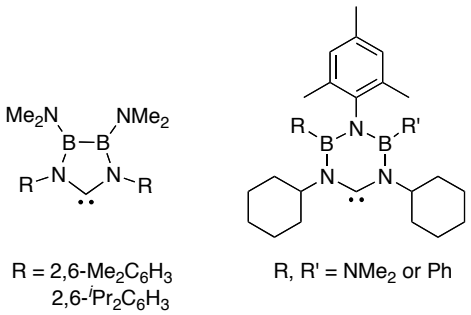

Figure 5. Boron-substituted NHCs

2. Steric factors

It is clear that the overall availability of the carbene lone pair is dependent of a combination of steric and electronic properties of the ligand in a given coordination environment.[56] In general, from structural studies one can only conclude that bulkiness of the groups bound to the nitrogen atoms of the NHC ligands and more importantly, the short metal–carbon distances in these complexes, increase the steric congestion around the metal center when compared to tertiary phosphines.

In order to quantify the steric requirements of these ligands, a new model was designed: the percent of the volume occupied by ligand atoms in a sphere centered on the metal (%V_{Bur}, see Figure 6). This model allows for a more realistic comparison with other ligands, particularly tertiary phosphines. The model also takes into account the high asymmetry of these ligands. For [Cp*Ru(L)Cl] complexes, the experimental (and theoretical) bond-dissociation energies (BDEs) plotted versus %V_{Bur} resulted in a linear correlation, indicating that the BDEs are essentially controlled by the steric requirements of the ligand.[30]

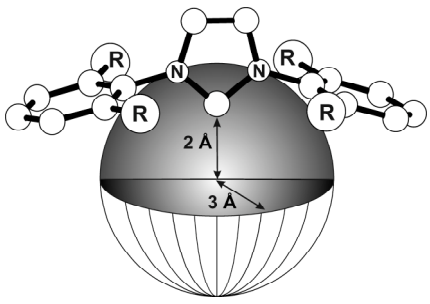

Figure 6. Representation of the sphere dimensions for steric parameter determination (%V_{Bur}) of NHC ligands

[56] Arduengo, A. J., III; Krafczyk, R. *Chem Z.* **1998**, *32*, 6–14.

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As mentioned previously, only small electronic differences were experimentally observed in [(NHC)Ni(CO)$_n$] complexes.[42] This was reinforced by theoretical studies indicating that any difference between NHC ligands is mainly steric in nature (Table 2).

Table 2. BDE and %V_{bur} values in [(L)Ni(CO)$_2$] and [(L)Ni(CO)$_3$] (kcal.mol^{-1})

Ligand	BDE of CO in [(L)Ni(CO)$_3$]	BDE of L in [(L)Ni(CO)$_3$]	BDE of L in [(L)Ni(CO)$_2$]	%V_{bur}
ItBu	13.3	24.0	44.3	37
IAd	7.6	20.4	46.5	37
IMes	28.3	41.1	46.5	26
SIMes	26.8	40.2	47.2	27
IPr	26.7	38.5	45.4	29
SIPr	25.6	38.0	46.1	30
ICy	27.0	39.6	46.3	23
PPh_3	30.4	26.7	30.0	22
P(*t*-Bu)$_3$	27.4	28.0	34.3	30

In fact, the larger values of %V_{Bur} for ItBu and IAd ligands relative to IMes, SIMes, IPr, SIPr and ICy ligands were in qualitative agreement with the different calculated BDEs. Moreover, calculation of %V_{Bur} for PR_3 systems allowed for a direct comparison between the two ligand families showing that interestingly, the two most sterically demanding carbenes are bulkier than P(*t*-Bu)$_3$. Nevertheless, as depicted in Figure 7, the steric impact of tertiary phosphines and NHCs on a metal center is very distinct and direct comparison should be made with caution.

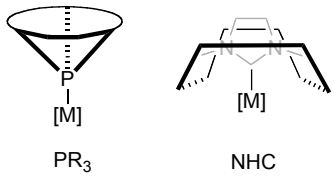

Figure 7. Schematic representation of the steric impact of phosphines and NHCs

3. Implication for catalysis

The right combination of electronic and steric factors characterizing NHCs has been key in rationalizing the stabilization of otherwise highly reactive species. Triscarbene-nickel-hydride complexes are a representative example.[57] Prepared by oxidative addition of

[57] Clement, N. D.; Cavell, K. J.; Jones, C.; Elseiver, C. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1277–1279.

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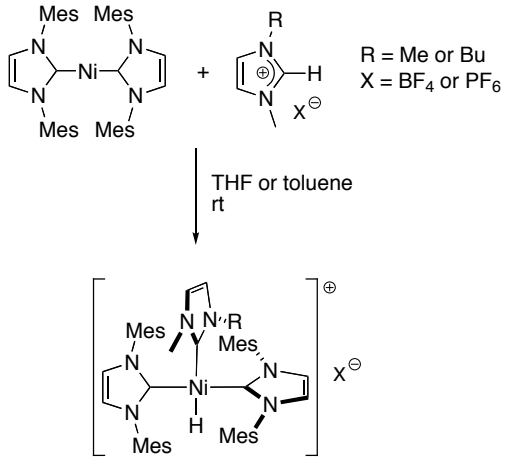
electron-rich [$(NHC)_2Ni$] complexes into the C2–H bond of imidazolium salts (Scheme 12), these first reported (NHC)nickel–hydrides turn out to be surprisingly stable in solution, in the solid state and even in air. The stabilization of these hydrides was explained by the directional distribution of the steric bulk and the electronic properties of carbene ligands. The 'steric factor' has also been evoked in the study of other nickel(0) complexes and their catalytic activity in the C–C and C–F activation reactions.[58]



Scheme 12. Preparation of [$(NHC)_3NiH$] complexes

Structural and catalytic studies on [(NHC)Pd(allyl)Cl] complexes showed a striking difference of activity in aryl amination reactions between the IPr-containing complex and the SIPr analogue, the latter being up to 60 times faster in catalysis than the former.[59] This variation in reactivity was associated with the increased hindrance associated to the SIPr ligand, rather than its electronic donor ability.

Nevertheless, an excessive steric pressure around the metal center can render labile the NHC–metal bond. Relief of this pressure would be a significant driving force leading to ligand dissociation. For instance, the reaction of a PPh_3-bearing cobalt complex with free IPr did not led to a displacement of the phosphine by the NHC, as expected.[60] On the contrary, the reaction reached an equilibrium that allowed for the collection of thermodynamic data for the interchange of phosphine and carbene ligands (Scheme 13). Furthermore, addition of a less demanding tertiary phosphine to the reaction mixture led to the complete displacement of the carbene ligand.

[58] Schaub, T.; Radius, U. *Chem.–Eur. J.* **2005**, *11*, 5024–5030.
[59] Viciu, M. S.; Navarro, O.; Germaneau, R. F.; Kelly, R. A., III; Sommer, W.; Marion, N.; Stevens, E. D.; Cavallo, L.; Nolan, S. P. *Organometallics* **2004**, *23*, 1629–1635.
[60] Simms, R. W.; Drewitt, M. J.; Baird, M. C. *Organometallics* **2002**, *21*, 2958–2963.

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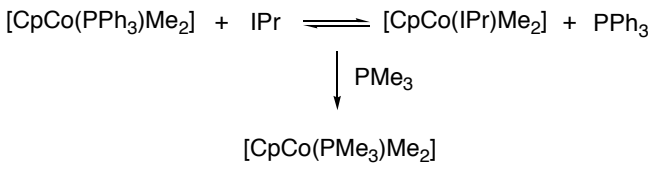

Scheme 13. Phosphine-NHC exchange reactions in cobalt complexes

This work illustrates the need of carefully interpreting the catalytic results. During the reaction, loss of the carbene and formation of new species with greater catalytic activity can lead to incorrect assumptions regarding the activity of the original carbene-ligated complex.

IV. Nature of the NHC–metal bond

For decades it has been accepted that divalent carbon species **:**CR^1R^2 exhibit σ-donor and π-acceptor properties upon binding to transition metals. The coordination of conventional carbenes depends mainly on π back-bonding since they are weak σ-donor, but early studies suggested that the π-acceptor ability of NHCs, lying between those of nitriles and pyridine, was negligible.[61] However, more recent results point to a more flexible behavior of NHCs where back-donation might contribute importantly to the stabilization of the metal center.[62]

A. NHC ligands as pure σ-donors

The potential of NHCs to bind metal centers incapable of π back-donation has long been used as an empirical evidence of their pure σ-donor character. NHC-bearing complexes of main group elements and rare earth metals can be viewed as donor adducts, just like ammonia and ether complexes.[63] Magnesium,[64] boron,[65] aluminum,[66] gallium,[67] thallium,[68] or silicon[69] as well as ytterbium and samarium[70] form stable adducts with NHCs.

[61] (a) Öfele, K.; Kreiter, C. G. *Chem. Ber.* **1972**, *105*, 529–540. (b) Öfele, K.; Herberhold, M. *Z. Naturforsch* **1973**, *28*, 306–309.
[62] Tafipolsky, M.; Scherer, W.; Öfele, K.; Artus, G.; Pedersen, B.; Herrmann, W. A.; McGrady, G. S. *J. Am. Chem. Soc.* **2002**, *124*, 5865–5880.
[63] Frison, G.; Sevin, A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1692–1697.
[64] (a) Arduengo, A. J., III; Dias, H. V. R.; Davidson, F.; Harlow, R. L. *J. Organomet. Chem.* **1993**, *462*, 13–18. (b) Schummann, H.; Gottfriedsen, J.; Glanz, M.; Dechert, S.; Demtschuk, J. *J. Organomet. Chem.* **2001**, *617–618*, 588–600.

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The complexation chemistry of the heavier members of group 2 was first reported by Arduengo.[71] A number of mono-carbene metallocene adducts derived from Mg, Ca, Sr, and Ba were carefully studied by NMR and crystallographic techniques. It was found that the nature of the carbene-metal bond ranges from somewhat covalent for magnesium to rather ionic for barium.

Later, Arnold and co-workers reported the synthesis of metal complexes bearing bidentate amido-NHC ligands.[72] These lithium, magnesium and uranium complexes showed significant distortion of the NHC–metal bond that did not translate in a decrease of the bond strength. This fact indicates that, in these cases, bonding is predominantly electrostatic in nature.

Theoretical analysis of the bonding situation in beryllium carbene complexes showed that the population of the p(π) orbital of the carbenic carbon is the key factor in the isolation of carbene complexes.[73] Since no back-donation would be possible in the case of beryllium, π-donation from the substituents of the carbene, enhanced by the coordination to a pure acceptor metal, would explain the stability of this complex. A number of experimental and/or theoretical studies have also suggested that π-back donation is negligible in NHC–transition metal bonding.[74]

B. Importance of the π interaction in NHC-bearing complexes

The simplified picture of NHCs as mere σ-donors is now obsolete and several reports

[65] (a) Kuhn, N.; Henkel, G.; Kratz, T.; Kreutzberg, J.; Boese, R.; Maulitz, A. H. *Chem. Ber.* **1993**, *126*, 2041–2045. (b) Wacker, A.; Pritzkow, H.; Siebert, W. *Eur. J. Inog. Chem.* **1998**, 843–849.
[66] Arduengo, A. J., III; Dias, H. V. R.; Calabrese, J. C.; Davidson, F. *J. Am. Chem. Soc.* **1992**, *114*, 9724–9725.
[67] Li, X.-W.; Su, J.; Robinson, G. H. *Chem. Commun.* **1996**, 2683–2684.
[68] Nakai, H.; Tang, Y. J.; Gantzel, P.; Meyer, K. *Chem. Commun.* **2003**, 24–25.
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[73] Fröhlich, N.; Pidun, U.; Stahl, M.; Frenking, G. *Organometallics* **1997**, *16*, 442–448.
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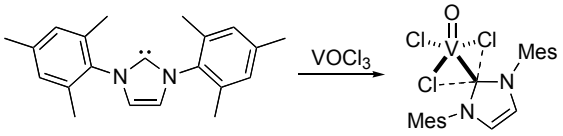
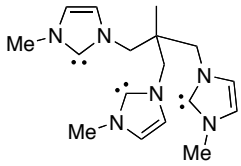
have suggested that empty π, π* orbitals on the NHC ring can contribute to the NHC–metal bond.[75] Already in 1975, the existence of π back-bonding in ruthenium(II) complexes bearing a carbon-bound xanthine was reported.[76] Similar interactions were reported to allow for the isolation of a NHC–vanadium(V) trichloro-oxo complex (Eq 10).[77]



(10)

In this first report concerning NHC as stabilizing ligands of high oxidation state transition metal complexes, unexpectedly short distances were observed between the *cis* chlorine atoms and the carbenic carbon (2.849 and 2.887 Å, respectively). The strong interaction between chlorine lone pairs electron-density and the formally vacant p(π)-orbital of the carbenic carbon was illustrated by DFT calculations and it can be considered as a form of back-donation in which the electron density comes from the chlorine ligands rather than the metal center.[78] Similarly, Shukla et al. found that there is an electron-density transfer from the chloride ligands to the p(π) orbital of the carbenic carbon of the $[(IMes)TiCl_2(NMe_2)_2]$ adduct.[79]

Non-negligible π-interaction between group 11 metals and NHC ligands had also been previously postulated,[80] but it was Meyer and co-workers who showed their existence by computational analysis.[81] First reported with silver, copper and gold complexes bearing tripodal polycarbene ligands $TIME^{Me}$ (1,1,1-tris[3-methylimidazol-2-ylidene)methyl]ethane) were also subjected to DFT calculations. An overall σ-donation from the ligand to the metal, in accordance with the well-known strong Lewis basicity of NHCs, was



$TIME^{Me}$

[75] For selected reports, see: (a) Arduengo, A. J., III; Gamper, S. F.; Calabrese, J. C.; Davidson, F. *J. Am. Chem. Soc.* **1994**, *116*, 4391–4394. (b) Gérard, H.; Clot, E.; Eisenstein, O. *New. J. Chem.* **1999**, *23*, 495–498. (c) Huang, J.; Schanz, H. J.; Stevens, E. D.; Nolan, S. P. *Inorg. Chem.* **2000**, *39*, 1042–1045. (d) McGuinness, D. S.; Saendig, N.; Yates, B. F.; Cavell, K. J. *J. Am. Chem. Soc.* **2001**, *123*, 4029–4040. (e) Jazzar, R. F. R.; Macgregor, S. A.; Mahon, M. F.; Richards, S. P.; Whittlesey, M. K. *J. Am. Chem. Soc.* **2002**, *124*, 4944–4945. (f) Deuvel, D. V. *Organometallics* **2002**, *21*, 4303–4305. (g) Termaten, A. T.; Schakel, M.; Ehlers, A. W.; Lutz, M.; Spek, A. L.; Lammertsma, K. *Chem.–Eur. J.* **2003**, *9*, 3577–3582. (h) Sübner, M.; Plenio, H. *Chem. Commun.* **2005**, 5417–5419.

[76] Clarke, M. J.; Taube, H. *J. Am. Chem. Soc.* **1975**, *97*, 1397–1403.

[77] Abernethy, C. D.; Codd, G. M.; Spicer, M. D.; Taylor, M. K. *J. Am. Chem. Soc.* **2003**, *125*, 1128–1129.

[78] Kapp, J.; Schade, C.; El-Nahasa, A. M.; Schleyer, P. von R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2236–2238.

[79] Shukla, P.; Johnson, J. A.; Vidovic, D.; Cowley, A. H.; Abernethy, C. D. *Chem. Commun.* **2004**, 360–361.

[80] (a) Garrison, J. C.; Simons, R. S.; Kofron, W. G.; Tessier, C. A.; Youngs, W. J. *Chem. Commun.* **2001**, 1780–1781. (b) Tulloch, A. A. D.; Danopoulos, A. A.; Kleinhenz, S.; Light, M. E.; Hursthouse, M. B.; Eastham, G. *Organometallics* **2001**, *20*, 2027–2031.

[81] Hu, X.; Tang, Y.; Gantzel, P.; Meyer, K. *Organometallics* **2003**, *22*, 612–614.

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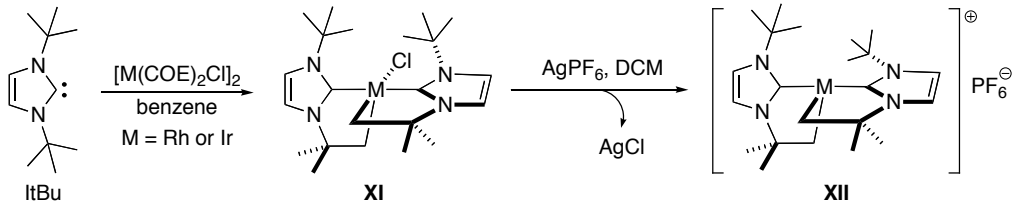
established. Nevertheless the π back-bonding interactions were estimated to contribute to 15-30% of the complexes overall orbital interaction energies, which can hardly be considered as negligible.

Similar conclusions were drawn from EDA calculations (EDA = energy decomposition analysis) on group 11 complexes with NHC ligands.[82] In fact, calculated data suggested that the π back-donation in these complexes is not substantially smaller than in classic Fischer carbene complexes bearing two π-donor groups.[83]

In comparison to transition metals or lanthanides, only few examples of NHC–actinide metal complexes have been reported so far.[84] Computational analysis of low-valent uranium complexes coordinated to N-heterocyclic carbene ligands revealed that the stabilization of the electron-rich uranium center was achieved due to the π-accepting character of NHCs.[85]

Recently, a new aspect in the bonding interaction of NHC with metal center was revealed by the study of the interaction of the bulky and very basic ItBu with $[M(COE)_2Cl]_2$ (M = Rh or Ir), leading to bis-cyclometalated compounds **XI**.[86] Chloride abstraction in these dicyclometalated complexes led to the isolation and characterization of the corresponding 14-electron complexes **XII** (Scheme 14). Remarkably, no agostic interactions, nor formation of metal–ligand adducts with σ-donor ligands such as THF or acetone, were observed in these cationic complexes.



Scheme 14. Synthesis of 'bare' 14-electron complexes

Molecular orbital analysis of these 'bare' complexes indicated that the ability of NHC ligands to act as π electron-donors is essential in understanding the unusual stability of these complexes. These represent additional examples of stabilizing effects afforded by NHC coordination. This bonding ability had not been considered before and it might have

[82] Nemcsok, D.; Wichmann, K.; Frenking, G. *Organometallics* **2004**, *23*, 3640–3646.
[83] Lein, M.; Szabó, A.; Kovács, A.; Frenking, G. *Faraday Discuss.* **2003**, *124*, 365–378.
[84] Oldham, W. J.; Oldham, S. M.; Scott, B. L.; Abney, K. D.; Smith, W. H.; Costa, D. A. *Chem. Commun.* **2001**, 1348–1349.
[85] Nakai, H.; Hu, X.; Zakharov, L. N.; Rheingold, A. L.; Meyer, K. *Inorg. Chem.* **2004**, *43*, 855–857.
[86] (a) Dorta, R.; Stevens, E. D.; Nolan, S. P. *J. Am. Chem. Soc.* **2004**, *126*, 5054–5055. (b) Scott, N. M.; Dorta, R.; Stevens, E. D.; Correa, A.; Cavallo, L.; Nolan, S. P. *J. Am. Chem. Soc.* **2005**, *127*, 3516–3526.

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important implications in catalysis. Notably, it could play an important role in explaining the higher thermal stability of NHC-based systems when compared to tertiary phosphine-based complexes.

V. NHC–Metal Complexes: Formation and Applications

A. Synthesis of NHC-containing complexes

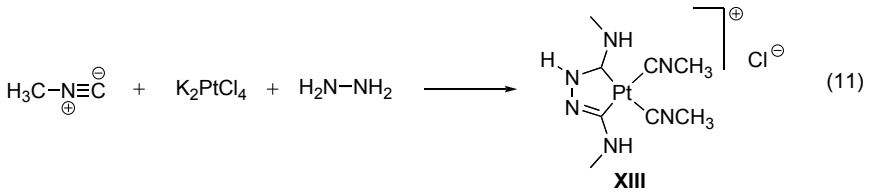
As an introductory remark of this section, we would like to emphasize the fact that for almost every metal of the periodic table, NHC-containing complexes have been reported, spanning from the alkali metals to borderline metalloid elements such as boron and silicon, without forgetting lanthanides and all transition metals. Without surprise, some metals exhibit an amazing collection of NHC complexes (notably Ni, Ru, Rh, and Pd), while for others only a handful of compounds have been synthesized to date.

1. First observations

The formation of metal complexes containing a N-heterocyclic carbene ligand has blossomed since the groundbreaking isolation of a NHC by Arduengo.[5] Nevertheless, it should be noted that a handful examples of NHC-bearing complexes were known previously.

The Chugaev's salt

Hence, in 1915, Chugaev et al. reported that hydrazine reacts with isocyanide complexes of platinum(II) to yield new hydrazine-bridged platinum complexes such as **XIII** (Eq 11).[87]



XIII

Unfortunately they did not have the required spectroscopic techniques to reveal, in fact, the first synthesis of a metal-carbene complex. An erroneous carbene-containing

[87] (a) Chugaev, L.; Skanavy-Grigorizeva, M. *J. Russ. Chem. Soc.* **1915**, *47*, 776–778. (b) Chugaev, L.; Skanavy-Grigorizeva, M.; Posniak, A. *Z. Anorg. Allg. Chem.* **1925**, *148*, 37.

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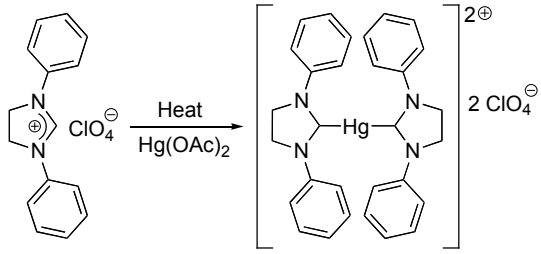
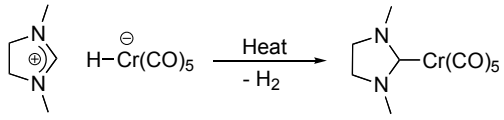
structure was first proposed in 1970,[88] and led to the definitive structure, later resolved in 1973 by NMR and X-ray single crystal diffraction.[89]

First recognized NHC-containing complexes

In the 1960's, Wanzlick was interested in isolating carbenes and believed that diaminocarbenes would be stable. He proposed the synthesis of the 1,3-diphenyl-2-imidazolidinylidene via 1,3-diphenyl-2-trichloromethylimidazolidine.[90] The carbene was not isolated and only the corresponding enetetramine was recovered. He also reported different carbene adducts using thiophosgene, thionylchloride, cyclopentanone, and benzaldehyde.[91] In 1968, Wanzlick and Öfele independently reported two different NHC–metal complexes of mercury[92] and chromium[93] respectively (Eq 12 and 13), more than twenty years before the first isolation of a NHC.



(12)



(13)

2. Common synthetic procedures

There are many ways of synthesizing NHC-containing metal complexes, and the description of every available protocol is beyond the scope of the present introduction.[94]

[88] Rouschias, G.; Shaw, B. L. *J. Chem. Soc., Chem. Commun.* **1970**, 183.
[89] Butler, W. M.; Enemark, J. H.; Parks, J.; Balch, A. L. *Inorg. Chem.* **1973**, *12*, 451–457.
[90] Wanzlick, H. W.; Fjedor, E.; Jerg, K. H. *Chem. Ber.* **1963**, *96*, 1208–1212.
[91] (a) Wanzlick, H. W.; Lachmann, B.; Schikora, E. *Chem. Ber.* **1965**, *98*, 3170–3177. (b) Wanzlick, H. W.; Schikora, E. Patent: DE 1240086, **1967**.
[92] Wanzlick, H. W.; Schönherr, H.-J. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 141–142.
[93] (a) Öfele, K. *J. Organomet. Chem.* **1968**, *12*, P42. (b) Öfele, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 739–740. (c) Öfele, K. *J. Organomet. Chem.* **1970**, *22*, C9–C11.
[94] For instance, while rarely utilized nowadays, Lappert and co-workers have thoroughly developed the synthesis of NHC–complexes from electron-rich tetraamino olefins. With this method, a wide array of complexes, possessing between one and four carbene ligands, were synthesized employing $Cr^{0/I}$, $Mo^{0/II}$, $W^{0/II}$, Mn^{I}, $Fe^{-II/0/I/II}$, $Ru^{-II/0/II}$, Os^{II}, $Co^{-I/II/III}$, $Rh^{I/III}$, $Ir^{I/III}$, $Ni^{0/I/II}$, Pd^{II}, Pt^{II}, Au^{I} and Hg^{II}. For key references, see: (a) Cetinkaya, B.; King, G. H.; Krishnamurthy, S. S.; Lappert, M. F.; Pedley, J. B. *J. Chem. Soc., Chem. Commun.* **1971**, 1370–1371. (b) Lappert, M. F. *J. Organomet. Chem.* **1975**, *100*, 139–159. (c) Cetinkaya, E.; Hitchcock, P. B.; Kuecuekbay, H.; Lappert, M. F. *J. Organomet. Chem.* **1994**, *481*, 89–95. (d) Cetinkaya, E.; Hitchcock, P.

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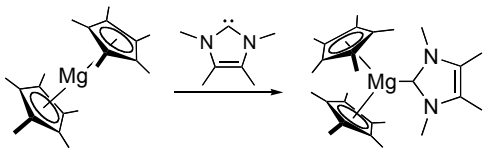
Therefore, in this section, we will describe only the most commonly employed procedures. For more information, we invite the reader to refer to excellent reviews.[95]

Coordination to an empty site

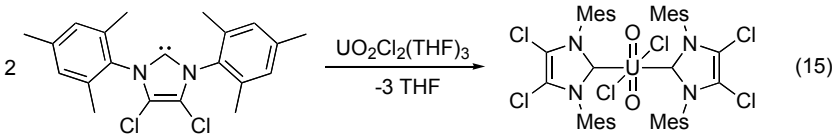
The simplest method affording NHC—metal complexes is arguably the reaction of a free NHC with an open shell metallic center able to accommodate an additional ligand in its coordination sphere, as shown in the example below (Eq 14). Typically, this type of reaction requires a non-encumbering NHC.



(14)

Ligand displacement

As one of the bases of coordination chemistry, ligand displacement is evidently one of the most employed method – if not the most – to bind a NHC to a metal. A wide variety of metal complexes from every period have been synthesized using this type of reaction, as highlighted by the synthesis, upon displacement of THF molecules, of a rare [(NHC)U^{VI}] complex (Eq 15).[96]



(15)

As discussed in parts III and IV of this introduction chapter, NHCs binds strongly to metals, which allows them to displace numerous types of ligands, whether neutral or anionic,

B.; Kuecuekbay, H.; Lappert, M. F.; Al-Juaid, S. *J. Organomet. Chem.* **1995**, *491*, C7. (e) Gok, Y.; Cetinkaya, E.; Ozdemir, I.; Cetinkaya, B.; Lappert, M. F. *Acta Chim. Slov.* **2004**, *51*, 437–446. For a review, see: (f) Lappert, M. F. *J. Organomet. Chem.* **1988**, *358*, 185–214 and references therein.

[95] (a) Liddle, S. T.; Edworthy, I. S.; Arnold, P. L. *Chem. Soc. Rev.* **2007**, *36*, 1732–1744. (b) Colacino, E.; Martinez, J.; Lamaty, F. *Coord. Chem. Rev.* **2007**, *251*, 726–764. (c) Lin, I. J. B.; Vasam, C. S. *Coord. Chem. Rev.* **2007**, *251*, 642–670. (d) Pugh, D.; Danopoulos, A. A. *Coord. Chem. Rev.* **2007**, *251*, 610–641. (e) Kühl, O. *Chem. Soc. Rev.* **2007**, *36*, 592–607. (f) Arnold, P. L.; Pearson, S. *Coord. Chem. Rev.* **2007**, *251*, 596–609. (g) Lappert, M. F. *J. Organomet. Chem.* **2005**, *690*, 5467–5473. (h) Braband, H.; Kückmann, T. I.; Abram, U. *J. Organomet. Chem.* **2005**, *690*, 5421–5429. (i) Scott, N. M.; Nolan, S. P. *Eur. J. Inorg. Chem.* **2005**, 1815–1828. (j) Crudden, C. M.; Allen, D. P. *Coord. Chem. Rev.* **2004**, *248*, 2247–2273. (k) Weskamp, T.; Böhm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *600*, 12–22. (l) Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2162–2187.

[96] (a) Liddle, S. T.; Arnold, P. L. *Organometallics* **2005**, *24*, 2597–2605. (b) Arnold, P. L.; Liddle, S. T. *Chem. Commun.* **2006**, 3959–3971.

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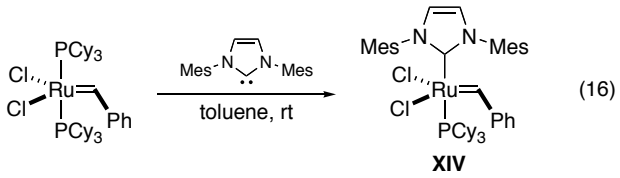
including the ubiquitous tertiary phosphines as shown in the synthesis of Grubbs II-type catalyst **XIV** (Eq 16).[97]

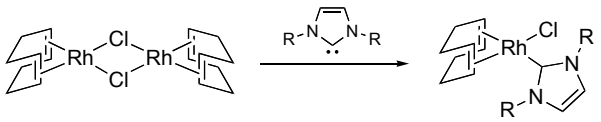


(16)

Splitting of bridged metal-dimers

This class of reactions is actually a sub-category of the aforementioned ligand displacement synthesis. Nevertheless, we address it separately since the ligand displaced is not "eliminated" and remains in the final complex.

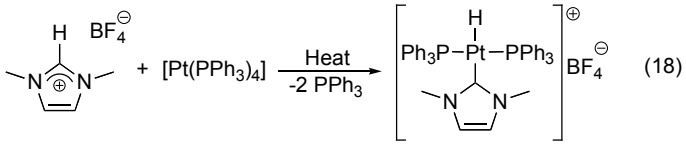
Numerous species, organic or inorganic in nature, form bridged metal dimers or polymers that can be broken upon addition of a free NHC. The most used are arguably halogen-bridged dimers, which usually afford high yields and clean reactivity profiles (Eq 17).



(17)

Oxidative addition of imidazolium salts

Zerovalent Group 10 metals, especially platinum and nickel complexes, are prompt to react with imidazolium and 2-haloimidazolium salts to form NHC-complexes by oxidative addition.[98] The activation energy barrier of the reaction is very low for bromo- and iodoimidazolium salts. It should be noted that, even if strongly limited in scope, the oxidative addition of imidazolium salts is an interesting approach to generate metal hydride NHC complexes (Eq 18).[57,99]



(18)

Recently, Peris *et al*. have extended the reaction to the Group 9 with the synthesis of

[97] Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc*. **1999**, *121*, 2674–2678.
[98] (a) McGuiness, D. S.; Cavell, K. J.; Yates, B. F.; Skelton, B. W.; White, A. H. *J. Am. Chem. Soc*. **2001**, *123*, 8317–8328. (b) McGuiness, D. S.; Cavell, K. J.; Yates, B. F. *Chem. Commun*. **2001**, 355–356. (c) Gründemann, S.; Albrecht, M.; Kovacevic, A.; Faller, J. W.; Crabtree, R. H. *J. Chem. Soc., Dalton Trans*. **2002**, 2163–2167. (d) Fürstner, A.; Seidel, G.; Kremzow, D.; Lehmann, C. W. *Organometallics* **2003**, *22*, 907–909.
[99] Duin, M. A.; Clement, N. D.; Cavell, K. J.; Elsevier, C. J. *Chem. Commun*. **2003**, 400–401.

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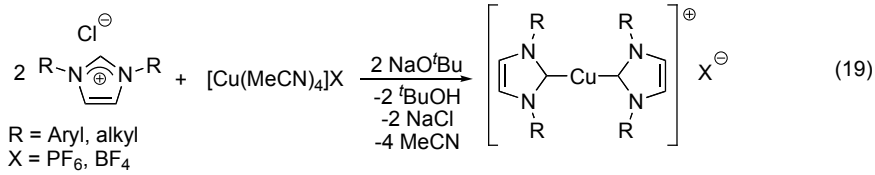
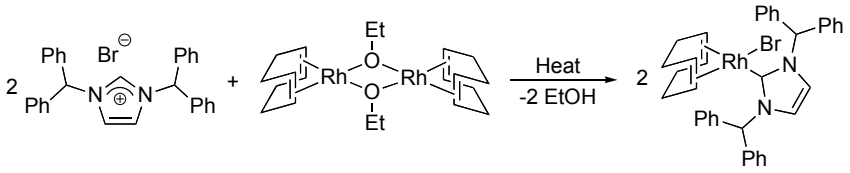
an iridium(III) hydride complex by oxidative addition of an imidazolium salt to the chloro(1,5-cyclooctadiene)iridium(I) dimer.[100]

In situ deprotonation of imidazolium salts

To conclude this section on the synthesis of NHC—metal complexes, it should be added that most procedures where a free NHC is used can be carried out with the corresponding imidazolium salt and a base, which will generate in situ the free NHC (Eq 19 and 20).[26c,101]

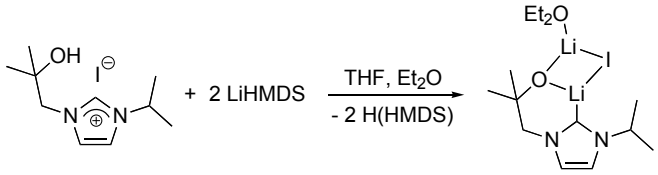


(19)



(20)

Interestingly, when deprotonation of an imidazolium salt was carried out with LiHMDS and in the absence of any other metal source, formation of the NHC—lithium adduct was observed (Eq 21).[102]



(21)

Finally, simple metal oxides, such as silver(I) and copper(I) oxides, can act as both the base and the metal source, leading to NHC—metal complexes upon release of water. In the case of silver(I), the formed complexes can be viewed as free NHC surrogates and are used for transmetalation reactions.[103]

[100] Viciano, M.; Mas-Marzá, E.; Poyatos, M.; Sanaú, M.; Crabtree, R. H.; Peris, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 444–447.
[101] Díez-González, S.; Stevens, E. D.; Scott, N. M.; Petersen, J. L.; Nolan, S. P. *Chem.–Eur. J.* **2008**, *13*, 158-168.
[102] (a) Alder, R. W.; Blake, M. E.; Borlotti, C.; Bufali, S.; Butts, C. P.; Linehan, E.; Oliva, J. M.; Orpen, A. G.; Quayle, M. J. *Chem. Commun.* **1999**, 241–242. (b) Arnold, P. L.; Rodden, M.; Davis, K. M.; Scarisbrick, A. C.; Blake, A. J.; Wilson, C. *Chem. Commun.* **2004**, 1612–1613. (c) Arnold, P. L.; Rodden, M.; Wilson, C. *Chem. Commun.* **2005**, 1743–1745.
[103] Wang, H. M. J.; Lin, I. J. B. *Organometallics* **1998**, *17*, 972–975.

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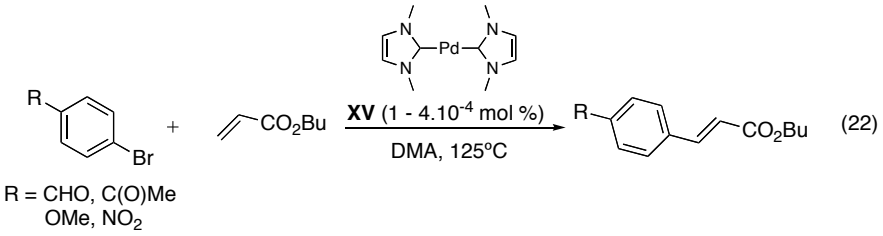
B. NHCs in homogeneous catalysis

1. First breakthroughs

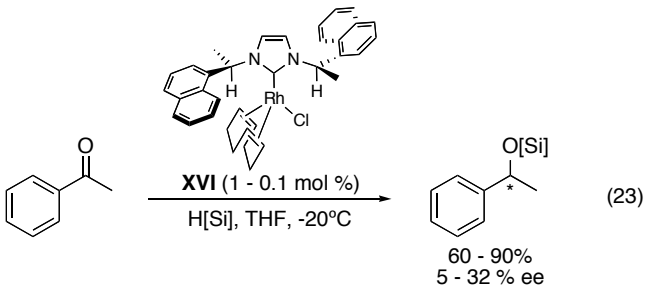
Palladium-catalyzed cross-coupling

In 1995, Herrmann and co-workers reported the first application in homogeneous catalysis of a N-heterocyclic carbene ligand.[104] In this groundbreaking study, the authors studied the activity of different NHC-containing palladium catalysts in the Heck reaction (Eq 22). The best candidate, the bis-NHC palladium(0) **XV**, was found to be active with as low as 4.10^{-4} mol % catalyst loading.



Asymmetric rhodium-catalyzed hydrosilylation

In 1996, appeared the first report where chiral inductions were obtained with an asymmetric NHC.[105] The hydrosilylation of acetophenone in the presence of diphenylsilane and rhodium catalyst **XVI**, produced the corresponding enantio-enriched silyl ether in excellent yield (Eq 23). Despite low ee's (≈ 30% ee at best), this report validated the possibility of asymmetric synthesis with NHC ligands.



It should be noted that concomitantly to this study, Enders disclosed the application of a chiral NHC–palladium complex in the Heck reaction, but extremely poor chiral induction (< 8%) was observed.[106]

[104] Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371–2374.
[105] Herrmann, W. A.; Goossen, L. J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2805–2807.
[106] Enders, D.; Gielen, H.; Raabe, G.; Runsink, J.; Teles, J. H. *Chem. Ber.* **1996**, *129*, 1483–1488.

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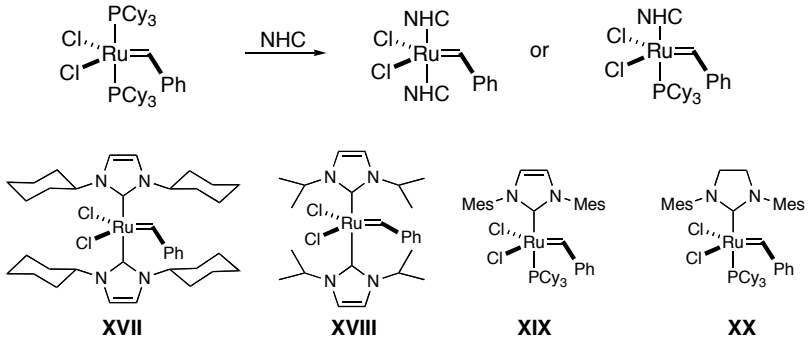
Ruthenium-catalyzed olefin metathesis

In 1998, the ruthenium-catalyzed olefin metathesis reaction was already well established when Herrmann and co-workers disclosed the synthesis of analogues of the Grubbs' catalyst (today called "Grubbs I") bearing NHCs instead of phosphines.[107]

Employing NHCs with poor steric hindrance, both tertiary phosphines on the ruthenium center are displaced by two carbenes, as shown in **XVII** and **XVIII** (Scheme 15). These bis-NHC Ru^{III} complexes were found more active in ring-opening metathesis-polymerization (ROMP) and ring-closing metathesis (RCM) than the Grubbs I catalyst.



Scheme 15. NHC-Containing ruthenium metathesis catalysts

Shortly after, our research group, concomitantly with the Grubbs' group, reported the synthesis of catalysts **XIX** and **XX** respectively.[108] The increased bulkiness of the NHC ligand, when compared to **XVII** and **XVIII**, led to mono-NHC complexes that were found even more active in ROMP and RCM than their alkyl counterparts. Of note, these mixed NHC—phosphine complexes are now widely used and known as "Grubbs II" or "Grubbs second generation" metathesis catalysts.

2. Main applications

As seen above, the first successes of NHCs as ancillary ligands in homogeneous catalysis were obtained in Pd-catalyzed cross-couplings and Ru-catalyzed olefin metathesis. These fields were intensively investigated before the appearance of NHCs and have remained highly competitive domains of research. Taking advantage of this context, NHCs have gained popularity in the organometallic community and are now well-established as efficient versatile ligands for homogeneous catalysis.

[107] Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2490–2493.
[108] Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247–2250.

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It would be vain to try to establish here, even as a summary, a list of the reactions in which NHC-containing catalytic systems proved active. Furthermore, this would go beyond the scope of the work performed during this Ph.D., where we have focused our attention on palladium, gallium, and gold; chemistries that will be properly introduced in each relevant chapter. Nevertheless, for the sake of completeness, and as a guide for the reader, we would like to indicate some reviews dealing with one aspect or another of the applications of NHCs in homogeneous catalysis.

Several general reviews have appeared in the last ten years that will give a good overview of the outstanding abilities of NHCs in catalysis.[8a,109] Additionally, two books, covering a wide range of applications, were recently published on this topic.[110]

More focused reviews, still in catalysis, can also be found on the following topics:

- ruthenium-catalyzed transformations[111]
- copper-catalyzed transformations[112]
- ruthenium-catalyzed olefin metathesis[113]
- palladium-catalyzed cross-couplings[114]
- asymmetric catalysis[115]
- supported NHC complexes[116]
- chelate- and pincer-NHCs[117]
- redox processes[118]

[109] (a) Clavier, H.; Nolan, S. P. *Annu. Rep. Prog. Chem., Sect. B* **2007**, *103*, 193–222. (b) Díez-González, S.; Nolan, S. P. *Annu. Rep. Prog. Chem., Sect. B* **2005**, *101*, 171–191. (c) Jafarpour, L.; Nolan, S. P. *Adv. Organomet. Chem.* **2001**, *46*, 181–222.
[110] (a) Glorius, F., Ed. *N-Heterocyclic Carbenes in Transition Metal Catalysis, Top. Organomet. Chem., Vol. 28*; Springer-Verlag: Berlin/Heidelberg, 2007. (b) Nolan, S.P., Ed. *N-Heterocyclic Carbenes in Synthesis*; Wiley-VCH: New York, 2006.
[111] Dragutan, V.; Dragutan, I.; Delaude, L.; Demonceau, A. *Coord. Chem. Rev.* **2007**, *251*, 765–794.
[112] Díez-González, S.; Nolan, S. P. *Synlett* **2007**, 2158–2167.
[113] (a) Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55–66. (b) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243–251. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.
[114] (a) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768–2813. (b) Herrmann, W. A.; Öfele, K.; Preysing, D. v.; Schneider, S. K. *J. Organomet. Chem.* **2003**, *687*, 229–248. (c) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69–82. (d) Hillier, A. C.; Nolan, S. P. *Platinum Metals Rev.* **2002**, *46*, 50–64.
[115] (a) Douthwaite, R. E. *Coord. Chem. Rev.* **2007**, *251*, 702–717. (b) Gade, L. H.; Bellemin-Laponnaz, S. *Coord. Chem. Rev.* **2007**, *251*, 718–725. (c) César, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619–636. (d) Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, *14*, 951–961.
[116] Sommer, W. J.; Weck, M. *Coord. Chem. Rev.* **2007**, *251*, 860–873.
[117] (a) Mata, J. A.; Poyatos, M.; Peris, E. *Coord. Chem. Rev.* **2007**, *251*, 841–859. (b) Peris, E.; Crabtree, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2239–2246.
[118] Cavell, K. J.; McGuinness, D. S. *Coord. Chem. Rev.* **2004**, *248*, 671–681.

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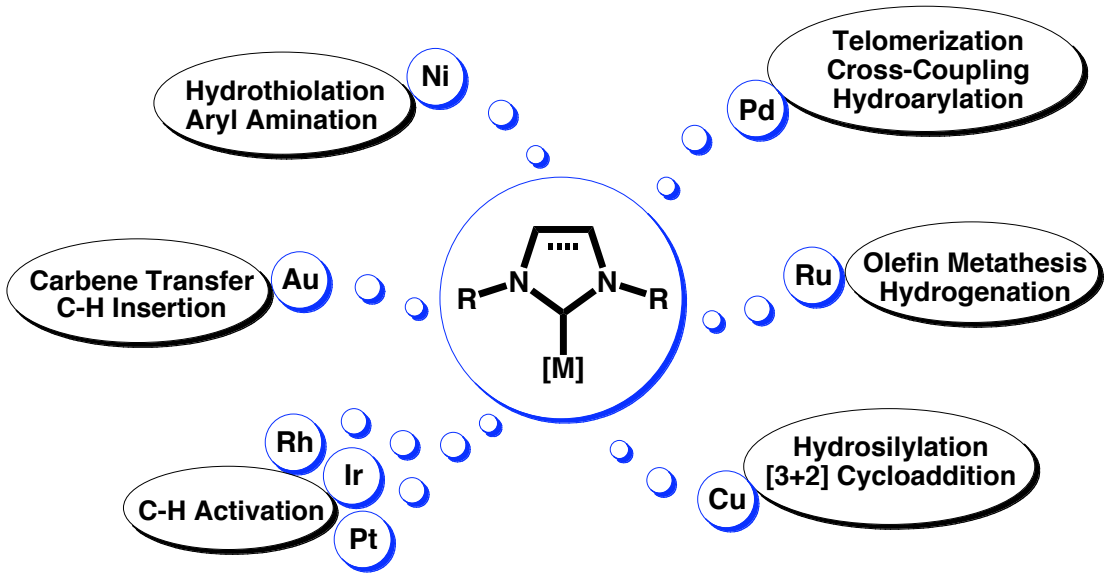
VI. Objectives of this work

A. Scientific line of the laboratory

N-Heterocyclic carbenes (NHC) have gained great popularity in organometallic chemistry and homogeneous catalysis since their first isolation in 1991. In the laboratory, the coordination chemistry of NHCs with transition metals has been explored, thereby generating novel catalyst compositions. A major goal has been the development of straightforward synthetic routes, leading, in few chemical steps and after rapid purification, to the desired well-defined pre-catalyst. Efforts are focused as well into the formation of benchtop-stable easy to handle pre-catalysts that will be activated in solution to release the true catalytically active species.

The application in homogeneous catalysis of the NHC-containing complexes synthesized in the laboratory is the natural development of our studies. It has led so far to numerous catalytic systems for ruthenium-based olefin metathesis, palladium cross-coupling reactions, and copper-based hydrosilylation, to name a few (Scheme 16).



Scheme 16. Applications in homogeneous catalysis developed in the laboratory

B. Objectives: NHCs as supporting ligands in homogeneous catalysis

1. Pd

Relying on previous catalytic systems developed in the laboratory for palladium-catalyzed cross-coupling reactions, two main goals were assigned for this Ph.D. work:

1) To develop a catalytic system that would be *extremely efficient* in cross-coupling.

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By “extremely efficient”, it was meant active at room temperature and/or at very low catalyst loadings with aryl chlorides.

2) To develop an *easily-synthesized*, stable pre-catalyst for cross-coupling reactions. By “easily-synthesized”, it was meant from commercially available starting materials and via an “all-benchtop” synthetic procedure.

2. Ga

The organometallic chemistry of NHC–gallium(III) is clearly underdeveloped. On the other hand, catalytic applications employing $GaCl_3$ or $[Ga(OTf)_3]$ have increased as of late. The main goal here was the design of novel NHC-containing gallium(III) species that would find catalytic applications. In a preliminary approach, and considering the lack of precedents in this field, the synthesis of gallium complexes was of greater importance than the catalytic applications.

3. Au

Some novel [(NHC)AuCl] complexes had been synthesized in the laboratory at the beginning of this work. At this time, homogeneous gold catalysis was just emerging and it was decided to engage in the development of novel catalytic transformations using the aforementioned complexes. For this purpose, alkyne- and alkene-based substrates were selected as potential precursors.

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CHAPTER I

Pd

Well-Defined [(NHC)Pd^{II}] Pre-Catalysts in Cross-Coupling Reactions

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I. Introduction

As presented in the *Objectives* section, the development of new NHC-containing palladium pre-catalysts and their use in cross-coupling reactions was a major thrust of this work. Relying on previous work from our laboratories, we chose to focus our studies on well-defined palladium(II) pre-catalysts containing one monodentate NHC. Therefore, in this introduction section, we present the main achievements to date with this type of compounds.

A. Generalities about palladium-catalyzed cross-couplings

1. Context

The impact of the palladium-catalyzed cross-coupling reactions, discovered in the 1970's, has been considerable and continues to be the focus of much organic and organometallic research.[119] It is almost impossible nowadays to find an issue of a journal in the field of organic or organometallic chemistry without a contribution dealing with some aspect of cross-coupling reactions.[120] Due to their wide applicability for C–C and C–X bond formation, these reactions belong to the arsenal of synthetic chemists and have clearly changed retro-synthetic analysis.[121] As a consequence of its versatility, the chemical industry has been significantly involved in this area and numerous methods have been patented.[122]

Even though ligandless systems are known,[123] strong σ-donor ligands are necessary to reach a high degree of efficiency.[124] Since the early studies, tertiary phosphines have attracted considerable attention and have allowed for the development of catalytic systems possessing a wide scope; the structures of highly active "state-of-the-art" tertiary phosphine ligands in cross-coupling are depicted in Figure 8.[125]

---

[119] For interesting accounts with an historical perspective, see: (a) Negishi, E.-i. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233–257. (b) Tamao, K.; Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 1–9.

[120] For an indispensable book on cross-coupling, see: *Metal-Catalyzed Cross-Coupling Reactions,* 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

[121] Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489.

[122] Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710.

[123] Tsuji, J. *Palladium Reagents and Catalysis, Innovation in Organic Synthesis*; John Wiley & Sons: Chichester, England, 1995; Chapter 4.1.

[124] For a review on late-generation ligand design, see: Miura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2201–2203.

[125] For representative reports, see: (a) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem.–Eur. J.* **2004**, *10*, 2983–2990. (b) Hill, L. L.; Moore, L. R.; Huang, R.; Cracium, R.; Vincent, A. J.; Dixon, D. A.; Chou, J.; Woltermann, C. J.; Shaughnessy, K. H. *J. Org. Chem.* **2006**, *71*, 5117–5125. (c) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452–459. (d) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10028–10029. (e) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723. (f) Guari, Y.; van Strijdonck, G. P. F.; Boele, M. D. K.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem.–Eur. J.* **2001**, *7*, 475–482. (g) Guari, Y.; van Es, D.

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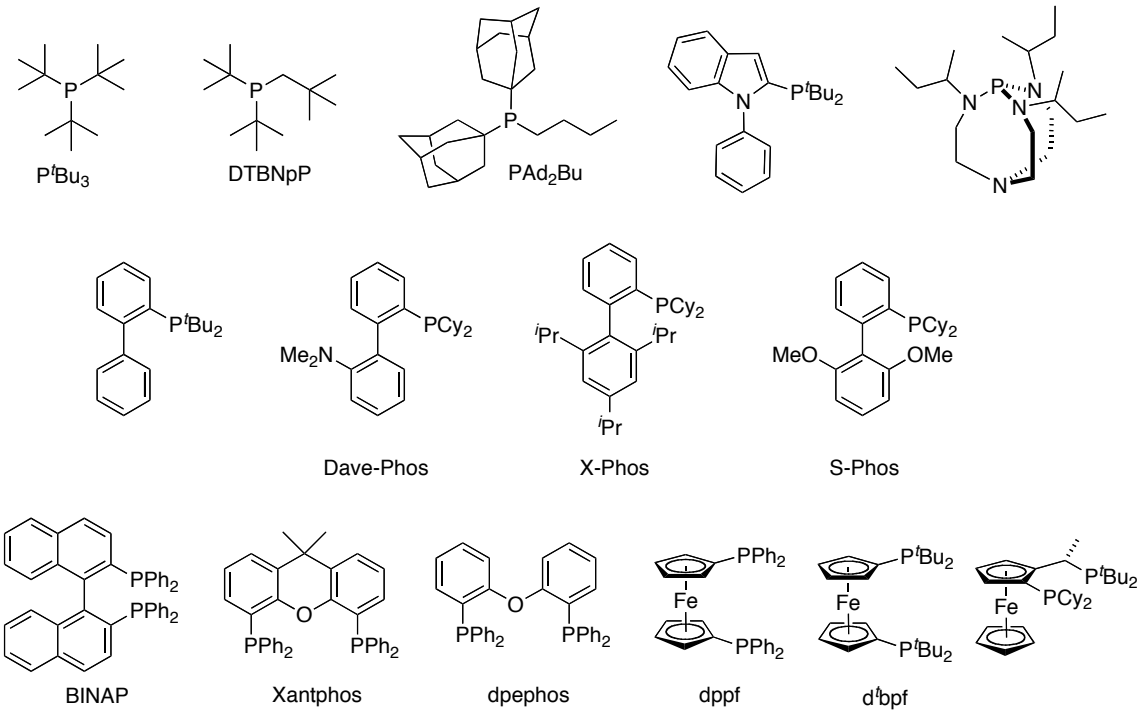
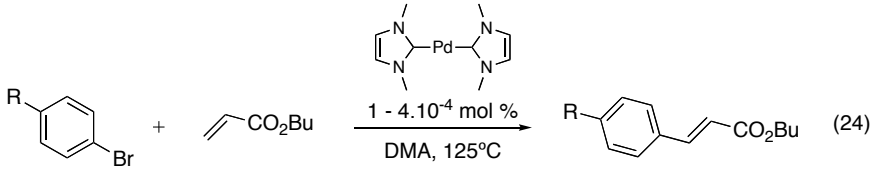


Figure 8. "State-of-the-art" phosphine ligands for cross-coupling reactions

Recently, bulky electron-rich alkylphosphines have enabled the use of extremely low levels of palladium, providing high turnover numbers (TON).[126] To date, N-heterocyclic carbenes are the only class of ligands that has been able to challenge the widely employed tertiary phosphines. Since Herrmann reported that well-defined NHC-containing palladium(0) and palladium(II) complexes efficiently catalyzed the Heck reaction (Eq 24),[104] NHCs have been advertised as potential alternatives to phosphines.



2. General catalytic cycle for cross-coupling reactions

A textbook mechanism of palladium-catalyzed cross-coupling reactions is depicted in Scheme 17. We present here only the basic steps (and their main characteristics) of the catalytic cycle of a cross-coupling reaction. Since the present work focused on catalytic acti-

S.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron Lett.* **1999**, *40*, 3789–3790. (h) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.

[126] For a review focused on TON, see: Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553–1582.

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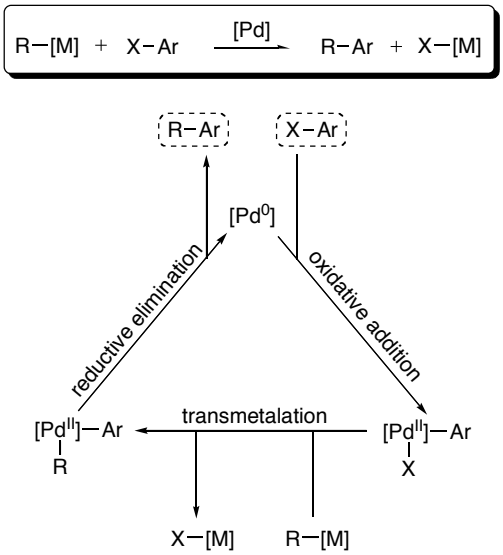
vity and not on mechanistic studies, we will only discuss briefly the general requirement of each basic step; for more in depth discussion, we refer the reader to the literature.[120,127]



Scheme 17. Schematic representations of a cross-coupling reaction and its catalytic cycle

The oxidative addition step

The first step of the catalytic cycle of a cross-coupling reaction is widely accepted to be the oxidative addition of a halide or pseudo-halide onto the palladium(0) center, generating an *oxidized* organo-palladium(II) species. The palladium formally losing two electrons in this step, it is facilitated when the palladium center is rich in electrons, which is usually achieved with the help of electron-donating ligands such as tertiary alkylphosphines or N-heterocyclic carbenes.

The transmetalation step

In the case of palladium-catalyzed cross-couplings, a wide array of organometallic reagents can be employed and efficiently transmetalate their organic moiety to the Pd center. Hence, lithium, boron, magnesium, aluminum, silicon, zinc, zirconium, and tin organoderivatives, to name the most famous, can be employed for C–C bond formation.

For the formation of C–X (X = N, O, S, P, B) bond, a Group 1 or Group 2 base is used in conjunction with a H–X-containing nucleophile (i.e. amine, alcohol, etc...). Even though mechanistically different, this step is also called by extension a transmetalation.

[127] Tsuji, J. *Palladium Reagents and Catalysis, Innovation in Organic Synthesis*; John Wiley & Sons: Chichester, England, 1995.

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The reductive elimination step

This step is the reverse of the aforementioned oxidative addition. Two fragments placed on the palladium(II) center form a bond, releasing a *reduced* palladium(0) species that can continue the catalytic cycle. Unlike the oxidative addition, here the palladium center needs to be electron-deficient for the reductive elimination to be favored. Additionally, it should be noted that the steric hindrance brought about by the ligands on palladium can promote rapid elimination by relief of steric pressure.

Overall catalytic cycle

The complete cycle is driven by the thermodynamically-favored formation of the C–C or C–X bond. The nature of the ancillary ligands on palladium is key for highly active catalytic systems. Strongly donating ligands promote the oxidative addition step while bulky ones facilitate the reductive elimination.

It should be added that, when compared to the oxidative and the reductive elimination, much less is known about the transmetalation step and that numerous factors have to be considered for a thorough understanding of this multi-molecular process, such as the nature of the base – sometimes of additives –, the number of ligands present on the palladium center at each stage, the nature of the solvent, etc... Additionally, the palladium precursor is often a Pd^{II} species, requiring a reductive activation step, which can complicate mechanistic studies.[128]

The present *Introduction* will now focus on the synthesis of well-defined monodentate-NHC palladium(II) complexes, which are the type of complexes studied during this Ph.D., and their use in cross-coupling reactions.

B. Palladium dimers with bridging halogens

Dinuclear palladium(II) complexes containing one NHC per metal center and two bridging halogen ligands are amongst the most popular [(NHC)Pd^{II}] compounds. This is notably due to their straightforward synthesis, most often from readily available [$Pd(OAc)_2$]

[128] For complementary reviews on mechanistic aspects of cross-coupling reactions, see: (a) Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936–1947. (b) Knowles, J. P.; Whiting, A. *Org. Biomol. Chem.* **2007**, *5*, 31–44. (c) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609–679. (d) de Vries, J. G. *Dalton Trans.* **2006**, 421–429. (e) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704–4734.

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and the imidazolium precursor of the NHC. Several protocols have been reported, involving the addition of inorganic salts (LiCl, NaBr, NaI, NaOAc) and requiring prolonged heating in polar solvents.[129] The structures of some of these complexes are depicted in Figure 9. Interestingly, the addition of a base is not necessary,[130] and alternative synthetic routes from [MePd(COD)Cl],[131] [(NHC)Pd(allyl)Cl],[132] or $[Pd(PhCN)_2Cl_2]$[133] have been described. It should be noted that heating a mixture of $[Pd(OAc)_2]$ and imidazolium salt can produce a highly unexpected type of complex $[(NHC)(NHC')PdCl_2]$, where NHC' is bound by the backbone (C4 or C5) to the palladium center.[13] Therefore, using a $[Pd(OAc)_2]$/imidazolium salt mixture in catalysis can result in a number of catalytic species and varied activities.

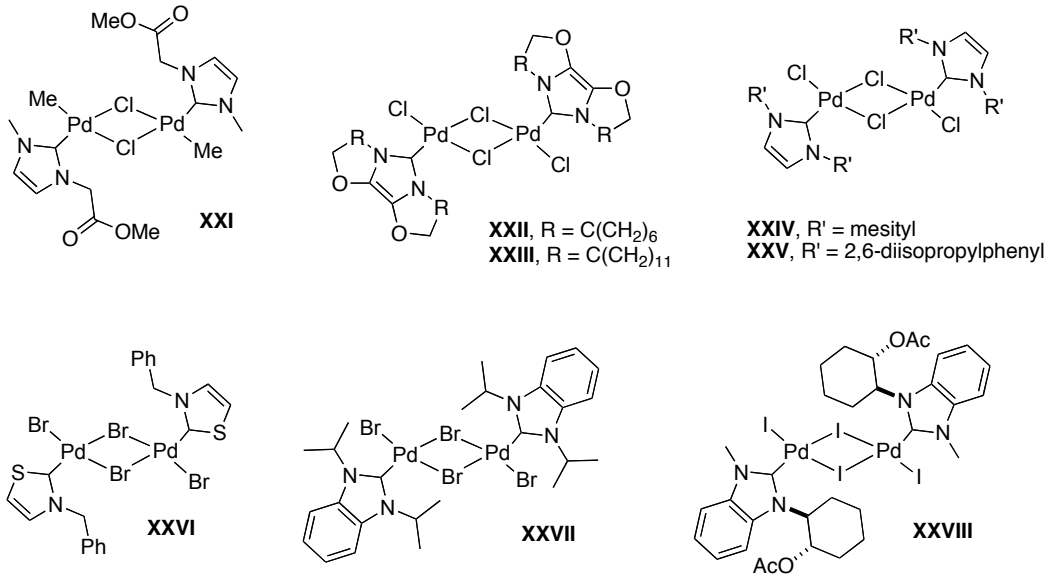

Figure 9. Structures of NHC-Pd dimers

In terms of catalysis, the activity of these complexes has been scarcely examined, i.e. only in the Heck, the Suzuki-Miyaura and the Buchwald-Hartwig reactions. Compound **XXI** was found to catalyze the coupling of 4-bromoacetophenone and butyl acrylate at low

[129] (a) Xu, L.; Chen, W.; Xiao, J. *Organometallics* **2000**, *19*, 1123–1127. (b) Xu, L.; Chen, W.; Bickley, J. F.; Steiner, A.; Xiao, J. *J. Organomet. Chem.* **2000**, *598*, 409–416. (c) Altenhoff, G.; Goddard, G.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195–15201. (d) Shi, M.; Qian, H.-X. *Appl. Organomet. Chem.* **2005**, *19*, 1083–1089. (e) Huynh, H. V.; Han, Y.; Ho, J. H. H.; Tan, G. K. *Organometallics* **2006**, *25*, 3267–3274.

[130] (a) Ma, Y.; Song, C.; Jiang, W.; Xue, G.; Cannon, J. F.; Wang, X.; Andrus, M. B. *Org. Lett.* **2003**, *5*, 4635–4638. (b) Yen, S. W.; Koh, L. L.; Hahn, F. E.; Huynh, H. V.; Hor, T. S. A. *Organometallics* **2006**, *25*, 5105–5112.

[131] Green, M. J.; Cavell, K. J.; Skelton, B. W.; White, A. H. *J. Organomet. Chem.* **1998**, *554*, 175–179.

[132] Jensen, D. R.; Sigman, M. S. *Org. Lett.* **2003**, *5*, 63–65.

[133] Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 2229–2231.

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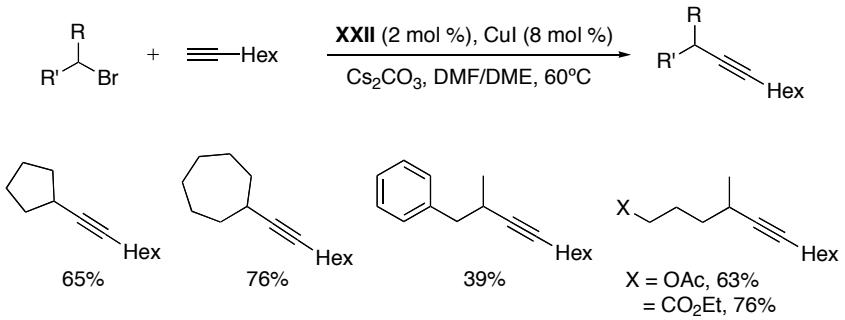
catalyst loadings but was only studied for limited examples.[134] On the other hand, **XXVI** showed only poor activity in the Heck reaction, probably because of the lack of steric pressure from the thiazolydene ligand.[130b]

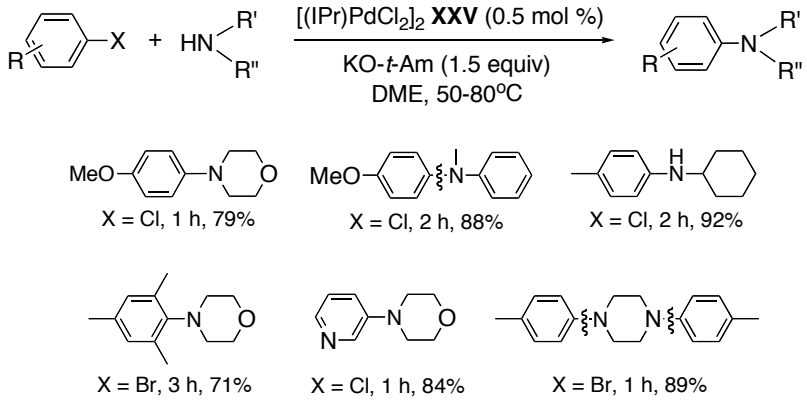
In 2004, Glorius reported the outstanding activity of **XXII** and **XXIII** in the Suzuki-Miyaura reaction.[129c] These complexes, possessing a NHC of the IBiox family, allowed for the formation of a tetra-*ortho*-substituted biphenyl compound in high yield. Tested as well in the Suzuki-Miyaura coupling, complex **XXVII** was found efficient for the coupling of aryl bromides and chlorides in water[129e] while **XXVIII** coupled only bromides but with a larger scope, including unactivated and sterically hindered substrates.[129d]

The activity of **XXII** was further investigated by the Glorius group in the Sonogashira reaction with unactivated secondary alkyl bromides.[135] Under relatively mild reaction conditions, functionalized alkyl bromides could be coupled with alkyl-substituted terminal alkynes; a representative scope is shown in Scheme 18.



Scheme 18. Activity of **XXII** in the Sonogashira reaction

In 2002, the activity of **XXV** in the *N*-aryl amination reaction was studied in our research group (Scheme 19).[133]



Scheme 19. Activity of **XXV** in the Buchwald-Hartwig reaction

[134] McGuinness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 741–748.
[135] Altenhoff, G.; Würtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925–2928.

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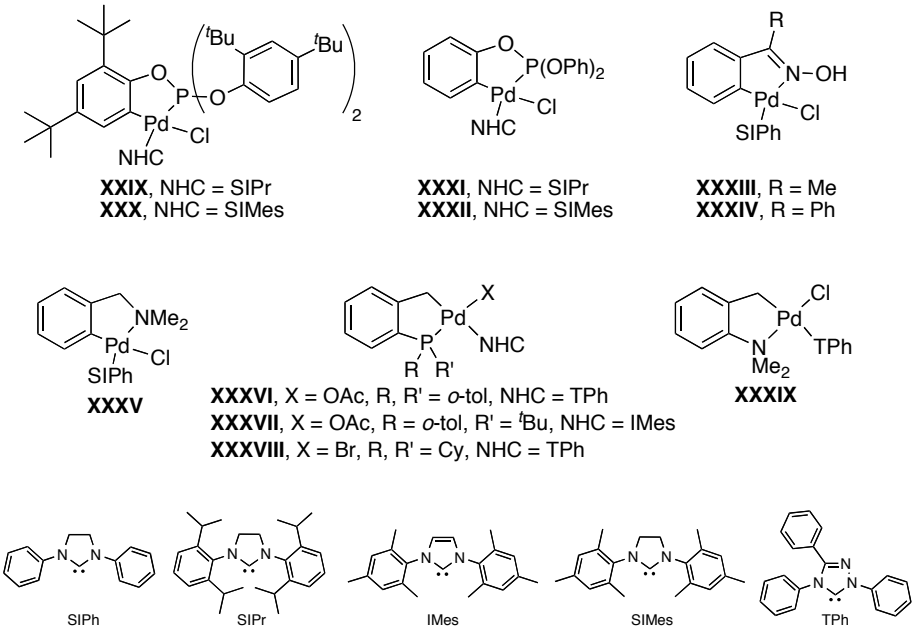
This complex was found highly efficient for the coupling of aryl bromides and chlorides. A variety of amines could be coupled with activated, unactivated, encumbered and heteroaromatic halides in high yields and in short reaction times. Interestingly, thanks to the robustness of **XXV**, reactions could be carried out on the benchtop under aerobic conditions without appreciable loss of activity.

C. Palladacycles

Palladacycles have recently gained importance in catalysis notably because of their flexible framework and robustness.[136] Although promising, the conjugation of a palladacyclic scaffold and a NHC has been scarcely studied. In fact, only a handful of NHC-palladacycles have been synthesized (see Figure 10).



XXIX, NHC = SIPr
XXX, NHC = SIMes

XXXI, NHC = SIPr
XXXII, NHC = SIMes

XXXIII, R = Me
XXXIV, R = Ph

XXXV

XXXVI, X = OAc, R, R' = *o*-tol, NHC = TPh
XXXVII, X = OAc, R = *o*-tol, R' = ^{t}Bu, NHC = IMes
XXXVIII, X = Br, R, R' = Cy, NHC = TPh

XXXIX

Figure 10. Structures of NHC-containing palladacycles

Typically, NHC-containing palladacycles are synthesized in high yields by addition of a nucleophilic carbene to an acetate- or halogen-bridged palladacycle dimer. Bedford and co-workers reported the formation of phosphite palladacycles **XXIX**-**XXXII** and studied their activity in the Suzuki-Miyaura reaction.[137] Overall, these catalysts performed quite poorly (**XXX** being the most efficient) and could only couple unhindered and activated aryl

[136] For a review, see: Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev*. **2005**, *105*, 2527–2571.
[137] Bedford, R. B.; Betham, M.; Coles, S. J.; Frost, R. M.; Hursthouse, M. B. *Tetrahedron* **2005**, *61*, 9663–9669.

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bromides.[33] In 2003, Iyer described the synthesis and applications of palladacyles **XXXIII**-**XXXV**.[138] These pre-catalysts were tested in the Heck reaction where they displayed good to high activity. Using aryl bromides, TONs between 40000 and 90000 were observed, whereas the use of chlorides was less successful. The activity of compound **XXXIV** was further studied in the Suzuki-Miyaura reaction where, as observed in the Heck, aryl bromides were easily coupled and aryl chlorides were found more reluctant partners. A large series of NHC-containing phosphapalladacycles, including **XXXVI**-**XXXIX**, was reported by Herrmann.[139] Their catalytic activity in the Heck reaction was investigated, showing promising results for further improvement. Notably, the use of **XXXIX** allowed for the coupling of aryl chlorides without the need for additives.

In 2003, the synthesis of amino-palladacycles **XL** and **XLI** (Figure 11) was reported by our group.[140]

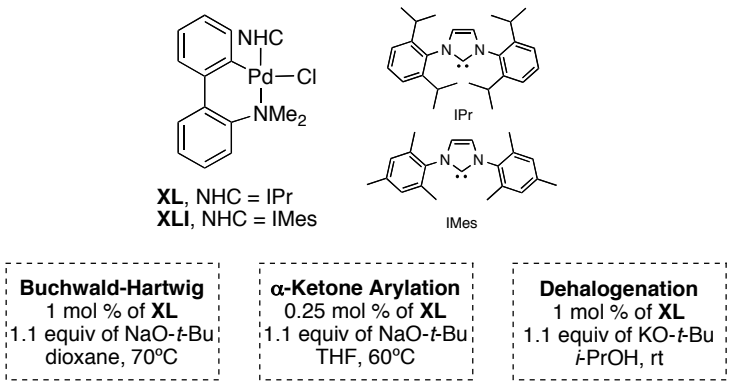

Figure 11. Structures and activity of **XL** and **XLI**

Since then, the activity of the most efficient one, the IPr-containing **XL**, has been investigated in the Buchwald-Hartwig, the α-ketone arylation, the reductive dehalogenation and the Suzuki-Miyaura reactions. Reactions could be performed at low catalyst loadings (1 – 0.05 mol %) and under mild conditions (rt to 65ºC). Pre-catalyst **XL** proved to be versatile and displayed a wide scope in numerous cross-coupling reactions. Aryl chlorides, bromides and triflates, including heteroaromatics, reacted efficiently with a wide array of nucleophilic partners. In the Buchwald-Hartwig amination, primary and secondary alkyl and aryl amines were coupled in high yields.[140] Similarly, in the α-ketone arylation, aryl and alkyl ketones

[138] Iyer, S.; Jayanthi, A. *Synlett* **2003**, 1125–1128.
[139] Frey, G. D.; Schütz, J.; Herdtweck, E.; Herrmann, W. A. *Organometallics* **2005**, *24*, 4416–4426.
[140] Viciu, M. S.; Kelly, R. A., III; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett.* **2003**, *5*, 1479–1482.

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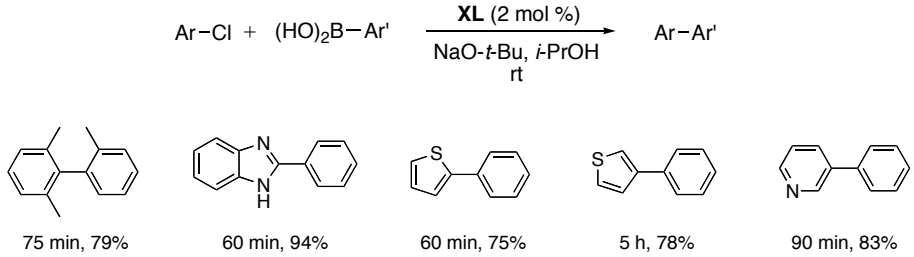
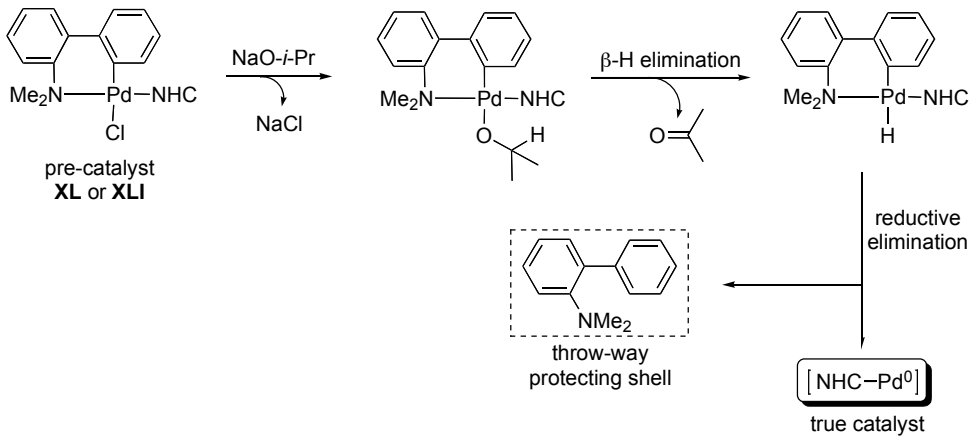
reacted well.[141] Additionally, reactions could be carried out under microwave heating without loss of yield, allowing for extremely short reaction times (i.e. 2 min). Compound **XL** was further found to catalyze the dehalogenation of aryl chlorides, a relevant process for environmental issues keeping in mind the high toxicity of polychlorinated compounds.[142] Again, as a testimony to the high activity of **XL**, reactions occurred at room temperature in isopropanol, serving both as solvent and hydride donor.[141]

Adding to the high activity and versatility of **XL** described above, its most impressive performance was observed in the Suzuki-Miyaura reaction. Biphenyls were produced smoothly at room temperature and in short reaction times in technical grade isopropanol; a representative scope is given in Scheme 20.[143]



Scheme 20. Activity of palladacycle **XL** in the Suzuki-Miyaura reaction

Regarding its mechanism of activation ($Pd^{II} \rightarrow Pd^{0}$), it was proposed, based on NMR studies, that in the presence of isopropanol, a Pd-hydride could be formed, enabling the reductive elimination of the aminobiphenyl shell and producing the active [(IPr)Pd^{0}] species (Scheme 21).



Scheme 21. Activation pathway of NHC-palladacycles **XL** and **XLI**

[141] Navarro, O.; Marion, N.; Oonishi, Y.; Kelly, R. A., III; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 685–692.
[142] Hutzinger, O.; Safe, S.; Zitko, V. *The Chemistry of PCBs*; CRC Press: Cleveland, OH, 1974.
[143] Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194–16195.

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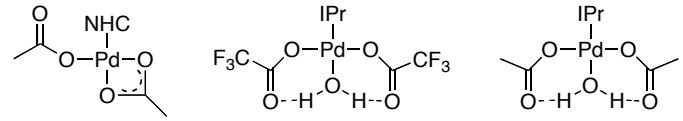
Additionally, it was postulated that isopropoxide, formed *in situ* from isopropanol, would form, upon addition onto boronic acid, a tetravalent boronate species, facilitating the transmetalation step in the catalytic cycle. This method notably allowed for the straightforward synthesis of tri-*ortho*-subsituted and heteroaromatic biaryls from aryl chlorides or triflates.[141,143] It should be noted that, despite its high activity, tetra-*ortho*-substituted biaryls could not be produced with this catalytic system.[144]

D. Palladium acetate and acetylacetonate complexes

1. Palladium acetate derivatives

Among the multiple sources of simple palladium(II) salts available for carrying cross-coupling reactions in conjunction with external ligands, $[Pd(OAc)_2]$ is one of the most employed. It is therefore surprising that only a handful of well-defined NHC-containing palladium acetate complexes have been reported and studied in catalysis.



XLII, NHC = IPr
XLIII, NHC = IMes

XLIV

XLV

Figure 12. Carboxylate-containing NHC-palladium complexes

Simple addition of IPr ligand to a toluene solution of $[Pd(OAc)_2]$ produced compounds **XLII** and **XLIII**, where the two acetate molecules are bound differently (Figure 12). Interestingly, as a function of the synthetic route, closely related complexes **XLIV** and **XLV**, where a molecule of water occupies a coordination site, can be obtained, the latter being extremely active in palladium-catalyzed aerobic oxidation of alcohols.[145] These pre-catalysts, primarily tested in the hydroarylation of alkynes,[146] were later found to be efficient in the Suzuki-Miyaura[147] and the α-ketone arylation reactions.[148]

An interesting application of the activity of **XLII** in α-ketone arylation using *p*-haloarylketones **XLVI** to produce poly-α-arylketones **XLVII** was reported by Matsubara; it

[144] Tetra-*ortho*-substituted biaryls are still one of the greatest challenges of the Suzuki-Miyaura reaction, for rare catalytic systems enabling their formation, see: Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871–1876 and ref. 129c.
[145] Mueller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9724–9734.
[146] Viciu, M. S.; Stevens, E. D.; Petersen, J. L.; Nolan, S. P. *Organometallics* **2004**, *23*, 3752–3755.
[147] Singh, R.; Viciu, M. S.; Kramareva, N.; Navarro, O.; Nolan, S. P. *Org. Lett.* **2005**, *7*, 1829–1832.
[148] Singh, R.; Nolan, S. P. *J. Organomet. Chem.* **2005**, *690*, 5832–5840.

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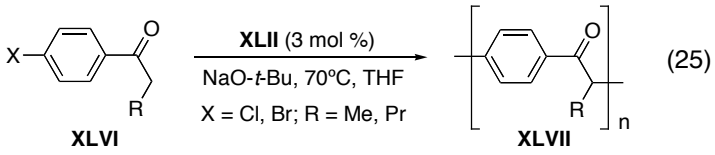
is depicted in Eq 25.[149]



(25)

Importantly, the authors observed that while **XLII** was extremely efficient, a combination of $[Pd(OAc)_2]$ and IPr·HCl afforded only poor yields. This is not surprising since a mixture of $[Pd(OAc)_2]$ and NHC·HCl generally furnishes chloride bridged palladium dimers (see section **B** of this chapter) and not an acetate-containing palladium species. These last observations highlight the advantage of using well-defined complexes in lieu of mixtures of palladium salts and ligands.

2. Palladium acetylacetonate derivatives

Similarly to $[Pd(OAc)_2]$, $[Pd(acac)_2]$ (acac = acetylacetonate) has only scarcely been used to form NHC-containing Pd^{II} complexes. Cavell and co-workers reported the first synthesis of [(NHC)Pd(acac)L] (where L = Me) complexes.[150] They were shown to efficiently catalyze the Heck reaction of activated aryl bromides, reaching high TONs (≈100 000).

E. Pyridine-Containing Palladium Complexes

Surprisingly, while chelating bidentate pyridine-NHC ligands are well-known, pyridine adducts of monodentate NHC-containing palladium(II) compounds are scarce and have only recently been recognized as efficient pre-catalysts for coupling reactions. Hence, Organ and co-workers, capitalizing on the development of third generation Grubbs catalyst,[151] recently reported the synthesis of complexes of general formulae $[(NHC)PdCl_2(pyr)]$. Prolonged heating of IPr·HCl with palladium(II) dichloride in the presence of excess base in neat 3-chloropyridine led to compound **XLVIII** in high yield (Eq 26).[152] These pyridine adducts, and especially the IPr-containing **XLVIII**, showed good activity in the Suzuki-Miyaura reaction, enabling the coupling of heteroaromatics and the

[149] Matsubara, K.; Okazaki, H.; Senju, M. *J. Organomet. Chem.* **2006**, *691*, 3693–3699.
[150] McGuinness, D. S.; Green, M. J.; Cavell, K. J.; Skelton, B. W.; White, A. H. *J. Organomet. Chem.* **1998**, *565*, 165–178.
[151] Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4035–4037.
[152] (a) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem.–Eur. J.* **2006**, *12*, 4743–4748. For a recent report of Suzuki-Miyaura alkyl–alkyl coupling

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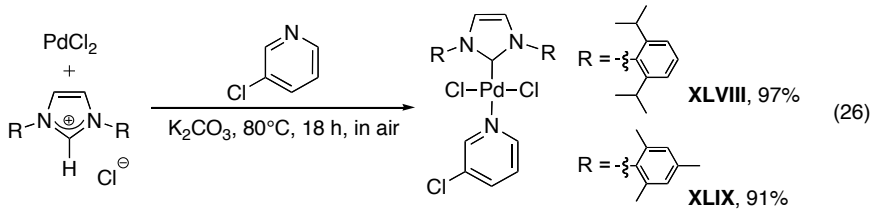
formation of tri-*ortho*-substituted biaryls under mild conditions.



(26)

The same group further investigated the catalytic activity of **XLVIII** in the Negishi coupling. Remarkably, this pre-catalyst allowed for sp^3-sp^3, sp^2-sp^2, and both types of sp^2-sp^3 couplings of zinc reagents with halide derivatives.[153] As a tentative mechanism for the activation of the pyridine palladium(II) pre-catalyst, the authors proposed a double transmetalation between **XLVIII** and the organometallic nucleophile leading, upon reductive elimination, to homocoupling of the boron or zinc reagent and to a [(NHC)Pd^0] species, the remaining pyridine acting as a throw-away ligand. Pursuing their examination, they reported the use of **XLVIII** in the Kumada-Tamao-Corriu and the Buchwald-Hartwig reaction.[154] The scope of the catalytic system proved to be wide and tolerant to heteroaromatics including thiophenes, pyridines, pyrazoles and benzothiazoles.

Very recently, Lee disclosed the synthesis of compounds **L**-**LII** (Figure 13) and studied their behavior in the Suzuki-Miyaura reaction.[155] In the coupling of aryl bromides and phenyl boronic acid, **L** was found more efficient than **LI**. Furthermore, relying on their comparative studies, the authors nicely demonstrated that monodentate NHCs are better performing than chelating bidentates for cross-coupling reactions, supporting the concept of a bare monoligated palladium(0) as the true active species.[156] Pyridine-free palladium complex **LIII** (Figure 13), reported as early as 2001 by Batey and co-workers, is clearly related to compounds **XLVIII**-**LII**. Interestingly, its synthesis from $Pd(OAc)_2$ is unique and involves release of *N*-methylimidazole from a second equivalent of the NHC precursor.[157]

---

with this system, see: (b) Valente, C.; Baglione, S.; Candito, D.; O'Brien, C. J.; Organ, M. G. *Chem. Commun.* **2008**, 735-737.

[153] Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. A *Chem.–Eur. J.* **2006**, *12*, 4749–4755.

[154] Kumada-Tamao-Corriu: (a) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O'Brien, C. J.; Valente, C. *Chem.–Eur. J.* **2007**, *13*, 150–157. Buchwald-Hartwig: (b) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Sayah, M.; Valente, C. *Chem.–Eur. J.* **2008**, *14*, 2443–2452. For a sequential aryl amination/Heck reaction with the same catalytic system, see: (c) Shore, G.; Morin, S.; Mallik, D.; Organ, M. G. *Chem.–Eur. J.* **2008**, *14*, 1351–1356.

[155] (a) Liao, C.-Y.; Chan, K.-T.; Zeng, J.-Y.; Hu, C.-H.; Tu, C.-Y.; Lee, H. M. *Organometallics* **2007**, *26*, 1692–1702. For recent developments with this type of pre-catalysts, see: (b) Ray, L.; Shaikh, M. M.; Ghosh, P. *Dalton Trans.* **2007**, 4546–4555.

[156] For a review, see: Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366–374.

[157] Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411–1414.

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The good activity of **LIII** in the Sonogashira reaction allowed for the coupling of aryl iodides and terminal alkynes at room temperature. Aryl bromides were found reluctant and required elevated temperature while aryl chlorides could not be coupled.

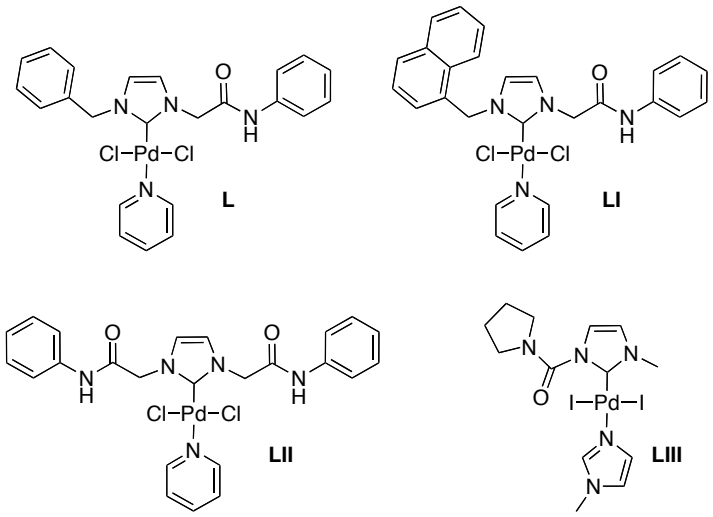

Figure 13. Structures of compounds **L**-**LIII**

F. Concluding remarks and perspectives

Since 1998, an important development effort in our laboratory has been devoted to palladium-mediated cross-coupling chemistry. Our studies were initiated using *in situ* formed catalysts,[158] and have led us to what we now favor, well-defined species. As can be seen from the above review of the literature, the use of well-defined NHC-containing palladium(II) pre-catalysts is still an underdeveloped aspect in Pd-catalyzed cross-coupling.

We have been attracted to well-defined species and NHC ligands for several reasons. Besides the inherent advantages associated with NHC ligands (i.e. stability, steric and electronic tunability),[159] this class of pre-catalysts exhibits high stability in the solid-state and in solution, allowing for indefinite storage and easy handling. Furthermore, the use of well-defined complexes permits a strict control of the Pd/ligand ratio (optimally 1/1),[156] avoiding

[158] For early work from the laboratory using *in situ* formed catalyst, see: (a) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804–3805. (b) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307–1309. (c) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889–9890. (d) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053–2055. (e) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119–122. (f) Yang, C.; Lee, H. M.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1511–1514. (g) Viciu, M. S.; Grasa, G. A.; Nolan, S. P. *Organometallics* **2001**, *20*, 3607–3612. (h) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729–7737. (i) Yang, C.; Nolan, S. P. *Synlett* **2001**, 1539–1542. (j) Yang, C.; Nolan, S. P. *Organometallics* **2002**, *21*, 1020–1022. (k) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866–2873.

[159] See the Introduction Chapter.

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the use of excess ligand that usually requires removal in workup procedures.[160] Finally, employing well-defined pre-catalysts ensures the binding mode of the NHC ligand,[161] and partly removes the "black box" character often associated with cross-coupling chemistry and catalyst formation.

II. [(NHC)Pd(R-allyl)Cl] Pre-catalysts[162,163]

A. Preliminary results

In 2002, a number of [(NHC)Pd(allyl)Cl] were synthesized in our laboratory (Figure 14, **LIV**-**LX**), which notably enabled the evaluation of the steric properties of the entire series of NHCs.[59] They were produced from $[(allyl)PdCl]_2$ upon addition of two equivalents of NHC ligand. Of note, Bellemin-Laponnaz and co-workers reported recently the synthesis of complex **LXI**, which did not show catalytic activity in cross-coupling.[164]

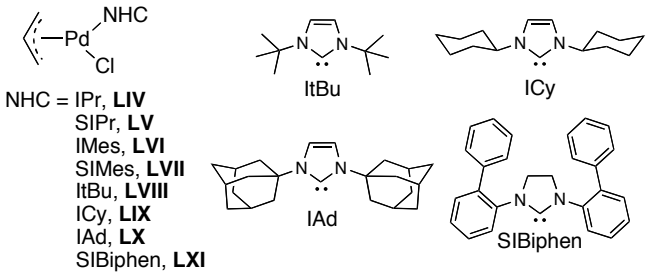

Figure 14. Structures of [(NHC)Pd(allyl)Cl] complexes **LIV**-**LXI**

In the course of the comparison of their activity in cross-coupling reactions,[165] optimization of the NHC ligand on the Pd center showed IPr and SIPr to be the most efficient ligands in aryl amination reactions, with a clear advantage for SIPr, which performed best at room temperature. Further investigation showed **LIV** and **LV** able to perform a wide array of cross-coupling reactions (Suzuki-Miyaura, Buchwald-Hartwig,

[160] A fact worth mentioning since late-generation phosphine ligands are by far more expensive than common palladium sources.
[161] For an unexpected NHC–Pd binding mode observed under cross-coupling conditions, see: Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P. *J. Am. Chem. Soc.* **2004**, *126*, 5046–5047.
[162] Marion, N.; Navarro, O.; Mei , J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101–4111.
[163] Navarro, O.; Marion, N.; Mei, J.; Nolan, S. P. *Chem.–Eur. J.* **2006**, *12*, 5142–5148.
[164] Fliedel, C.; Maisse-François, A.; Bellemin-Laponnaz, S. *Inorg. Chim. Acta* **2007**, *360*, 143–148.
[165] (a) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053–4056. (b) Viciu, M. S.; Germaneau, R. F.; Navarro–Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470–5472.

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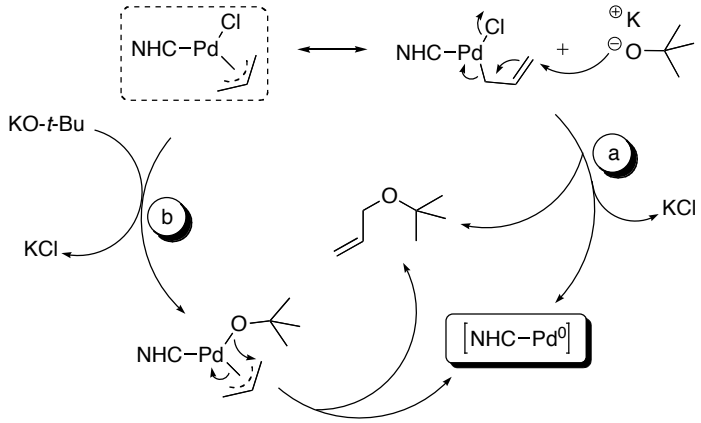
dehalogenation, ketone arylation) at low catalyst loading and under mild reaction conditions.[166]

It was postulated that for these [(NHC)Pd(allyl)Cl], the activation mode would occur either through a nucleophilic attack at the allyl moiety (path a) or through a chloride/alkoxide anionic metathesis followed by reductive elimination (path b), liberating in both cases a [(NHC)Pd^0] species (Scheme 22).



Scheme 22. Proposed activation pathways for [(NHC)Pd(allyl)Cl]

These pre-catalysts can be synthesized in a one-pot procedure from the corresponding imidazolium chloride that is deprotonated *in situ*[167] and present the advantage of being active for a number of cross-coupling reactions as seen above. Nevertheless, they still require activation at 70°C to perform effectively, in aryl amination for instance. To overcome this sluggish activation step, we focused on the design of a more labile framework that would be closely related to the [(NHC)Pd(allyl)Cl] system, since it can be easily synthesized. Having in mind that substitution on the allyl moiety decreases the overall stability of the palladium complex by increasing steric bulk around the metal center and by decreasing the back-bonding from the metal to the olefin,[168] we thought that modification of this site could facilitate the activation pathway by rendering the allyl scaffold less tightly bound to the palladium center and more prone to nucleophilic attack or to reductive elimination, depending on which activation mode is considered. As a result, we focused our studies on the effect of substitution at the allyl moiety in the generation of the active species

[166] (a) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *64*, 3173–3180. (b) Marion, N.; Navarro, O.; Kelly, R. A., III; Nolan, S. P. *Synthesis* **2003**, 2590–2592.
[167] Navarro, O.; Nolan, S. P. *Synthesis* **2006**, 366–367.
[168] Trost, B. M.; Weber, L.; Strege, P. E.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3416–3426.

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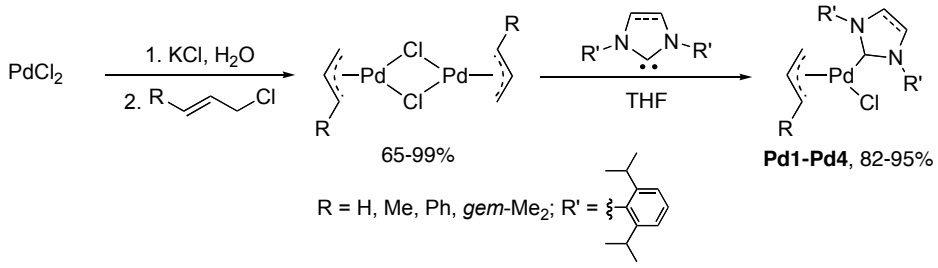
[(NHC)Pd^0] and synthesized a series of modified [(NHC)Pd(allyl)Cl] with general formulae [(NHC)Pd(R-allyl)Cl].

B. Synthesis and comparative study of modified [(NHC)Pd(allyl)Cl] pre-catalysts

1. Synthesis and structural studies

The syntheses of the new complexes were very straightforward and involved the simple fragmentation of the corresponding [Pd(R-allyl)Cl]$_2$ dimer by the IPr and SIPr carbenes in dry THF (Scheme 23). The palladium dimers were either purchased from commercial sources or easily prepared from $PdCl_2$ and (R-allyl)chloride following the literature procedure.[169] The reaction involving a free NHC and the appropriate dimer was followed by evaporation of the solvent, trituration of the complex in pentane and filtration in air. This led to the desired complexes in very good yields (≥ 82%).



Scheme 23. Synthesis of [(NHC)Pd(R-allyl)Cl] complexes

Following this procedure on a 2 mmol scale, we synthesized and fully characterized four derivatives of [(IPr)Pd(allyl)Cl] **LIV**: [(IPr)Pd(crotyl)Cl] (crotyl = 3-methylallyl) **Pd1**, [(IPr)Pd(prenyl)Cl] (prenyl = 3,3-dimethylallyl) **Pd2**, [(IPr)Pd(cinnamyl)Cl] (cinnamyl = 3-phenylallyl) **Pd3** and [(SIPr)Pd(cinnamyl)Cl] **Pd4** that are depicted in Figure 15.

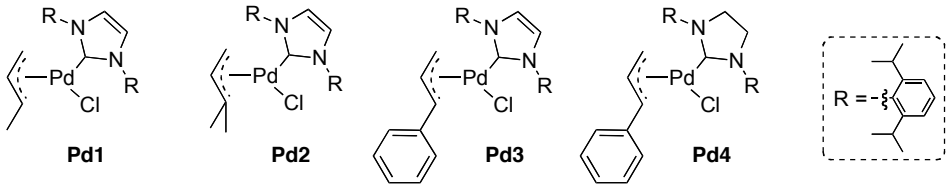


Figure 15. Structures of complexes **Pd1**-**Pd4**

As in the case of the unsubstituted π-allyl complexes **LIV** and **LV**, these new complexes are air- and moisture-stable and can be stored indefinitely on the shelf in air

[169] Palenik, R. C.; Palenik, G. J. *Synth. React. Inorg. Met.–Org. Chem.* **1992**, *22*, 1395–1399.

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without observable decomposition.[170] Single crystals suitable for X-ray diffraction of **Pd1**-**Pd4** were obtained from concentrated solutions of CH_2Cl_2/hexanes. Ball-and-stick representations of the X-ray diffraction study results for **Pd1**-**Pd3** are presented in Figure 16.

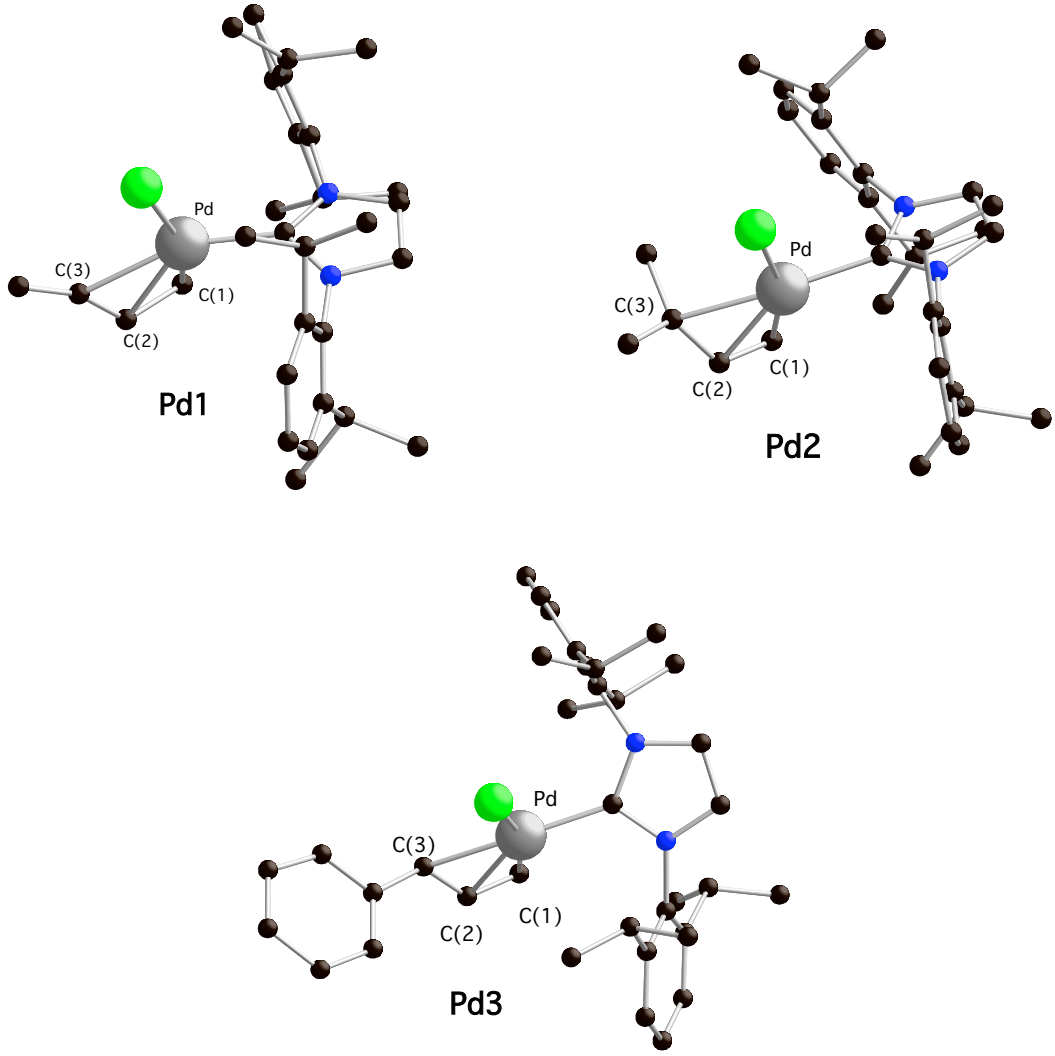

Figure 16. Ball-and-stick representations of [(IPr)Pd(crotyl)Cl] **Pd1**, [(IPr)Pd(prenyl)Cl] **Pd2** and [(IPr)Pd(cinnamyl)Cl] **Pd3** (hydrogen atoms are omitted for clarity)

A comparison of selected bond distances is shown in Table 3.[171] For a more accurate discussion on the effect of terminal substitution on the allyl moiety, we will consider IPr-bearing complexes (**LIV**, **Pd1**, **Pd2** and **Pd3**) separately from the SIPr-bearing complexes (**LV** and **Pd4**).

[170] As a testimony to their stability, samples of **Pd3** and **Pd4** retrieved from our laboratories in New Orleans showed no decomposition after being subjected for 2 months to harsh environmental conditions (35°C, high humidity and high level of volatile chemicals) imposed by Hurricane *Katrina*.

[171] Owing to the slightly lower quality of structural data for [(IPr)Pd(crotyl)Cl] **Pd1** (despite repeated attempts) higher error factors preclude a bond length discussion involving **Pd1**; it is of note that an increase of the dissymmetry of the allyl moiety is observed with increased steric substitution at the allylic terminal position.

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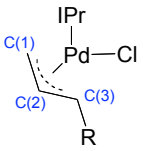
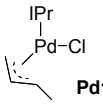
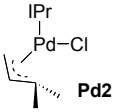
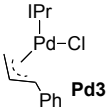
Table 3. Selected bond distances for **LIV** and **Pd1**-**Pd3**



(Å)	 **LIV**	 **Pd1**	 **Pd2**	 **Pd3**
Pd–C(1)	2.098(6)	2.147(18)	2.095(4)	2.082(9)
Pd–C(2)	2.124(7)	2.122(18)	2.137(5)	2.136(10)
Pd–C(3)	2.210(6)	2.209(16)	2.252(5)	2.284(9)

While the Pd–C(1) distances remain fairly constant, the Pd–C(3) distances become longer upon terminal substitution at the allyl moiety. Strikingly, when compared to **LIV**, the increase of dissymmetry in **Pd2** and **Pd3** is respectively of 40% and 80%.[172] As previously mentioned, both electronic and steric factors appear to play a role in this increase of dissymmetry in the coordination of the allyl moiety: terminal phenyl substitution is less electron donating than methyl substitution,[173] but the elongation of the Pd–C(3) distance in **Pd3** is even larger than the one observed in **Pd2**.

As for **Pd1**-**Pd3**, single crystals of **Pd4**, suitable for X-ray diffraction, were obtained from a concentrated CH_2Cl_2/hexanes mixture. Ball-and-stick representations of the X-ray diffraction study results for **LV** and **Pd4** are presented in Figure 17.

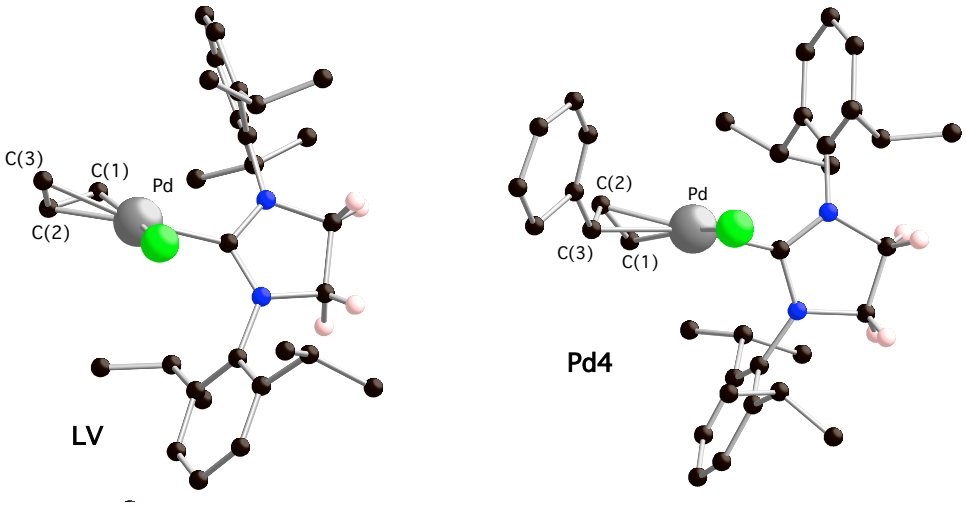


Figure 17. Ball-and-stick representations of [(SIPr)Pd(allyl)Cl] **LV** and [(SIPr)Pd(cinnamyl)Cl] **Pd4** (most hydrogen atoms are omitted for clarity)

[172] Calculation for the increase of dissymmetry: $\{[(Pd–C(3))-(Pd–C(1))]^{R\text{-}allyl}-[(Pd–C(3))-(Pd–C(1))]^{allyl}\}/[(Pd–C(3))-(Pd–C(1))]^{allyl}$.
[173] Smith, M. B., March, J. *Advanced Organic Chemistry*; 5th ed.; John Wiley & Sons: New York, NY, pp. 368–375.

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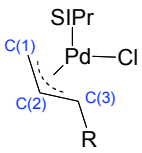
A comparison of the solid-state structures of [(SIPr)Pd(allyl)Cl] **LV** and [(SIPr)Pd(cinnamyl)Cl] **Pd4** revealed that substitution of the allyl moiety by a phenyl group increases the distances between the palladium center and the three bound carbons of the allyl scaffold (Table 4).

Table 4. Selected bond distances from **LV** and **Pd4**



(Å)	SIPr Pd–Cl **LV**	SIPr Pd–Cl Ph **Pd4**
Pd–C(1)	2.118(6)	2.136(10)
Pd–C(2)	2.132(7)	2.137(8)
Pd–C(3)	2.203(6)	2.279(10)

We previously noticed that even though the allyl group is symmetrical, in the [(SIPr)Pd(allyl)Cl] the carbon *trans* to the chlorine atom, C(1), is closer to the palladium center than the carbon *trans* to the SIPr, C(3). This dissymmetry is increased by 68% in the new complex **Pd4**.[172] Regardless of which of the pathways for the allyl elimination is preferred, the observed elongation of the Pd–C(3) distance should lead to an easier activation process leading to the [(IPr)–Pd^0] species. To determine if this feature allows for a more facile activation step, we tested the complexes in the Suzuki-Miyaura and the Buchwald-Hartwig cross-coupling reactions.

2. Comparative studies of the activity of [(NHC)Pd(R-allyl)Cl] complexes in cross-coupling reactions

The Suzuki-Miyaura reaction

Whether the observed structural insights could lead to an improved activation and result in an increase in the amount of active Pd species in solution was worth examining on test substrates. A comparison of the performance of four [Pd(R-allyl)] complexes in the Suzuki-Miyaura reaction of 4-chlorotoluene and phenylboronic acid at room temperature is shown in Table 5. Only the substituted allyl complexes **Pd1**-**Pd3** allowed for the coupling to proceed in high yields at room temperature, even when sterically hindered substrates were tested (Table 6). Complex **LIV** afforded no more than 40% yield for the coupling of 2,6-dimethylphenyl chloride with 1-naphthaleneboronic acid at room temperature, despite extending the reaction time to several hours.

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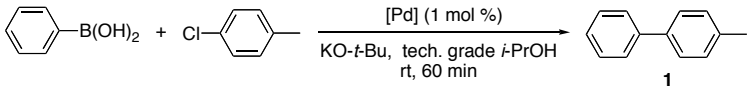
Table 5. Effect of the substitution at the allyl moiety on pre-catalyst performance in the Suzuki-Miyaura coupling of simple substrates[a]

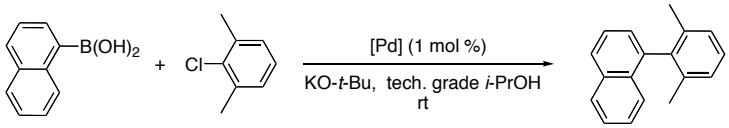


1

Entry	[Pd]	GC conv. (%)[b]
1	[(IPr)Pd(allyl)Cl] **LIV**	12
2	[(IPr)Pd(crotyl)Cl] **Pd1**	86
3	[(IPr)Pd(prenyl)Cl] **Pd2**	90
4	[(IPr)Pd(cinnamyl)Cl] **Pd3**	90

[a] Reaction conditions: aryl chloride (1 mmol), boronic acid (1.05 mmol), [Pd] (1 mol %), KO-*t*-Bu (1.1 mmol), tech. grade *i*-PrOH (1 mL). [b] Average of two runs.

Table 6. Effect of the substitution at the allyl moiety on pre-catalyst performance in the Suzuki-Miyaura coupling of hindered substrates[a]



2

Entry	[Pd]	Time (min)	GC conv. (%)[b]
1	[(IPr)Pd(crotyl)Cl] **Pd1**	45	91
2	[(IPr)Pd(prenyl)Cl] **Pd2**	25	95
3	[(IPr)Pd(cinnamyl)Cl] **Pd3**	25	94

[a] Reaction conditions: aryl chloride (1 mmol), boronic acid (1.05 mmol), [Pd] (1 mL), KO-*t*-Bu (1.1 mmol), tech. grade *i*-PrOH (1 mL). [b] Average of two runs.ol %),

In the present system, only trace amounts of the undesired dehalogenation by-products were observed. These pre-catalysts, and notably **Pd3**, were further studied in the context of the Suzuki-Miyaura reaction and proved to be extremely efficient towards numerous couplings, even at extremely low catalyst loadings.[162] An added advantage of complexes **Pd1**-**Pd3** is that the slow addition of the aryl chloride is not required. This already overcomes a drawback encountered in our palladacyclic-NHC system.[141,143]

The Buchwald-Hartwig reaction

Previous studies conducted in our laboratories with [(SIPr)Pd(allyl)Cl] **LV** showed that 1,2-dimethoxyethane (DME) and NaO-*t*-Bu were the most efficient solvent and base for

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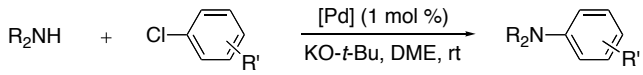
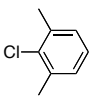
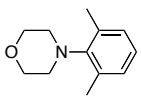
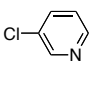
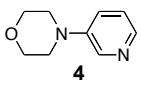
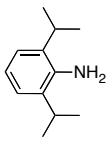
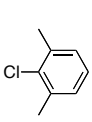
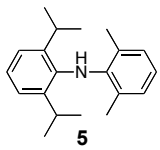
N-aryl amination.[20a] We reexamined these conditions and found that with KO-*t*-Bu only 1.1 equivalents of base, instead of 1.4, were necessary. Furthermore, we were able to dramatically reduce the amount of solvent from 4 mL to 1 mL, which had, in fact, an accelerating effect on the reaction.

As it was previously reported that SIPr performs better than IPr in the Buchwald-Hartwig amination,[59,133,174] we tested the activity of [(SIPr)Pd(cinnamyl)Cl] **Pd4** versus [(SIPr)Pd(allyl)Cl] **LV** along with their IPr counterparts **Pd3** and **LIV** (Table 7). The results, all obtained with challenging substrates, clearly show the tremendous effect of both the ancillary ligand on the palladium center (from IPr to SIPr) and of the substitution at the terminal position of the allyl scaffold (from allyl to cinnamyl). When combined, these two aspects generate a highly efficient pre-catalyst, [(SIPr)Pd(cinnamyl)Cl] **Pd4**, that can perform room temperature *N*-aryl amination in minutes using aryl chlorides. Thus, the reaction of 2,6-diisopropylaniline and 2-chloro-*m*-xylene, which could not be completed even after 20 hours in the presence of [(IPr)Pd(allyl)Cl], reached completion after only 6 hours when [(IPr)Pd(cinnamyl)Cl] was used. More strinkingly, [(SIPr)Pd(cinnamyl)Cl] performed this reaction four times faster.

Table 7. Effect of the NHC and the substitution at the allyl moiety at room temperature in the Buchwald-Hartwig reaction[a]



Amines	Ar-Cl	Product	[Pd]	Time	GC conv. (%)[b]
		 **3**	[(IPr)Pd(all)Cl] **LIV**	5 h	98
			[(SIPr)Pd(all)Cl] **LV**	2.5 h	99
			[(IPr)Pd(cin)Cl] **Pd3**	2 h	100
			[(SIPr)Pd(cin)Cl] **Pd4**	20 min	100
		 **4**	[(IPr)Pd(all)Cl] **LIV**	20 h	31[c]
			[(SIPr)Pd(all)Cl] **LV**	20 h	62[c]
			[(IPr)Pd(cin)Cl] **Pd3**	5 h	100
			[(SIPr)Pd(cin)Cl] **Pd4**	5 min	100
		 **5**	[(IPr)Pd(all)Cl] **LIV**	20 h	73[c]
			[(SIPr)Pd(all)Cl] **LV**	15 h	90[c]
			[(IPr)Pd(cin)Cl] **Pd3**	6 h	98
			[(SIPr)Pd(cin)Cl] **Pd4**	1.5 h	97

[a] Reaction conditions: aryl chloride (1 mmol), amine (1.1 mmol), [Pd] (1 mol %), KO-*t*-Bu (1.1 mmol), DME (1 mL). [b] Average of two runs. [c] No further conversion.

[174] Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423–1426.

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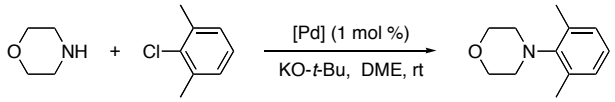
Finally, to confirm the effect of the substitution at the allyl moiety previously observed in the Suzuki-Miyaura reaction, we examined pre-catalysts **Pd1**-**Pd3** in the Buchwald-Hartwig reaction (Table 8). As expected, the prenyl and the cinnamyl derivatives displayed similar activities (Entries 2 and 3) while the crotyl was found slightly less efficient (Entry 1).

Table 8. Effect of the substitution at the allyl moiety at room temperature in the Buchwald-Hartwig reaction[a]



3

Entry	[Pd]	Time	GC conv. (%)[b]
1	[(IPr)Pd(crotyl)Cl] **Pd1**	3.5 h	91
2	[(IPr)Pd(prenyl)Cl] **Pd2**	2 h	95
3	[(IPr)Pd(cinnamyl)Cl] **Pd3**	2 h	100
4	[(SIPr)Pd(cinnamyl)Cl] **Pd4**	20 min	100

[a] Reaction conditions: aryl chloride (1 mmol), amine (1.1 mmol), [Pd] (1 mol %), KO-*t*-Bu (1.1 mmol), DME (1 mL). [b] Average of two runs.

We chose to use cinnamyl derivative **Pd4** and not its prenyl counterpart from this point on because of the relative lower cost of the corresponding allyl chloride precursor.[175]

C. Activity of [(SIPr)Pd(cin)Cl] (Pd4) in the Buchwald-Hartwig reaction

1. Room temperature coupling of aryl bromides

A wide range of aryl bromides were tested under the reaction conditions previously described for the comparison of the different pre-catalysts, these results are presented in Table 9. Overall, amines, and notably secondary cyclic ones, reacted in astonishingly short reaction times. Hence, [(SIPr)Pd(cin)Cl] **Pd4**, in conjugation with KO-*t*-Bu, produced, in less than 20 minutes, *ortho*-substituted (Entry 1), electron-poor (Entry 4) and electron-rich (Entry 6) anilines at room temperature. Even less reactive aryl bromides such as di-*ortho*-substituted mesitylbromide or sterically hindered and unactivated 2-bromoanisole were coupled at room temperature within one hour in high yields (Entries 2 and 3).

[175] According to the Aldrich catalog 2004-2005, cinnamyl chloride (by 100 g) and prenyl chloride (by 25 g) cost respectively $94.2/mol and $398.7/mol.

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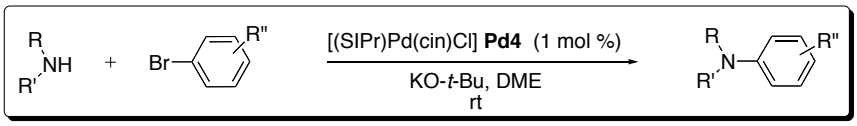
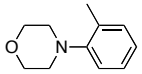
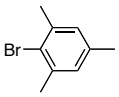
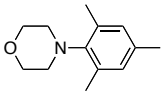
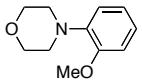
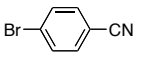
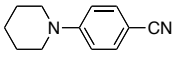
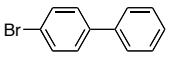
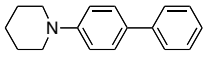
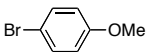
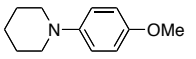
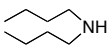
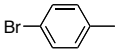
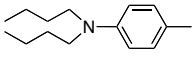
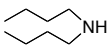
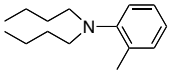
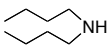
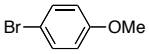
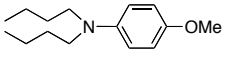
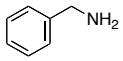
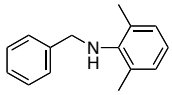
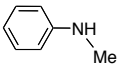
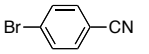
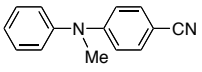
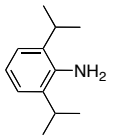
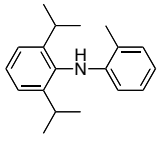
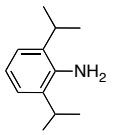
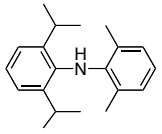
Table 9. *N*-Aryl amination using aryl bromides[a]



Entry	Amines	Ar-Br	Product		Time (min)	Yield[b] (%)
1				**6**	1	96
2				**7**	30	94
3				**8**	60	88
4				**9**	5	90
5				**10**	5	83
6				**11**	20	93
7				**12**	40	98
8				**13**	30	88
9				**14**	60	94
10				**15**	1	99
11				**16**	15	97
12				**17**	90	96
13				**5**	75	87

[a] Reaction conditions: aryl bromide (1 mmol), amine (1.1 mmol), [(SIPr)Pd(cin)Cl] **Pd4** (1 mol %), KO-*t*-Bu (1.1 mmol), DME (1 mL). [b] Isolated yields, average of two runs.

It is worth noting that, for reactions completed in less than 15 minutes, we observed a strong exotherm immediately after the addition of the aryl bromide. We attribute this feature

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to the exothermicity of the coupling reaction associated with the generation of high concentration of the catalytically active species. The same trend was observed when 4-biphenyl bromide and piperidine were coupled to yield, in only 5 minutes, *N*-(4-biphenylyl)piperidine **10** (Entry 5). The construction of such a framework is appealing from a synthetic point of view as the diphenylamino group is of great interest for the elaboration of conjugated donor-acceptor polymers.[176] Dibutylamine, as expected, was found to be less reactive than piperidine, but still yielded almost quantitatively, in less than an hour, dialkylanilines even with unactivated aryl bromides (Entries 7-9). The reaction between benzylamine and 2-bromo-*m*-xylene required only one minute to reach completion (Entry 10). More interestingly, when this reaction was carried out with an equimolar amount of amine and bromide, a simple extraction followed by a filtration through Celite afforded the pure coupled product **15** without the need of purification by column chromatography.

Finally, primary and secondary anilines were efficiently arylated (Entries 11-13). Gratifyingly, sterically encumbered tri- and tetra-*ortho*-diarylamines were produced in high yields, highlighting the tolerance of our catalytic system to sterically hindered substrates.

2. Room temperature coupling of aryl chlorides

Next, we carried out coupling reactions of a wide array of aryl chlorides and amines. Aryl chlorides are very attractive halides due to their low cost and wide diversity and availability. Historically, their use in cross-coupling reactions has been somewhat limited due to their poor reactivity, attributed to the strength of the C–Cl bond.[177] Remarkably, no loss of activity was observed when we carried out reactions at room temperature. As shown in Table 10, all reactions reached completion almost as fast as when aryl bromides were used.

Secondary cyclic amines were easily coupled with activated (Entry 4), neutral (Entries 1-3) and unactivated chlorides (Entries 5 and 6). As in the reactions with aryl bromides, a strong exotherm was observed after the addition of the chloride for every reaction completed within 15 minutes. Again, the exothermicity of the reaction is a testimony to an extremely efficient activation step.

We then looked at the reactivity of the less reactive, sterically hindered dibutylamine, which reacted smoothly with both 2-chlorotoluene and 4-chloroanisole (Entries 7 and 9).

[176] Leung, M.-K.; Chou, M.-Y.; Su, Y. O.; Chiang, C. L.; Chen, H.-L.; Yang, C. F.; Yang, C.-C.; Lin, C.-C.; Chen, H.-T. *Org. Lett.* **2003**, *5*, 839–842.
[177] For a review in palladium-catalyzed coupling reactions of aryl chlorides: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.

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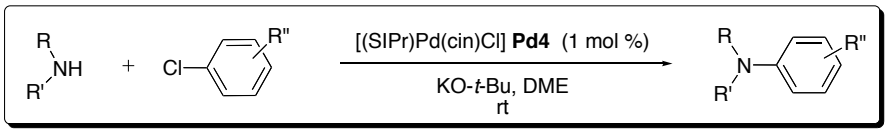
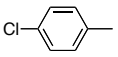
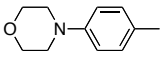
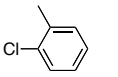
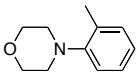
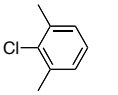
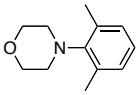
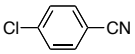
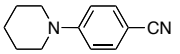
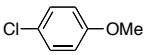
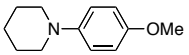
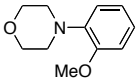
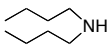
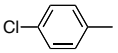
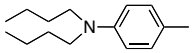
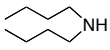
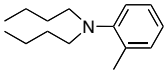
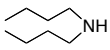
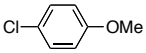
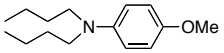
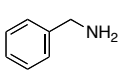
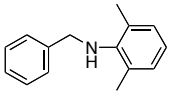
Table 10. *N*-Aryl amination using aryl chlorides[a]



Entry	Amines	Ar-Cl	Product		Time (min)	Yield[b] (%)
1				**18**	2	95
2				**6**	2	92
3				**3**	20	93
4				**9**	5	96
5				**11**	40	95
6				**8**	60	92
7				**12**	90	87
8				**13**	75	90
9				**14**	120	95
10				**15**	40	90

[a] Reaction conditions: aryl chloride (1 mmol), amine (1.1 mmol), [(SIPr)Pd(cin)Cl] **Pd4** (1 mol %), KO-*t*-Bu (1.1 mmol), DME (1 mL). [b] Isolated yields, average of two runs.

More interestingly, we produced a dialkyl-*o*-arylamine **13** in 90% isolated yield (Entry 8). To the best of our knowledge, this is the first example of a coupling involving an acyclic dialkylamine and an *ortho*-substituted aryl chloride; moreover it was achieved at room temperature and in a short reaction time.

Anilines represent another family of substrates that are compatible with our catalytic system, yielding diarylamines within one hour (Table 11). We were particularly interested in the very sterically hindered 2,6-diisopropylaniline. 2- And 4-chlorotoluene could be coupled in high yields (Entries 1, 3, and 4). Remarkably, even the di-*ortho*-substituted 2-chloro-*m*-

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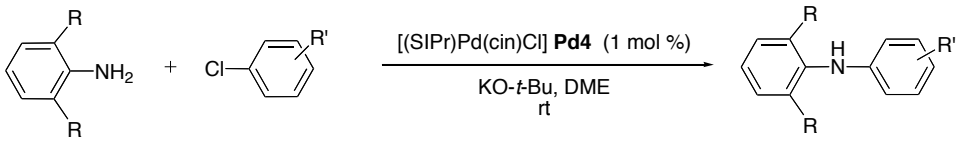
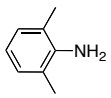
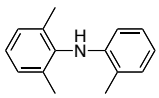
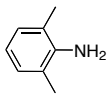
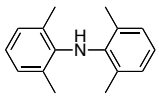
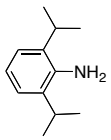
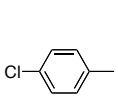
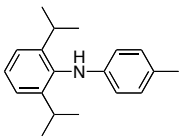
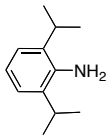
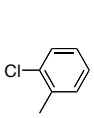
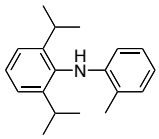
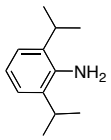
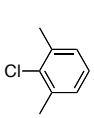
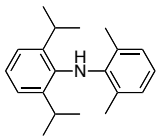
xylene reacted in less than 2 hours to yield 97% of the extremely bulky diarylamines **5** and **20** (Entries 2 and 5). A short survey of the literature revealed that much harsher reaction conditions and the use of a bromide[178] or a nonaflate[179] were previously required to produce this compound.

Table 11. *N*-Aryl amination of sterically hindered anilines[a]



Entry	Amines	Ar-Cl	Product		Time (min)	Yield[b] (%)
1				**19**	30	90
2				**20**	40	86
3				**21**	150	87
4				**17**	120	93
5				**5**	90	97

[a] Reaction conditions: aryl chloride (1 mmol), amine (1.1 mmol), [(SIPr)Pd(cin)Cl] **Pd4** (1 mol %), KO-*t*-Bu (1.1 mmol), DME (1 mL). [b] Isolated yields, average of two runs.

These last results finally highlight a general trend of the present catalytic system: its high compatibility for the assembly of hindered compounds, regardless of which substrate, the amine or the halide, is encumbered. This has allowed us to synthesize, always in high yields, tri- or tetra-*ortho*-substituted diarylamines even from less reactive di-*ortho*-substituted aryl chlorides.

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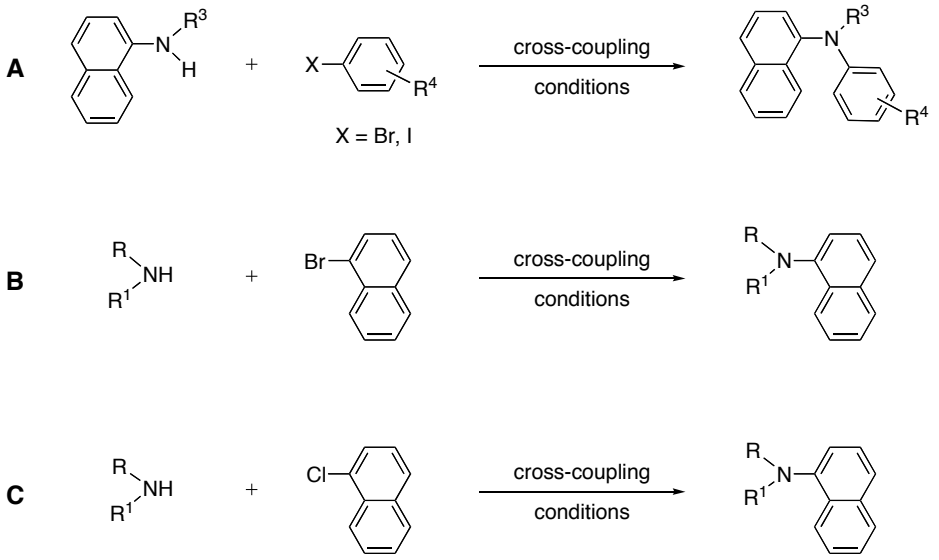
3. Room temperature reactions of naphthyl and anthryl halides

In our continuing search for substrates of synthetic interest, we realized the increasing potential of naphthyl- and anthrylamines in materials chemistry and biochemistry. Well-known as hole transport materials[180] or photoactive chromophores,[181] they have been used lately as ligands in dendrimers to produce luminescent organometallic complexes.[182] Their applications in medicinal chemistry are multiple, ranging from spacer to improve drug-delivery[183] to pharmacophore in a number of inhibitors.[184]



Scheme 24. Different approaches to *N*-naphthylamines

Despite their importance, the synthetic routes explored to date to produce naphthyl- or anthrylamines involve, in general, the use of naphthylamine and aryl bromides/iodides

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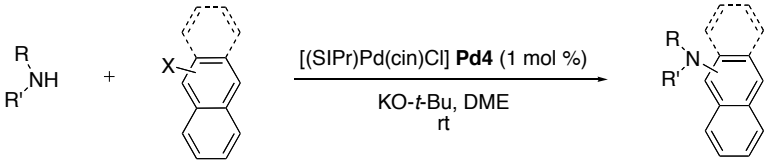
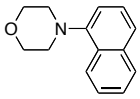
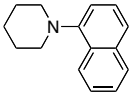
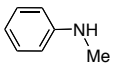
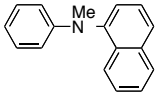
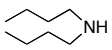
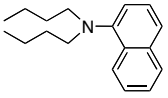
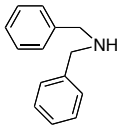
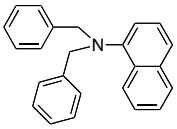
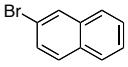
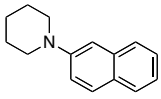
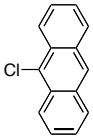
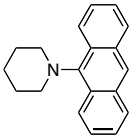
(Scheme 24, path A) or bromonaphthalene and amines (Scheme 24, path B). The high cost of bromonaphthalene compared to chloronaphthalene[185] does not favor approach B. Approach A, using naphthylamine (which is another expensive substrate), is then more appealing to produce arylnaphthylamines; however, this route excludes the possibility of producing dialkylnaphthylamines. To overcome these difficulties, we thought of using our catalytic system in the coupling of inexpensive chloronaphthalene and amines (Scheme 24, path C). Results, all obtained at room temperature, are presented in Table 12.

Table 12. *N*-Aryl amination of naphthyl and anthryl halides[a]



Entry	Amines	Ar-X	Product		Time (min)	Yield[b] (%)
1				**22**	5	91
2				**23**	5	87
3				**24**	120	89
4				**25**	60	95
5				**26**	30	74
6				**27**	5	92
7				**28**	60	95

[a] Reaction conditions: aryl chloride (1 mmol), amine (1.1 mmol), [(SIPr)Pd(cin)Cl] **Pd4** (1 mol %), KO-*t*-Bu (1.1 mmol), DME (1 mL). [b] Isolated yields, average of two runs.

[185] According to the Acros catalog 2006-2007, 1-chloronaphthalene and 1-bromonaphthalene when purchased by 100 mL cost respectively $28.9/mol and $57.6/mol respectively.

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We first attempted to react 1-chloronaphthalene with two cyclic secondary amines, morpholine and piperidine. We pleasantly observed that both reactions reached completion after only 5 minutes (Entries 1 and 2). We noticed similar reaction times between 2-bromonaphthalene and piperidine (Entry 6). Encouraged by these promising results, we carried out the coupling of the sterically hindered dibutylamine and dibenzylamine with 1-chloronaphthalene (Entries 4 and 5). Both reactions produced in high yields the corresponding *N*-naphthylamines **25** and **26** but, surprisingly, they proceeded faster than the one involving *N*-methylaniline (Entry 3), supposedly an easier coupling partner. Finally, the *N*-(9-anthryl)piperidine **28** was produced in high yield and interestingly, isolated pure without the need for purification by column chromatography on silica gel. Taking advantage of the low solubility of the product in alkanes, a simple pentane wash followed by a filtration was sufficient to isolate the anthrylamine.

4. Room temperature coupling of heteroaromatic halides

Heteroaromatics represent a recurring architectural motif found in various areas of chemistry, ranging from pharmaceutically active compounds[186,187] to polymers.[188] Although the Buchwald-Hartwig[189] reaction arguably is among the most powerful and widely used methods to assemble C–N bonds, heterocyclic compounds are usually not easily coupled in this reaction. Although the poisoning effect of sulfur in some palladium-catalyzed reactions is well known, it should also be mentioned that such undesired effects have also been observed with nitrogen containing substrates.[190] Furthermore, despite their importance and low cost, the coupling reactions of most *heteroaromatic chlorides* remain a challenge,[191] especially at low temperatures and/or low catalyst loadings.

In this context, we tested the activity of **Pd4** in a series of reactions involving the coupling of *N*-containing heteroaromatic halides with primary and secondary amines at room temperature (Table 13). 2-Bromo- and 2-chloropyridine were found to react very efficiently with a range of amines. Reactions with cyclic dialkylamines reached completion within 5

[186] Nakamura, I.; Yamamoto, Y. *Chem. Rev*. **2004**, *104*, 2127–2198.
[187] Koike, K.; Jia, Z.; Nikaido, T.; Liu, Y.; Zhao, Y.; Guo, D. *Org. Lett*. **1999**, *1*, 197–198.
[188] Persson, J. C.; Jannasch, P. *Chem. Mater*. **2003**, *15*, 3044–3045.
[189] (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res*. **1998**, *31*, 805–818. (b) Hartwig, J. F. *Acc. Chem. Res*. **1998**, *31*, 852–860. (c) Hartwig, J. F. In *Modern Amination Methods* (Ed.: A. Ricci), Wiley-VCH, Weinheim, 2000.
[190] Feuerstein, M.; Doucet, H.; Santelli, M. *J. Organomet. Chem*. **2003**, *687*, 327–336.
[191] For recent examples on how this challenge has been partially addressed, see: (a) For low catalyst loadings but elevated temperature protocol, Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed*. **2005**, *44*, 1371–1375. (b) For functional group compatibility and cost issues, Kudo, N.; Persighini, M.; Fu, G. C. *Angew. Chem., Int. Ed*. **2006**, *45*, 1282–1284.

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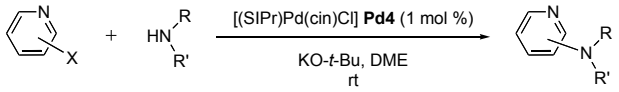
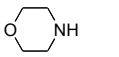
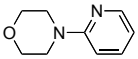
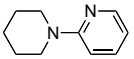
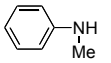
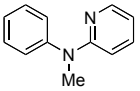
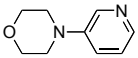
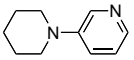
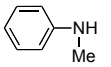
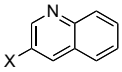
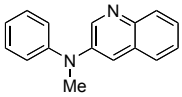
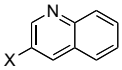
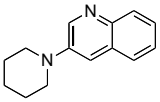
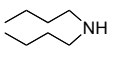
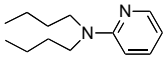
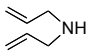
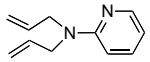
minutes (Entries 1-4) and are quantitative; leading in the case of **29** to a workup that simply required filtration through Celite without purification by column chromatography.

Table 13. Aryl amination of halo-pyridines and -quinolines[a]



Entry	Amine	Ar–X	Product		X	Time (min)	Yield (%)[b]
1				**29**	Br	1	94
2					Cl	2	89
3				**30**	Br	2	96
4					Cl	5	98
5				**31**	Br	10	92
6					Cl	15	92
7				**4**	Br	5	90
8					Cl	15	86
9				**32**	Br	5	72
10					Cl	45	82
11				**33**	Br	90	92
12				**34**	Br	40	87
13				**35**	Cl	15	94
14				**36**	Cl	60	92

[a] Reaction conditions: halide (1 mmol), amine (1.1 mmol), [(SIPr)Pd(cin)Cl] **Pd4** (1 mol %), KO-*t*-Bu (1.1 mmol), DME (1 mL). [b] Isolated yields, average of two runs.

As expected, the more sterically demanding dibutyl- and diallylamine required longer reaction times to provide in almost quantitative yields the corresponding 2-pyridyl derivatives **35** and **36** (Entries 13 and 14). It is noteworthy that this is the first example, to the best of our knowledge, of chloropyridines coupled with amines under such mild conditions and in such short reaction times.[191a,192] The same trend was observed with *N*-methylaniline which produced diaryl compounds within 15 minutes (Entries 5 and 6).

[192] The only report we were able to find for the palladium-catalyzed coupling reaction of diallylamine and 2-chloropyridine describes the following reaction conditions: 5 mol% of [Pd], T = 100°C, t = 3 h; see: Jaime-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett.* **1998**, *39*, 1313–1316.

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Surprisingly, coupling reactions with 3-chloro- and 3-bromopyridine, strongly unactivated compared to 2-pyridyl halides,[193] proceeded rapidly. This allowed for the formation of 3-pyridylamino compounds **4** and **32** at room temperature in no more than 45 minutes.

More strikingly, when 3-bromopyridine was added to reaction mixtures containing morpholine or piperidine, an intense exotherm was observed and these reactions reached completion within 5 minutes (Entries 7 and 9). Encouraged by the reactivity of 3-halopyridines, we carried out reactions with 3-bromoquinoline. *N*-Methylaniline and piperidine yielded the corresponding 3-aminoquinolines **33** and **34** (Entries 11 and 12). Considering the mild reaction conditions employed, this is a considerable advance since few reports on aryl amination involve haloquinolines.[194]

In order to extend the applications of the present catalytic system, we examined its reactivity towards *O*- and *S*-containing heterocyclic halides. All attempts to react halo-thiophenes, -furanes, or -benzoxazoles with diverse amines invariably failed. Higher temperature or higher catalyst loading did not improve these results.

It should be added that the activity of pre-catalysts **Pd3** in the Suzuki-Miyaura reaction was thoroughly investigated and that it was found extremely efficient towards the coupling of *N*-heteroaromatics at room temperature.[163]

5. Amination reactions at low catalyst loadings

Aryl bromides and chlorides

Decreasing the amount of palladium necessary to catalyze a process is desirable not only because of cost, but also to facilitate metal removal once the reaction is complete, especially in industrial settings where concerns of product purity, toxicity associated with residual metal and general environmental issues have significant health and economical consequences.[195] The very rapid reactions observed for a wide array of substrates naturally led us to examine the effect of reducing the catalyst loading.

Overall, the present catalytic system allowed for the use of pre-catalyst loadings as low as 10 part-per-million (ppm) of catalyst if the temperature was raised to 80°C (Table 14). It is noteworthy that, unlike what we observed in the Suzuki-Miyaura reaction,[162] the unsubstituted allyl complex [(SIPr)Pd(allyl)Cl] **LV** is not as efficient as the new complex

[193] Gribble, G.; Li, J. J. In *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*, Baldwin, J.; Williams, R. M.; Bäckvall, J.-E., Eds., Pergamon, Amsterdam, 2000.
[194] Wang, T.; Magnin, D. R.; Hamann, L. G. *Org. Lett.* **2003**, *5*, 897–900.
[195] Garret, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889–900.

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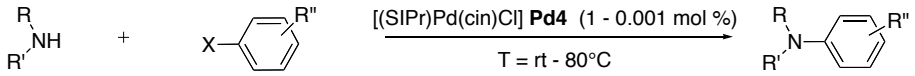
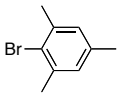
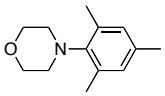
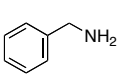
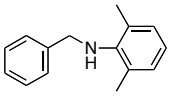
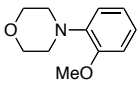
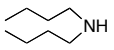
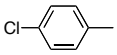
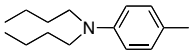
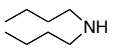
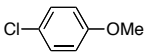
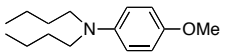
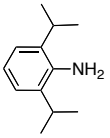
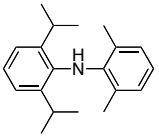
[(SIPr)Pd(cinnamyl)Cl] **Pd4** at elevated temperature and with extremely low catalyst loadings.

Table 14. Buchwald-Hartwig amination at low catalyst loading[a]



Entry	Amines	Ar-X	Product		Cat. loading (mol %)	Time	Yield[b] (%)
1				**7**	1 0.1 0.001	30 min 5 h 30 h	98 92 97[c]
2				**15**	1 0.1 0.001	1 min 2 h 40 h	99 92 88[c]
3				**8**	1 0.1 0.01	1 h 12 h 10 h	97 85 99[c]
4				**12**	1 0.1 0.01	1.5 h 20 h 15 h	97 85 97[c]
5				**14**	1 0.1 0.01	2 h 20 h 12 h	100 85 96[c]
6				**5**	1 0.1 0.01	1.5 h 22 h 10 h	97 98 93[c]

[a] Reaction conditions: aryl halide (1 mmol), amine (1.1 mmol), [(SIPr)Pd(cin)Cl] **Pd4** (1 - 0.001 mol %), KO-*t*-Bu (1.1 mmol), DME (1 mL).
[b] GC yields based on hexamethylbenzene as internal standard, average of two runs. [c] T = 80°C.

The reaction between morpholine and the sterically hindered bromomesitylene (Entry 1) can be conducted at room temperature with only 0.1 mol % catalyst reaching completion in a few hours. Moreover, with 10 ppm catalyst the reaction reached completion at 80 °C after 30 hours, providing a turnover number (TON) of 97 000, the highest observed to date for this type of substrate. The same trend was observed with a primary amine (Entry 2) that could be coupled with as low as 10 ppm of **Pd4**, providing a TON of 88 000. Interestingly, even strongly deactivated aryl chlorides (Entries 4 and 5) reacted with dibutylamine to yield in reasonable reaction times the corresponding arylamine with as low

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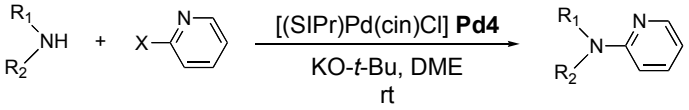
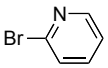
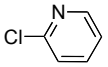
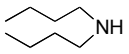
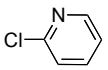
as 0.01 mol % catalyst. The extremely bulky 2,6-diisopropylaniline, reacted with a di-*ortho*-substituted aryl chloride in only 10 hours with 100 ppm of catalyst at 80°C (Entry 6).

Heteroaromatic halides

Similarly to all-carbon aryl halides, the very rapid reactions observed for a wide array of heteroaromatic halides naturally led us to examine the effect of reducing the catalyst loading (Table 15).

Table 15. Amination of 2-halopyridines at low catalyst loading[a]



Entry	Amine	Ar–X	Cat. loading (mol %)	Time	Yield(%)[b]
1			1	1 min	99
2			0.1	2 min	93
3			0.001	50 h	97
4[c]			0.001	12 h	91
5			1	1 min	100
6			0.1	5 min	93
7			0.001	48 h	95
8[c]			0.001	20 h	94
9			1	15 min	98
10			0.1	1 h	99
11			0.001	50 h	73
12[c]			0.001	40 h	93

[a] Reaction conditions: halopyridine (1 mmol), amine (1.1 mmol), KO-*t*-Bu (1.1 mmol), DME (1 mL).[b] GC yields (hexamethylbenzene as internal standard) average of two runs. [c] T = 80 ºC.

In a first attempt, we observed that the reaction between morpholine and 2-bromopyridine (Table 15, entry 2) can be conducted at room temperature with a catalyst loading of only 0.1 mol %; the reaction reaches completion in 2 minutes, corresponding to a turnover frequency (TOF) of 27 900 h^{-1}. Moreover, with a 10 ppm catalyst loading the reaction reached completion at room temperature but required 50 hours (Entry 3), providing a turnover number (TON) of 97 000. Remarkably, the reaction time could be reduced by a factor of 4 if the temperature was raised to 80 °C (Entry 4).

2-Chloropyridine reacted also very rapidly with morpholine with 0.1 mol % of pre-catalyst (Entry 6, TOF = 11 160 h^{-1}). A TON of 95 000 was obtained when 10 ppm catalyst were used (Entry 7). This TON value is quite similar to the one recently reported by

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Hartwig.[191a] Finally, we carried out the reaction between 2-chloropyridine and dibutylamine. Strikingly, even with this sterically demanding amine, high TON values were obtained at room temperature and at 80ºC (73 000 and 93 000 respectively, entries 11 and 12). It is of note that a literature search revealed that this particular coupling had been carried out with the corresponding bromide prior to the present study and required elevated temperatures (80ºC) and high catalyst loading (2-3 mol %).[196]

D. Concluding remark

In summary, we have shown how simple modifications of the scaffold surrounding palladium allow for dramatic changes in catalytic performance.[197]

We have synthesized, in a very straightforward manner, a family of new air- and moisture-stable Pd^{II} pre-catalysts derived from [(NHC)Pd(allyl)Cl] where the allyl moiety is substituted. As shown by X-ray studies, substitution at the terminal position of the allyl moiety increases the dissymmetry of the allyl scaffold bound to the palladium. This induces a more facile activation step, from Pd^{II} to Pd^0, for the new complexes. The ease of activation is then translated in a high catalytic activity even at room temperature.

Therefore, [(SIPr)Pd(cinnamyl)Cl] **Pd4** can perform the Buchwald-Hartwig coupling reaction of a wide range of amines with aryl chlorides at room temperature in minutes (only one minute for some substrates). We have also presented examples of couplings of heteroaromatic bromides and chlorides with amines at room temperature proceeding in extremely short reaction times. When the reaction temperature was raised to 80°C, this system could be effective with as low as 10 ppm of catalyst, providing the highest turnover numbers to date in this field.

As added advantages, complexes **Pd1**-**Pd4** are air- and moisture-stable and can be prepared in multigram quantities in high yields.

[196] (a) Marcoux, J.-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568–1569. (b) Urgaonkar, S.; Xu, J.-H.; Verkade, G. J. *J. Org. Chem.* **2003**, *68*, 8416–8423.
[197] Fairlamb and co-workers reported on a similar effect for η^2-dba complexes of Pd^0: Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435–4438.

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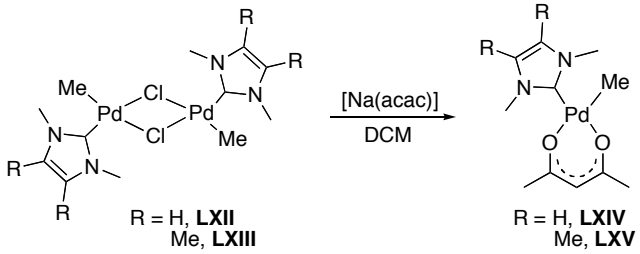
III. [(NHC)Pd(R-acac)Cl] Pre-catalysts[198,199,200]

A. Preliminary results

As mentioned in the Objectives of this Ph.D. (see Introduction, section **VI**), another goal of our research effort towards efficient Pd-based catalytic systems for cross-coupling reactions was the development of pre-catalysts that would be synthesized in an extremely straightforward manner.

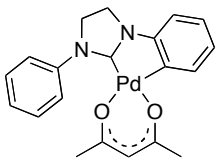
In the laboratory, several well-defined palladium(II) systems have been developed from simple Pd precursors such as $PdCl_2$ and $[Pd(OAc)_2]$.[146,165] The synthesis of most of these complexes is directly related to successful *in situ* systems involving the use of NHC and the corresponding palladium source. Our laboratory notably reported on a catalytic system for the Heck reaction involving the use of diazabutadiene ligands in conjunction with $[Pd(OAc)_2]$ or $[Pd(acac)_2]$ as palladium precursors.[201] Therefore, we decided to test whether using $[Pd(acac)_2]$ as starting material would lead to well-defined NHC–palladium species.

Well-defined [Pd(acac)LL'], where L or L' is a NHC are scarce. In 1998, Cavell and co-workers reported the synthesis of complexes **LXIV** and **LXV** from the reaction of the corresponding chloro-bridged dimer **LXII** and **LXIII** with sodium acac (Eq 27).[150]



(27)

While the catalytic activity of **LXV** was not examined, **LXIV** was tested in the Heck reaction of 4-bromoacetophenone and butylacrylate and demonstrated a promising potential, displaying a TON value of 74500. Of note, as early as 1980, Hiraki and Onishi reported the synthesis of palladacycle **LXVI**, the first NHC–Pd(acac) species.[202] Unfortunately, the authors did not perform any catalytic tests.



LXVI

[198] Navarro, O.; Marion, N.; Scott, N. M.; Gonzalez, J.; Amoroso, D.; Bell, A.; Nolan, S. P. *Tetrahedron* **2005**, *61*, 9716–9722.
[199] Marion, N.; Ecarnot, E. C.; Navarro, O.; Amoroso, D.; Bell, A.; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 3816–3821.
[200] Marion, N.; de Frémont, P.; Puijk, I. M.; Ecarnot, E. C.; Amoroso, D.; Bell, A.; Nolan, S. P. *Adv. Synth. Catal.* **2007**, *349*, 2380–2384.
[201] Grasa, G. A.; Singh, R.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2003**, *687*, 269–279.
[202] Hiraki, K.; Sugino, K.; Onishi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1976–1981.

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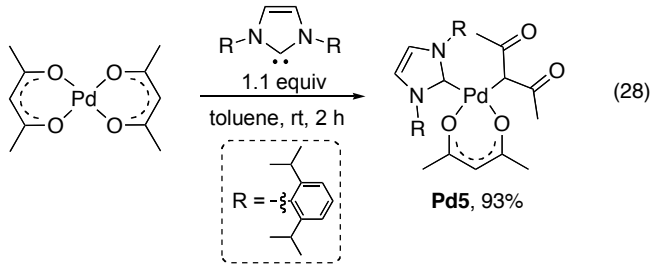
B. Synthesis of [(NHC)Pd(acac)Cl]

1. Free-NHC synthesis of [(NHC)Pd(acac)Cl]

Isolation of [(IPr)Pd(acac)$_2$]

We first carried out a direct reaction between free carbene IPr, present in a slight excess, and [Pd(acac)$_2$] at room temperature in dry toluene, which yielded a yellow powder. Relying on the analysis of both ^{1}H and ^{13}C NMR data, and with the help of a similar procedure performed with PPh_3 instead of IPr, we realized that we had synthesized a NHC-bearing analogue of the previously reported [(PPh_3)Pd{η^1-*C*-(acac)}{κ^2-*O*,*O*-(acac)}],[203] namely [(IPr)Pd{η^1-*C*-(acac)}{κ^2-*O*,*O*-(acac)}] **Pd5** (Eq 28).



(28)

The presence of one oxygen-chelating ligand and one *C*-bound ligand in the complex was apparent by both ^{13}C and ^{1}H NMR. In the ^{13}C NMR spectrum, six different signals above 160 ppm were observed at δ (ppm) = 207.5 (*C*-bound acac), 192.9, 188.1, 185.6, 183.3 (carbonyl carbons) and 161.2 (carbenic carbon). In the ^{1}H NMR spectrum, four methyl-proton singlet signals were observed at δ (ppm) = 2.63, 2.01, 1.63 and 1.31, together with two signals at δ (ppm) = 5.90 and 4.78. The lowest-field methyl peaks were assigned to the carbon-bonded acac, together with the lowest-field methenic hydrogen, while the other three signals were assigned to the oxygen-chelating ligand. It is of note that the PPh_3 analogue showed only one peak for the methyls of the carbon bound acac ligand, due to free rotation.[204] Clearly, the sterically demanding NHC ligand in **Pd5** inhibits this rotation. The disposition of the ligands was unequivocally assigned when the crystal structure was resolved by X-ray diffraction (Figure 18). A square planar configuration around the palladium center can be observed, with nearly no distortion. As expected, the Pd–C^{NHC} distance is in the range of a single Pd–C bond. The Pd–O bond *trans* to the NHC is elongated when compared to the other Pd–O bond due to a strong *trans* effect.

[203] (a) Baba, S.; Ogura, T.; Kawaguchi, S. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 665–668. (b) Kanda, Z.; Nakamura, Y.; Kawaguchi, S. *Chem. Lett.* **1976**, *5*, 199–200. (c) Kanda, Z.; Nakamura, Y.; Kawaguchi, S. *Inorg. Chem.* **1978**, *17*, 910–914.
[204] Horike, M.; Kai, Y.; Yasuoka, N.; Kasa, N. *J. Organomet. Chem.* **1974**, *72*, 441–451.

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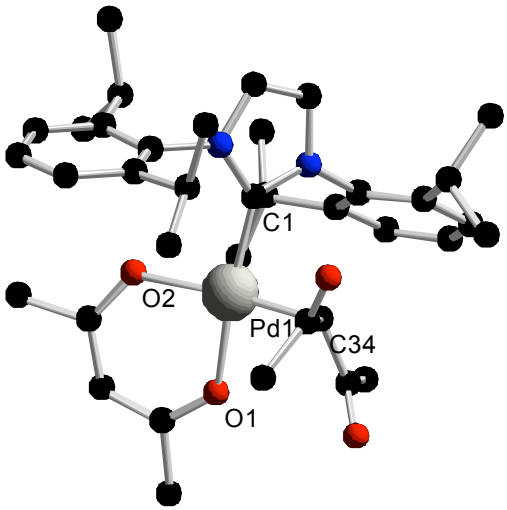
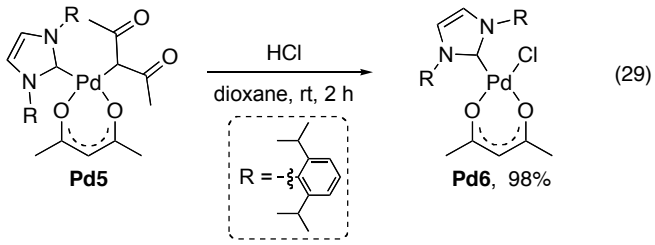


Figure 18. Ball-and-stick representation of [(IPr)Pd(acac)$_2$] **Pd5** (hydrogen atoms are omitted for clarity). Selected bond distances (Å): Pd(1)–C(1): 1.982(6), Pd(1)–C(34): 2.073(6), Pd(1)–O(1): 2.038(4), Pd(1)–O(2): 2.081(4). Selected angles (deg): O(2)-Pd(1)-O(1): 90.70(15), O(1)-Pd(1)-C(34): 86.4(2), C(34)-Pd(1)-C(1): 90.4(2), C(1)-Pd(1)-O(2): 93.2(2).

Reactivity of [(IPr)Pd(acac)$_2$] and synthesis of [(IPr)Pd(acac)Cl]

Kawaguchi reported on the reaction of [(PPh$_3$)Pd(acac)$_2$] with benzoyl chloride yielding [(PPh$_3$)Pd(acac)Cl]. For the formation of this mono-acac palladium species, the authors proposed a sequence of oxidative addition-reductive elimination reactions.[203a] In a similar way, we reacted compound **Pd5** with one equivalent of HCl at room temperature to produce the new species [(IPr)Pd(acac)Cl] **Pd6** as a yellow powder in nearly quantitative yield (Eq 29).



(29)

The loss of the *C*-bound ligand is again clearly evidenced by NMR. In the ^{13}C NMR spectrum, only two carbonyl carbons (187.1 ppm and 184.1 ppm) and the carbenic carbon (156.4 ppm) appear. In the ^{1}H NMR spectrum, only one acac ligand can be assigned: singlet at 5.12 ppm, accounting for one hydrogen, and two methylic singlets (1.84 ppm and 1.82 ppm). Again, the structure was unequivocally determined by single crystal X-ray diffraction studies (Figure 19). For this complex, a less marked *trans* effect of the NHC is observed, the Pd–O distances differing only by 0.08 Å, whereas the square planar coordination around

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the palladium center becomes slightly more distorted.

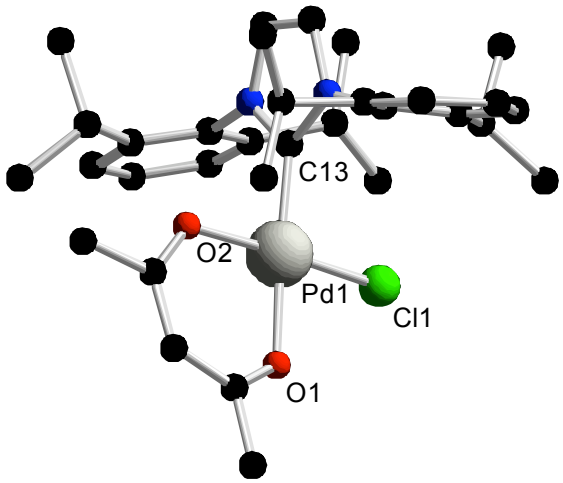
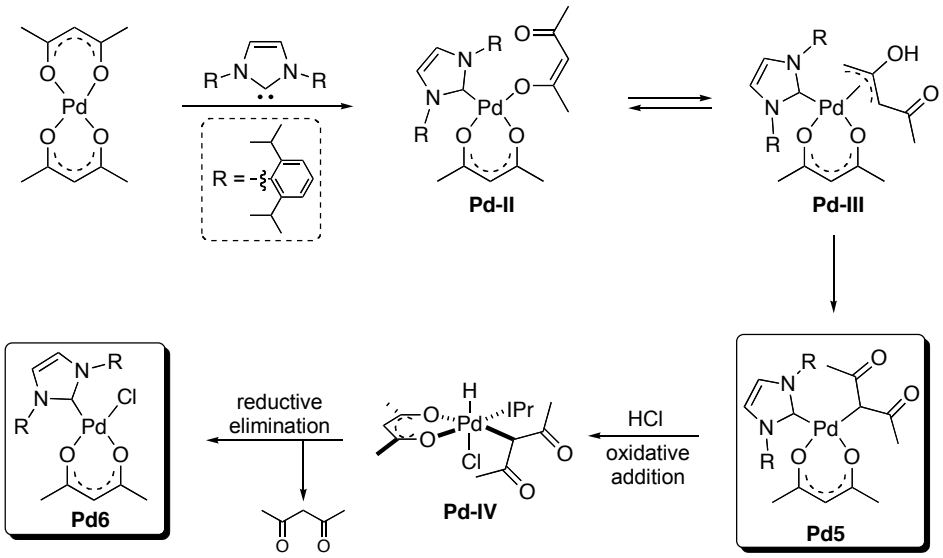


Figure 19. Ball-and-stick representation of [(IPr)Pd(acac)Cl] **Pd6** (hydrogen atoms are omitted for clarity). Selected bond distances (Å):C(13)–Pd(1): 1.9694(17), Pd(1)–O(2): 2.0362(15), Pd(1)–O(1): 2.0439(14), Pd(1)–Cl(1): 2.2820(6). Selected angles (deg): O(2)-Pd(1)-O(1): 92.89(6), O(1)-Pd(1)-Cl(1): 87.35(4), Cl(1)-Pd(1)-C(13): 93.89(5), C(13)-Pd(1)-O(2): 86.21(2).

Formation of **Pd5** and **Pd6** is postulated to occur by the pathway illustrated in Scheme 25.



Scheme 25. Proposed mechanism for the formation of **Pd5** and **Pd6**

Coordination of the sterically demanding IPr to the palladium center is accompanied by the transition of one acac ligand from the κ^2-*O*,*O*-chelate to the *O*-bound monodentate form, leading to **Pd-II**. Subsequent isomerization to the π-hydroxoallyl form of the acac ligand (**Pd-III**) would produce the η^1-*C*-bonded acac species **Pd5**. It should be noted that we

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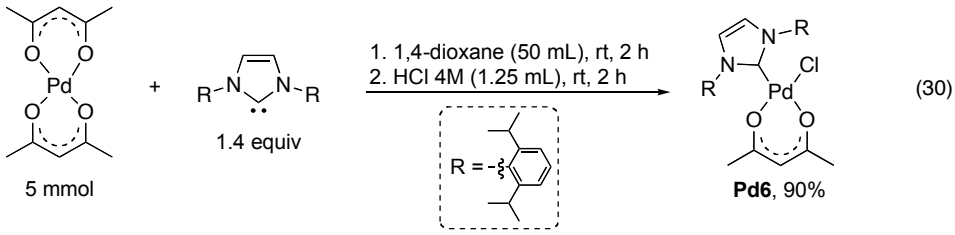
base our proposal on the pathway proposed by Shmidt for the formation of phosphine-containing analogues.[205] To further explain the formation of **Pd6** from the reaction of HCl with **Pd5**, we propose, following the Kawaguchi rationale,[203a] an oxidative addition of HCl onto **Pd5**, affording **Pd-IV**, followed by reductive elimination of acacH yielding **Pd6** (Scheme 25). Alternatively, the formation of **Pd6** from **Pd5** could be explained by protonation of the Pd–C^{acac} bond, followed by chloride coordination onto the palladium center.

One-pot synthesis of [(NHC)Pd(acac)Cl]

With the synthesis of [(IPr)Pd(acac)Cl] **Pd6** from **Pd5** in hands, we decided to investigate a possible one-pot protocol, without the need of isolating the [(IPr)Pd$(acac)_2$] intermediate. Satisfyingly, a multigram one-pot synthesis of **Pd6** was achieved in a straightforward manner, as summarized in Eq 30. Reaction of the free carbene IPr with [Pd$(acac)_2$] in dry 1,4-dioxane at room temperature, followed by the addition of an equimolecular amount of HCl, led to the formation of the desired product in high yield.



(30)

This one-pot procedure was also successfully applied to the synthesis of [(IMes)Pd(acac)Cl] **Pd7**, using free IMes ligand under similar reaction conditions. However, it should be noted that every attempt to synthesize the SIPr analogue of these complexes, [(SIPr)Pd(acac)Cl], resulted in the formation of an unidentified species that we have not been able to crystallize.

2. NHC·HCl synthesis of [(NHC)Pd(acac)Cl]

Despite the simplicity of the synthetic route leading to [(NHC)Pd(acac)Cl] complexes, it requires two steps and the isolation of the free carbene is mandatory. Our desire to design organometallic complexes with potential commercial and industrial applications prompted us to develop a synthetic route that would circumvent the aforementioned drawbacks.

[205] Shmidt, F. K.; Belykh, L. B.; Goremyka, T. V. *Russ. J. Coord. Chem.* **2002**, *28*, 199–200.

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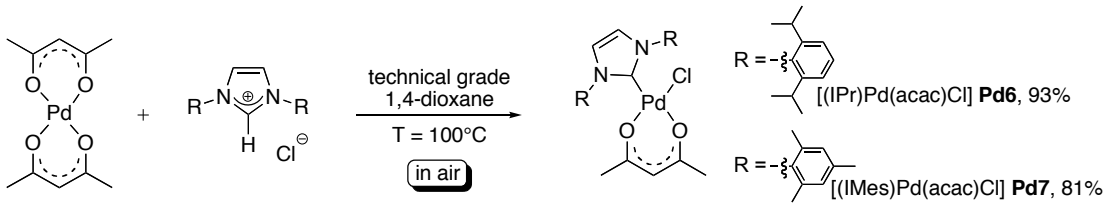
Our hypotheses for the formation of [(IPr)Pd(acac)Cl] **Pd6** involve either a NHC-coordination/HCl-oxidative addition sequence or a NHC-coordination/Pd–C^{acac}-protonation sequence. We then thought that the corresponding imidazolium chloride salt of the NHC could play the role of both the NHC and HCl.

The new synthetic pathway leading to pre-catalysts **Pd6** and **Pd7** is illustrated in Scheme 26.



Scheme 26. Improved synthesis of [(NHC)Pd(acac)Cl] **Pd6** and **Pd7**

Direct reaction of a slight excess of the imidazolium salt IPr·HCl with [$Pd(acac)_2$] in refluxing 1,4-dioxane for 44 hours led to the formation of **Pd6** in high yield (90%). Interestingly, this procedure is performed with only a slight excess of NHC·HCl salt (1.1 equiv),[206] and anhydrous conditions are not mandatory to obtain the desired complex. The reaction can be carried out in air with technical grade 1,4-dioxane with no loss of yield, when compared to anhydrous conditions. To further challenge this protocol, we carried out a *very large-scale synthesis* (from an academic laboratory point of view), starting with 7.16 g of [$Pd(acac)_2$]. Following the optimized procedure, we finally obtained 14.1 g of [(IPr)Pd(acac)Cl] **Pd6** pre-catalyst (i.e. 93% yield). It is noteworthy that with such an amount of **Pd6**, and considering cross-coupling reactions performed with 1 mol % of pre-catalyst on 1 mmol of substrate, more than 2200 reactions could be carried out.

The same protocol, albeit in shorter reaction time, can be applied to the synthesis of [(IMes)Pd(acac)Cl] **Pd7** again in very good yield (81%) starting from IMes·HCl. Complex **Pd7** has been characterized by ^1H and ^{13}C NMR spectroscopies and HRMS and its purity further established by elemental analysis. Of note, every attempt to obtain crystals of sufficient quality for X-ray diffraction studies revealed unfruitful.

Overall, this improved procedure simply requires the aerobic addition of technical grade 1,4-dioxane to a round-bottom flask previously loaded with a 1:1.1 mixture of [$Pd(acac)_2$] and NHC·HCl (both commercially available materials), followed by heating. Every manipulation can be done in air and none of the chemicals needs to be dried.

[206] We believe this is worth mentioning, considering the cost of IPr·HCl and IMes·HCl (128 €/g and 45 €/g respectively according to the 2005-2006 Aldrich catalog).

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C. Catalytic activity of [(IPr)Pd(acac)Cl] in cross-coupling

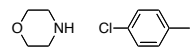
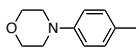
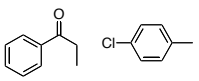
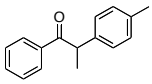
1. Pre-catalysts comparison

Optimization studies

Prior to the pre-catalysts comparison described above, we thoroughly investigated the effect of different solvents (along with concentration values) and bases on the outcome of both cross-coupling reactions using [(IPr)Pd(acac)Cl]. Optimization studies for the Buchwald-Hartwig reaction were conducted with 4-chlorotoluene and dibutylamine on 1 mmol scale at 50°C with 1 mol % of **Pd6**. THF was found almost as efficient as DME whereas toluene led to incomplete conversion. Different bases were tested and found less efficient than KO-*t*-Bu in the following order: NaO-*t*-Bu > KO-*t*-Am > KOMe ≈ NaOMe > NaOH ≈ KOH ≈ NaH. For the α-ketone arylation reaction, optimization studies were conducted with chlorobenzene and propiophenone on 1 mmol scale at 60°C with 1 mol % of **Pd6**. Toluene was the only solvent that led to a complete conversion in a short reaction time. Different bases were tested and found less efficient than NaO-*t*-Bu in the following order: KO-*t*-Bu ≈ KO-*t*-Am > KOMe ≈ NaOMe. Next, we performed the comparative studies employing the optimized reaction conditions.

We examined the activity of **Pd5**-**Pd7** in the Buchwald-Hartwig and the α-ketone arylation reactions (Table 16).

Table 16. Comparison of the activity of **Pd5**-**Pd7** in cross-coupling reactions[a]

substrates	product	[Pd]	T (°C)	time (h)	conv. (%)[b]
reaction A 	 **18**	**Pd5**	50	0.5	24
		Pd5	50	6	52
		Pd6	50	0.5	98
		Pd7	50	0.5	0
		Pd7	50	6	34
		Pd5	100	0.5	100[c]
		Pd6	100	0.5	100[c]
		Pd7	100	0.5	97[c]
reaction B 	 **37**	**Pd5**	60	1	47
		Pd5	60	6	98
		Pd6	60	1	97
		Pd7	60	1	4
		Pd7	60	6	21
		Pd5	100	0.5	94
		Pd6	100	0.5	98
		Pd7	100	0.5	87

[a] Reaction conditions: reaction A: morpholine (1.1 mmol), 4-chlorotoluene (1 mmol), **Pd5**-**Pd7** (1 mol %), KO-*t*-Bu (1.1 mmol), DME (1 mL). Reaction B: propiophenone (1.1 mmol), 4-chlorotoluene (1 mmol), **Pd5**-**Pd7** (1 mol %), NaO-*t*-Bu (1.5 mmol), toluene (1 mL). [b] GC conversions are the average of 2 runs. [c] Reaction performed in 1,4-dioxane.

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In a first approach, we clearly observed the lower activity of the IMes-bearing complex **Pd7**. Overall, the mono-acac complex **Pd6** was found more effective in both palladium-catalyzed couplings (Table 16). However, if the reaction temperature was increased, all pre-catalysts were found to have comparable performance.

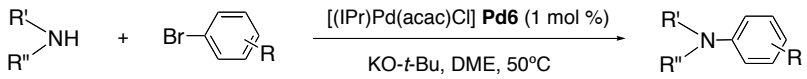
It should be added here that [(SIPr)Pd(acac)Cl] could not be included in this comparative study – even though it was likely to outperform its unsaturated counterpart **Pd6** in aryl amination – simply because we never succeeded to synthesize it. Every synthetic route discussed above was tested unsuccessfully. The reason for such a behavior of the SIPr ligand, especially compared to the IPr one, remains unclear.

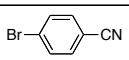
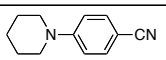
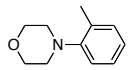
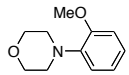
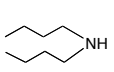
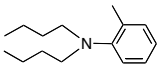
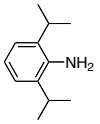
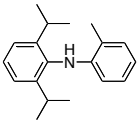
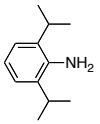
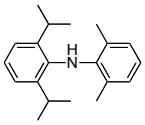
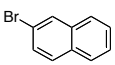
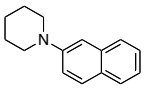
2. The Buchwald-Hartwig reaction

Aryl bromides

Results of the coupling reaction for a wide range of amines with aryl bromides are summarized in Table 17.

Table 17. *N*-Aryl amination of aryl bromides using **Pd6**[a]



Entry	Amine	Aryl bromide	Product		Time (h)	Yield (%)[b]
1				**9**	2	90
2				**6**	0.5	96
3				**8**	4	96
4				**13**	6	96
5				**17**	4	92
6				**5**	2	94
7				**27**	1.5	88

[a] Reaction conditions: aryl halide (1 mmol), amine (1.1 mmol), [(IPr)Pd(acac)Cl] **Pd6** (1 mol %), KO-*t*-Bu (1.1 mmol), DME (1 mL). [b] Isolated yields, average of two runs.

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Overall, the present catalytic system displayed good efficiency toward cyclic dialkylamines with activated (Entry 1), neutral (Entry 2) and unactivated bromides (Entry 3). In the latter entry, it is noteworthy that in addition to the unfavorable electronic effect, the *ortho*-substitution adding steric hindrance does not lead to loss of activity. Next, a secondary dialkylamine, traditionally more reluctant to be coupled, was reacted with *o*-bromotoluene in excellent yield (Entry 4). To further challenge the tolerance of **Pd6** to sterically encumbered substrate, we performed reactions with the 2,6-diisopropylaniline. Gratifyingly, tri- and even tetra-*ortho*-substituted diarylamines, **17** and **5** respectively, were obtained under mild reaction conditions (Entries 5 and 6). It is noteworthy that under the present reaction conditions (i.e. 50ºC in DME with KO-*t*-Bu) no palladium mirror was observed.[207]

Aryl chlorides

Encouraged by the promising results obtained with aryl bromides, we examined the reactivity of the less reactive aryl chlorides (Table 18). In a first approach, cyclic dialkylamines were efficiently coupled (Entries 1-3). More challenging, we found that even unactivated chlorides could be coupled with sterically hindered amine (Entry 5). As observed with the bromides, extremely encumbered substrates could be obtained in good yields in reasonable reaction times (Entries 6-8).

Finally, we were interested in the synthesis of 1- and 2-naphthylamines as a particularly valuable class of compounds. These are well-known as hole transport materials[180] or photoactive chromophores,[181] and play an important role as pharmacophore in a number of inhibitors.[184] Our catalytic system allowed a rapid coupling of this type of substrates producing naphthylamines **27**, **22**, and **24** in good yields under mild conditions (Table 17, entry 7 and table 18, entries 9 and 10).

Heteroaromatic halides

Heterocylic moieties are widely represented in biologically active molecules.[208] Therefore, heterocyclic halides and particularly heteroaromatic halides are coupling partners of great interest. Table 19 presents the results obtained with heteroaromatic bromides and chlorides. In the course of our investigations, we examined the reactivity of the present catalytic system towards *N*-, *O*- and *S*-containing heterocyclic halides.

[207] Issues on catalyst decomposition are addressed later in this chapter, see section **III.D.2**.
[208] (a) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*; Wiley: New York, NY, 1997. (b) Thomas, G. *Medicinal Chemistry*; Wiley: New York, NY, 2000.

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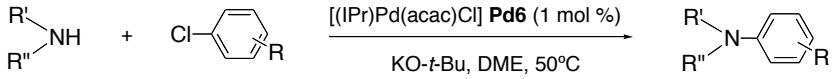
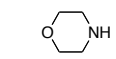
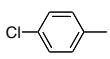
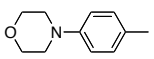
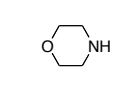
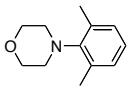
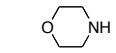
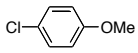
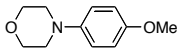
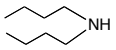
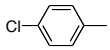
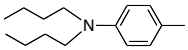
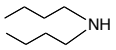
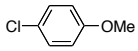
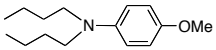
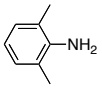
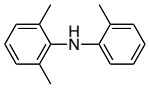
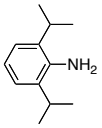
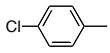
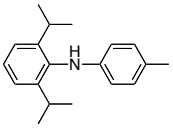
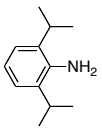
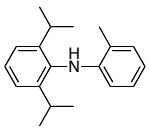
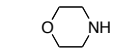
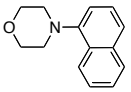
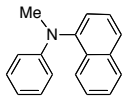
Table 18. *N*-Aryl amination of aryl chlorides using **Pd6**[a]



Entry	Amine	Aryl chloride	Product		Time (h)	Yield (%)[b]
1				**18**	0.5	97
2				**3**	1.5	90
3				**38**	4	99
4				**12**	6	95
5				**14**	4	86
6				**19**	0.5	85
7				**21**	6	97
8				**17**	4.5	89
9				**22**	2	86
10				**24**	3	95

[a] Reaction conditions: aryl halide (1 mmol), amine (1.1 mmol), [(IPr)Pd(acac)Cl] **Pd6** (1 mol %), KO-*t*Bu (1.1 mmol), DME (1 mL). [b] Isolated yields, average of two runs.

All attempts to react the two latter with diverse amines invariably failed. Higher temperature or higher catalyst loading did not improve these results. On the other hand, *N*-containing heterocyclic halides were found to be suitable coupling partners. 2-Halopyridines reacted in extremely short reaction times with secondary cyclic amines (Table 19, entries 1-3), secondary acyclic amine (Entry 7) and aniline (Entry 8). Even though reactions required longer time, the 3-halopyridine and quinoline, strongly unactivated when compared to 2-halopyridines,[193] could be coupled in high yields (Entries 4-6 and 9). Moreover, in the

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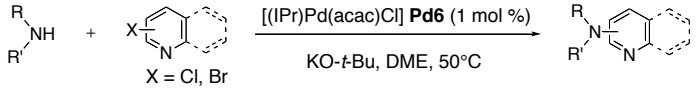
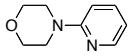
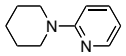
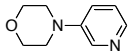
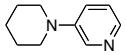
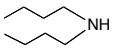
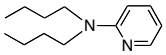
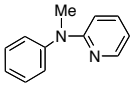
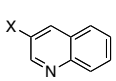
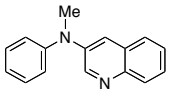
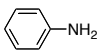
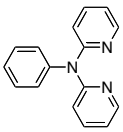
coupling of piperidine and 3-halopyridine we observed similar reaction times regardless of which halide was employed (Entries 5 and 6).

Table 19. Buchwald-Hartwig amination of heteroaromatics using **Pd6**[a]



Entry	Amine	Aryl halide	Product		X	Time (h)	Yield (%)[b]
1				**29**	Br	0.2	86
2					Cl	0.5	98
3				**30**	Cl	0.2	95
4				**4**	Cl	4	87
5				**32**	Br	3.5	79
6					Cl	4	87
7				**35**	Cl	4	86
8				**31**	Cl	4	91
9				**33**	Br	6	96
10[c]				**39**	Cl	10	93

[a] Reaction conditions: aryl halide (1 mmol), amine (1.1 mmol), [(IPr)Pd(acac)Cl] **Pd6** (1 mol %), KO-*t*-Bu (1.1 mmol), DME (1 mL). [b] Isolated yields, average of two runs. [c] 2.1 equiv of 2-chloropyridine were used.

As the synthesis of unsymmetrical tertiary amines starting with primary amines remains a challenge,[209] we investigated the reaction between aniline and 2-chloropyridine. One-pot syntheses of *N,N*-bis(2-pyridyl)amino ligands, especially with aryl chlorides,[210] are attractive due to the number of applications in which these compounds can take part: C–C bond formation,[211] homogeneous and heterogeneous catalysis,[212] DNA binding[213] and

[209] *Organic Functional Group Transformations*, Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: New York, 1995; Vol. 2, p 30.
[210] Yang, J.-S.; Lin, Y.-D.; Lin, Y.-H.; Liao, F.-L. *J. Org. Chem.* **2004**, *69*, 3517–1525.
[211] Elsevier, C. J. *Coord. Chem. Rev.* **1999**, *185–186*, 809–822.
[212] Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345.
[213] Ji, L.-N.; Zou, X.-H.; Liu, J.-G. *Coord. Chem. Rev.* **2001**, *216–217*, 513–536.

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nonlinear optical materials.[214] The formation of the double pyridilation product was observed in good yield when 2.1 equivalents of the chloride were used (Entry 10).

3. The α-ketone arylation reaction

Since pioneering work, notably by Buchwald and Hartwig,[215] palladium-catalyzed α-ketone arylation have gathered increasing interest, especially because this reaction has filled the deficiencies of "classic" organic methodology in this area.[216] Therefore, a large number of synthetic routes leading to biologically active compounds now employ these methods.[121] To further broaden the activity profile of **Pd6**, we decided to test its efficiency in the α-arylation of ketones. Despite having attracted less attention than the Buchwald-Hartwig reaction, it has benefited from its developments and has followed the same evolution. Presently, catalytic systems for the α-arylation of almost every type of enolizable compounds are available.[217] Nevertheless, only a few systems can perform well using hindered aryl chlorides.

Aryl chlorides and aryl bromides

We first attempted to carry out a reaction with the same catalytic system we used for the *N*-aryl amination reactions. Employing this procedure, the reaction between chlorobenzene and propiophenone reached completion after three hours. Further optimization studies showed that in addition to the nature of the solvent and base, the stoichiometry is crucial to the course of the reaction. When the reaction was performed with less than 1.5 equiv of NaO-*t*-Bu, either it did not reach completion or it required extended time. Attempts to run α-ketone arylation reactions at lower temperature resulted in sluggish conversions. The coupling of several ketones with different aryl chlorides and bromides was then examined (Table 20).

Remarkably, neutral and activated aryl chlorides reacted rapidly with propiophenone to yield compounds **42** and **43** (Entries 4 and 5). As expected, a less reactive ketone like α-tetralone required more time to reach full conversion (Entries 6 and 7). Next, we focused on the coupling of sterically hindered halides. *Ortho*-substituted 2-chloro- and 2-bromotoluene

[214] Di Bella, S. *Chem. Soc. Rev.* **2001**, *30*, 355–366.
[215] For early references on Pd-catalyzed α-ketone arylation, see: (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382–12383. (c) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36,* 1740–1742.
[216] For metal free-mediated formation of α-aryl ketones, see: Smith, M. B.; March, J. *Advanced Chemistry: Reactions, Mechanisms, and Structure,* 5th ed.; Wiley-Interscience: New York, NY, 2000.
[217] For a review on α-ketone arylation, see: Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245.

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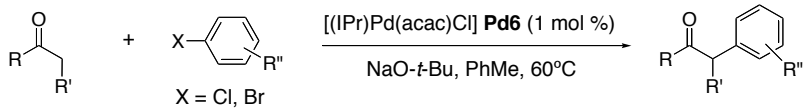
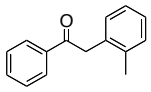
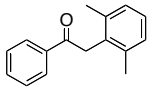
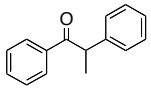
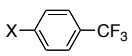
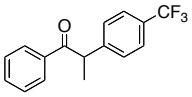
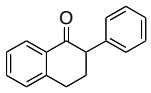
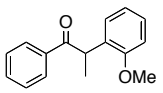
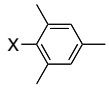
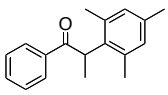
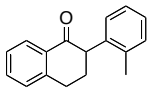
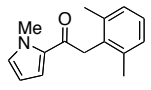
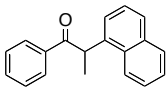
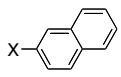
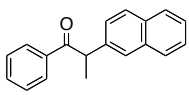
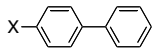
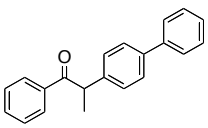
reacted efficiently with acetophenone (Entries 1 and 2) and α-tetralone (Entry 11). Even unactivated sterically demanding aryl chlorides could be coupled in relatively short time and high yields (Entry 8).

Table 20. α-Ketone arylation of aryl halides using **Pd6**[a]



Entry	Ketone	Aryl halide	Product		X	Time (h)	Yield (%)[b]
1				**40**	Cl	3.5	89
2					Br	2	90
3				**41**	Cl	2	90
4				**42**	Cl	1	98
5				**43**	Cl	0.75	93
6				**44**	Cl	4	62
7					Br	3.5	72
8				**45**	Cl	2.5	91
9					Br	1.5	83
10				**46**	Br	4.5	84
11				**47**	Br	3	87
12				**48**	Cl	3	96
13				**49**	Cl	2	96
14				**50**	Br	2	97
15				**51**	Br	1	95

[a] Reaction conditions: aryl halide (1 mmol), ketone (1.1 mmol), [(IPr)Pd(acac)Cl] **Pd6** (1 mol %), NaO-*t*-Bu (1.5 mmol), toluene (1 mL). [b] Isolated yields, average of two runs.

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Furthermore, the present catalytic system was found compatible with di-*ortho*-substituted substrates (Entries 3, 10, and 12), highlighting its high tolerance for extremely hindered substrates as we previously noticed in the Buchwald-Hartwig reaction. As an added advantage, a heteroaromatic ketone was α-arylated without loss of activity (Entry 12). Finally, we focused on the use of polyaromatic halides as coupling partners and produced three propiophenones possessing respectively the 1-naphthyl, 2-naphthyl and 4-biphenylyl moiety at the α position in near quantitative yields (Entries 13-15). Interestingly, we isolated these products without purification by column chromatography on silica gel. Taking advantage of the low solubility of the product in alkanes, a simple pentane wash followed by a filtration was sufficient to isolate pure compounds **49**-**51**. To the best of our knowledge, this is the first time that such compounds are synthesized using a Pd-catalyzed cross-coupling reaction.[218]

4. Large-scale cross-coupling reactions

We showed that **Pd6** performs efficiently in *N*-aryl amination and α-ketone arylation reactions with a variety of substrates, including unactivated aryl chlorides, hindered amines or heteroaromatic ketones. To extend further the scope of our catalytic system and make it an appealing tool for synthetic chemists at an academic or industrial level, we carried out four cross-coupling reactions on a 10-mmol scale (Table 21).

Overall, the present catalytic system was found to be highly efficient in large-scale couplings, yielding at least 88% of pure isolated arylated product. We deliberately chose challenging substrates to highlight the generality and the efficiency of the process (see Table 21). For example, two extremely hindered partners could be coupled in high yield, producing more than 2.5 g of a tetra-*ortho*-substituted diarylamine (Entry 1). Strongly unactivated heteroaromatic chlorides reacted also in high yield (Entry 2).

As an added advantage, the coupling products of both *N*-aryl amination reactions were found to be of very good purity (> 95%) by ^{1}H and ^{13}C NMR spectroscopies after a simple extraction with *tert*-butylmethyl ether followed by a filtration through a plug of Celite, therefore avoiding further purification by flash chromatography on silica gel.

[218] (a) **49** has been previously synthesized by thermolysis of benzoylbenzocycloheptene, see: Battye, P. J.; Jones, D. W. *J. Chem. Soc., Perkin Trans. 1* **1986**, *8*, 1479–1489. (b) **50** has not been reported. (c) **51** has been previously synthesized by a Friedel-Crafts/methylation sequence, see: Garcia-Garibay, M. A.; Shin, S.; Sanrame, C. N. *Tetrahedron Lett.* **2000**, *56,* 6729–6737.

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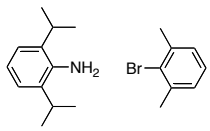
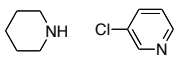
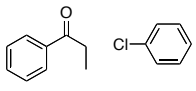
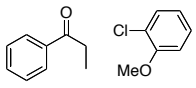
Table 21. Large-scale cross-coupling reactions using **Pd6**[a]

Entry	Substrates	Product	Time (h)	Yield (%)[b]	Amount of product (g)
1		**5**	8	92	2.58
2		**32**	4	96	1.43
3		**42**	3	93	1.95
4		**45**	6	88	2.12

[a] Reaction conditions: for entries 1 and 2: amine (10 mmol), aryl halide (10 mmol), **Pd6** (1 mol %), KO-*t*-Bu (11 mmol), DME (10 mL), 50°C. For entries 3 and 4: ketone (10 mmol,; aryl chloride (10 mmol), **Pd6** (1 mol %), NaO-*t*-Bu, 15 mmol), toluene (10 mL), 60°C. [b] Isolated yields, average of two runs.

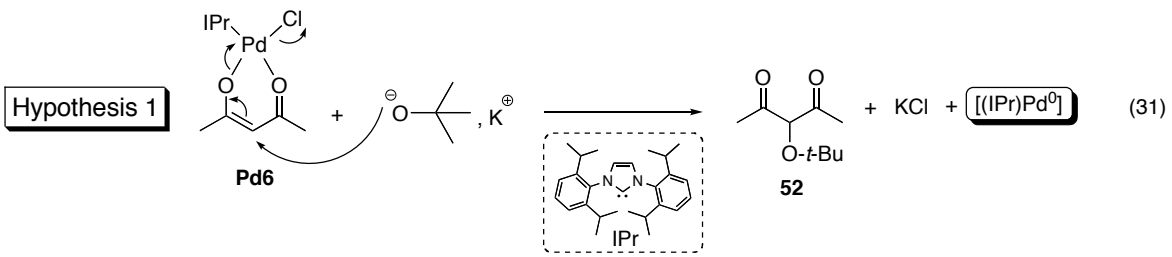
For the α-ketone arylation reactions we performed, the same trend was observed as above. Aryl chlorides, inexpensive and widely available when compared to bromides or iodides, reacted smoothly with propiophenone on a 10-mmol scale (Entries 3 and 4). Even the strongly unactivated and sterically hindered 2-chloroanisole could be coupled in near 90% yield.

D. Activation mechanism and observation of a [(NHC)Pd^0] species

As seen in section **I.A.2** of this chapter, the catalytic cycle of a cross-coupling reaction starts with a Pd^0 species. As a consequence, Pd^{II} pre-catalysts **Pd5**-**Pd7** need to be activated (i.e. reduced to Pd^0 species) under the reaction conditions.

1. Activation mechanism: hypothesis

The first hypothesis for the activation of pre-catalyst **Pd6** is described in Eq 31.



(31)

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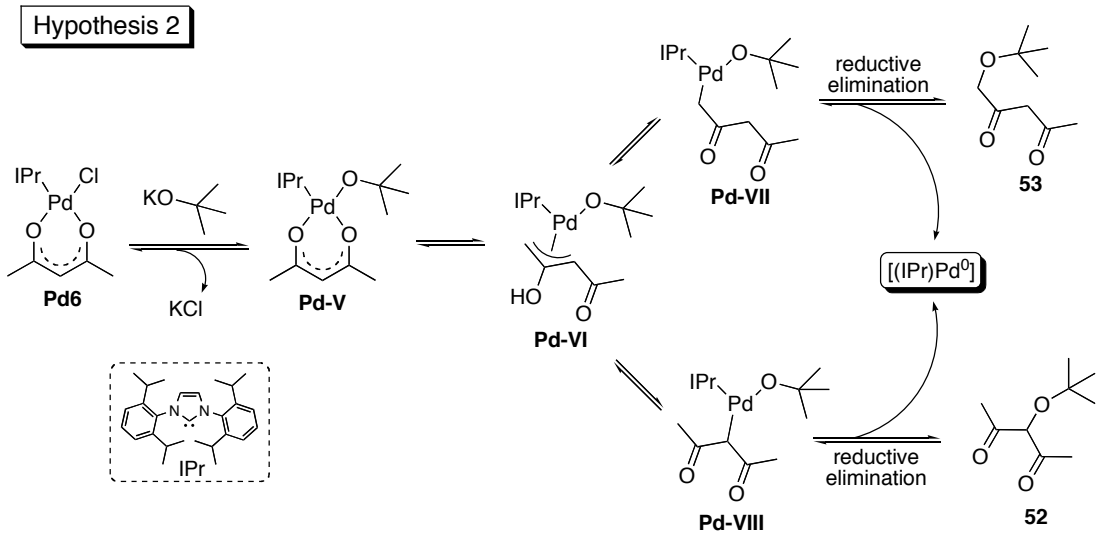
Nucleophilic attack of an alkoxide onto the bound acac ligand, accompanied by precipitation of potassium chloride, would lead to the active [(IPr)Pd^0] species.

Alternatively, anionic metathesis between the chloride on the palladium center and an alkoxide would lead to **Pd-V** (Scheme 27). Subsequent rearrangement via a π-hydroxyallyl palladium **Pd-VI** would afford *C*-bound acac ligand species, which, upon reductive elimination and C–O bond formation, would furnish the active catalyst along with **52** or **53** as a function of the preferred path. We favor the path leading to the release of diketone **52** since internal *C*-bound acac ligand, unlike external ones, have been reported.



Scheme 27. Possible pathways for the activation of **Pd6**

2. Inert atmosphere MALDI-TOF MS analysis and characterization of a monoligated 12-electron palladium(0) species

Several reports highlighting the high efficiency of the most recent generation of ligands in Pd-catalyzed cross-couplings have invoked the formation of monoligated 12-electron palladium(0) complex as the active catalysts.[219,220] Efforts aimed at isolating such species have been hampered by their high degree of unsaturation, and consequent susceptibility to decomposition and agglomeration.[221]

[219] (a) Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc*. **1995**, *117*, 5373–5374. (b) Lewis, A. K. de K.; Caddick, S.; Cloke, F. G. N.; Billingham, N. C.; Hitchcock, P. B.; Leonard, J. *J. Am. Chem. Soc*. **2003**, *125*, 10066–10073. (c) Barrios-Landeros, F.; Hartwig, J. F. *J. Am. Chem. Soc*. **2005**, *127*, 6944–6945.

[220] (a) For a review, see: ref. 157. (b) For an iconoclastic and highly interesting report proposing monoligated palladium as catalytically active species even with "traditional" ligands such as PPh_3, see: Ahlquist, M.; Fristrup, P.; Tanner, D.; Norrby, P.-O. *Organometallics* **2006**, *25*, 2066–2073.

[221] For a report on MALDI-TOF study of Pd-aggregation, see: Komano, T.; Iwasawa, T.; Tokunoga, M.; Obora, Y.; Tsuji, Y. *Org. Lett*. **2005**, *7*, 4677–4679.

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Hence, we thought of using IA MALDI-TOF MS techniques (IA MALDI-TOF MS = Inert Atmosphere Matrix-Assisted Laser Desorption/Ionisation-Time Of Flight Mass Spectrometry) to gain insights on the activation of **Pd6** and possibly be able to observe the bare [(NHC)Pd^0] catalyst. Additionally, we envisaged that insights related to catalyst decomposition might be gathered as well. To test this hypothesis, we carried out MALDI-TOF MS analysis under inert atmosphere using pyrene as the matrix.

We first analyzed an equimolar mixture of **Pd6** and KO-*t*-Bu in THF (Figure 20). Spectra were recorded at t = 0, 15 min, 24 h. Strikingly, the highly unsaturated [(IPr)Pd^0] was observed in the first two spectra, either as a single species or complexed to the matrix (pyrene). A control experiment,[222] performed without base, did not produce [(IPr)Pd^0], excluding its possible generation by fragmentation of **Pd6** and confirming the key role of the base in the activation of the pre-catalyst. This is, to the best of our knowledge, the first *direct* observation of a monoligated 12-electron palladium(0) species. These experiments have also revealed formation of the diketone **52**, consistent with the aforementioned mechanism of activation for **Pd6**.

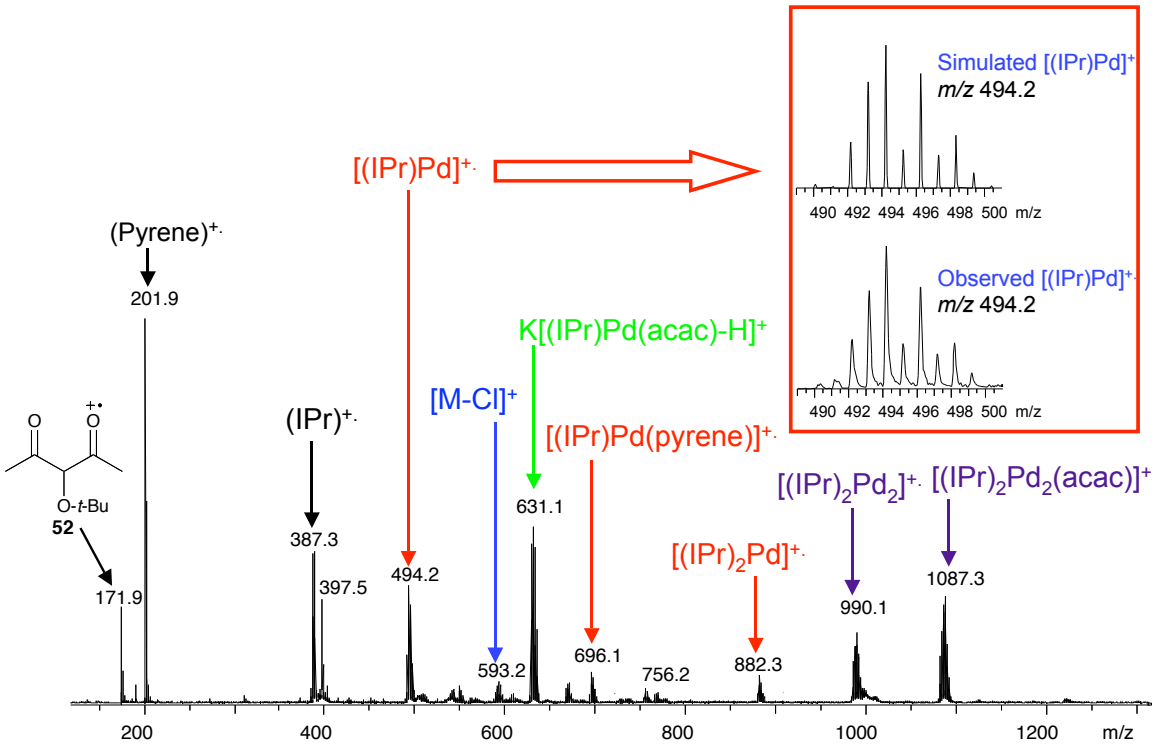

Figure 20. IA MALDI-TOF MS spectrum of [**Pd6** + 1 equiv of KO-*t*-Bu] after 15 min

Interestingly, the relative intensity of the signal for **52** increased with time, but was

[222] For the complete series of MS spectra, see the Experimental section of this chapter, section **V**.

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not observed at t_{24} (Figure 21, left). We believe this is due to an oligomerization process, which would account for our inability to isolate **52**.

We next focused on the decomposition of [(IPr)Pd^0]. Signals due to [(IPr)$_2$Pd] and [(IPr)$_2$Pd$_2$] were observed in the spectra collected at t_0 and t_{15}. Interestingly, in the t_{24} spectrum, the most abundant species is [(IPr)$_2$Pd].[223] We hypothesize that its formation results from a dynamic equilibrium between [(IPr)Pd^0], [(IPr)$_2$Pd] and NHC-containing palladium species of higher nuclearity [(IPr)$_n$Pd$_m$], in which [(IPr)$_2$Pd] is the most stable species. Aggregates of NHC-containing palladium could release free ligand and ultimately form, in a disfavored process, Pd black. This is consistent with our observation that appearance of Pd metal occurs only after several hours, [(IPr)$_2$Pd] being entirely soluble in THF. Furthermore, formation of [(IPr)$_2$Pd] may account for the prolonged catalytic activity we previously observed, this [(NHC)$_2$Pd] complex acting as a reservoir of catalytically active [(IPr)Pd^0].[224,225] The low concentration of free IPr observed is also in line with the high affinity and strong binding of N-heterocyclic carbene ligands to metals.[226]

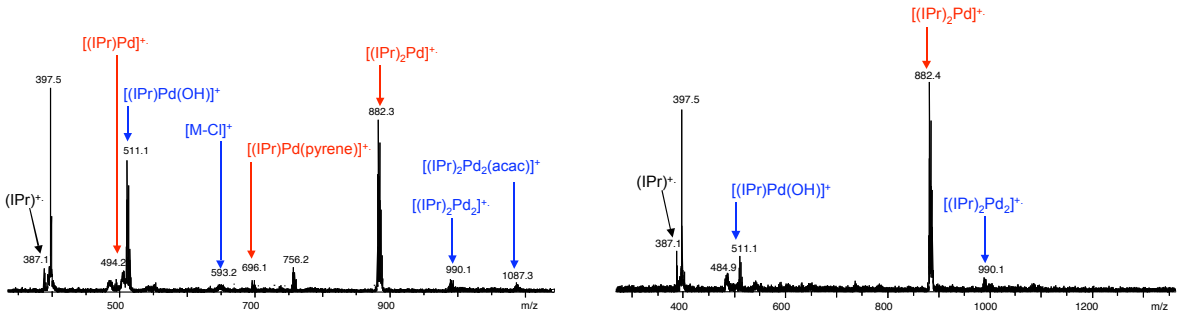

Figure 21. IA MALDI-TOF MS spectra after 24 h of [**Pd6** + 1 equiv of KO-*t*-Bu] (left) and [**Pd6** + 10 equiv of KO-*t*-Bu] (right)

Finally, we carried out an experiment with 10 equiv of KO-*t*-Bu in order to more closely mimic cross-coupling reaction conditions. No significant difference was observed (Figure 21, right), thereby validating the aforementioned observations as well as their interpretations under catalytic conditions.

[223] The formation of [(IPr)Pd(OH)], observable in the MS spectra, is attributed to the presence of residual water in KO-*t*-Bu and/or THF.
[224] [(NHC)$_2$Pd] complexes have been reported as enabling cross-coupling reactions, see for example ref. 3a and Arentsen, K; Caddick, S.; Cloke, F. G. N. *Tetrahedron* **2005**, *61*, 9710–9715.
[225] At this time, we cannot unequivocally exclude leaching of Pd^0 species from clusters of the type [(NHC)$_n$Pd$_m$] to be responsible for the catalytic activity. For more details on this hypothesis, see: (a) de Vries, A. H. M.; Mulders, J.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285–3288. (b) Thathagar, M. B.; ten Elshof, J. E.; Rothenberg, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2886–2890.
[226] Jafarpour, L.; Nolan, S. P. *Organometallics* **2000**, *19*, 2055–2057.

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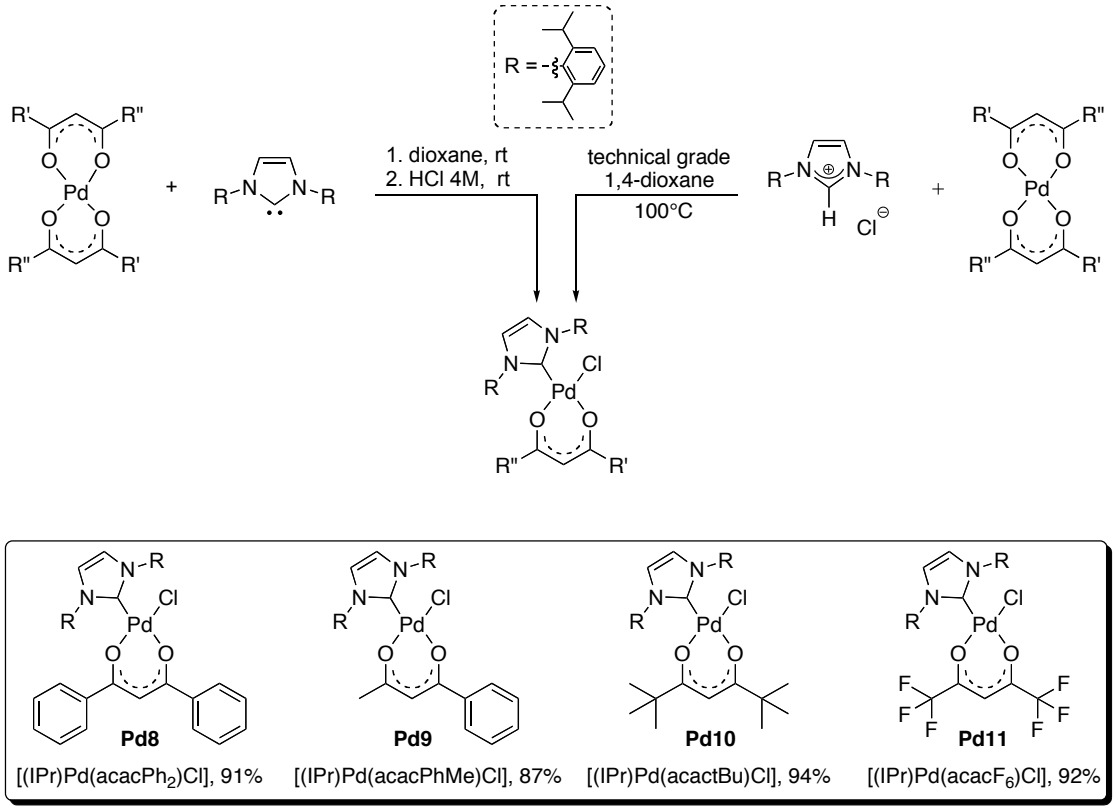
E. Synthesis and studies of [(NHC)Pd(R-acac)Cl] complexes

As presented in section **II** of this chapter, simple modifications of the surrounding ligands in Pd^{II} systems (i.e. from [(NHC)Pd(allyl)Cl] to [(NHC)Pd(cinnamyl)Cl]) can lead to enhanced catalytic performance. Hence, the success encountered with the "allyl family" encouraged us to examine the same concept with the "acac family". In addition to a possible amelioration of the catalytic activity, we thought that minute modifications in the framework of the acac ligand in [(NHC)Pd(acac)Cl] complexes could bring crucial insights regarding the activation mode of these pre-catalysts.

1. Synthesis of [(IPr)Pd(R-acac)Cl] complexes

Capitalizing on the synthetic routes developed earlier (see section **II.B** of this chapter), we synthesized several [(IPr)Pd(R-acac)Cl] derivatives employing indifferently free IPr or IPr·HCl and the corresponding [Pd(R-acac)$_2$] salt; results are summarized in Scheme 28. It should be noted that even though both routes can be used, better yields were generally obtained with the free IPr procedure.



Scheme 28. Synthesis of [(IPr)Pd(R-acac)Cl] derivatives **Pd8**-**Pd11**

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The four new complexes were fully characterized by ^{1}H and ^{13}C NMR and elemental analysis. Additionally, X-ray diffraction studies provided solid-state structures of **Pd8**, **Pd9** and **Pd10** (Figure 22). We have not been able to obtain such data for **Pd11** due to the lack of crystals of sufficient quality for crystallographic studies.

All structures display a near square planar arrangement around the palladium(II) center. Without surprise, in [(IPr)Pd(acacPhMe)Cl] **Pd9**, the only case with an unsymmetrical acac moiety, the phenyl-containing side is coordinated *trans* to the NHC and the less encumbered methyl-side is placed *cis* to the NHC, so that the steric pressure around the Pd is best accomodated.

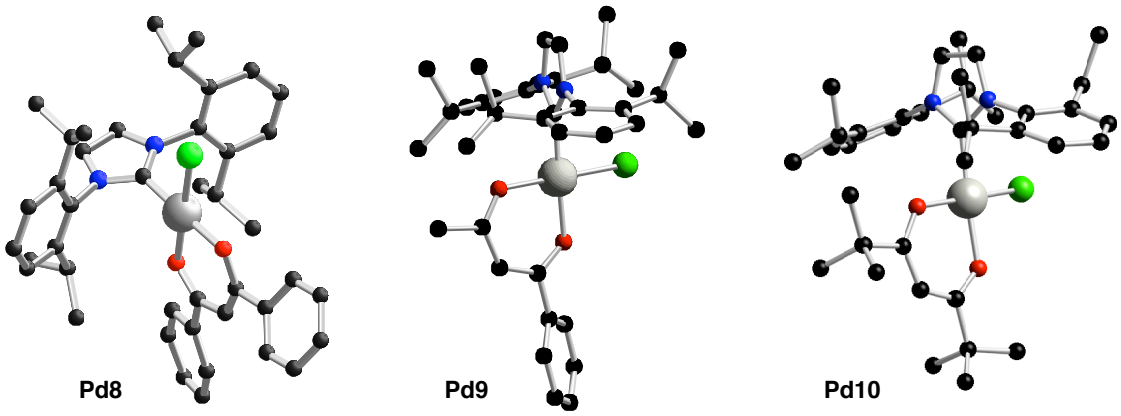

Figure 22. Ball-and-stick representations of **Pd8**-**Pd10** (hydrogen atoms are omitted for clarity)

2. Catalytic activity in the Buchwald-Hartwig reaction

Comparative study

We investigated the different catalytic activities of **Pd8**-**Pd11** in the Buchwald-Hartwig reaction and compared them with the "standard" [(IPr)Pd(acac)Cl] **Pd6**. We deliberately chose challenging coupling partners, 4-chlorotoluene and dibutylamine, so that differences in activity would be emphasized. The results obtained with **Pd8**-**Pd11** are gathered in Figure 23.

First, we observed that after 8 hours at 50ºC, [(IPr)Pd(acacF_6)Cl] **Pd11** did not yield any product.[227] When harsher conditions were tested (T = 80ºC, overnight), we did not notice any difference in reactivity. Interestingly, the apparition of Pd-black was never observed, the solution remaining pale yellow over time. These results tend to show that the active Pd^0

[227] This is in sharp contrast with the observation by Cavell and co-workers that [(IDM)Pd(acacF_3)Me] and [(IDM)Pd(acacF_6)Me] are active pre-catalysts for the Heck reaction, see ref. 150.

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species was not formed and therefore that electron-withdrawing groups inhibit the activation of the catalyst.

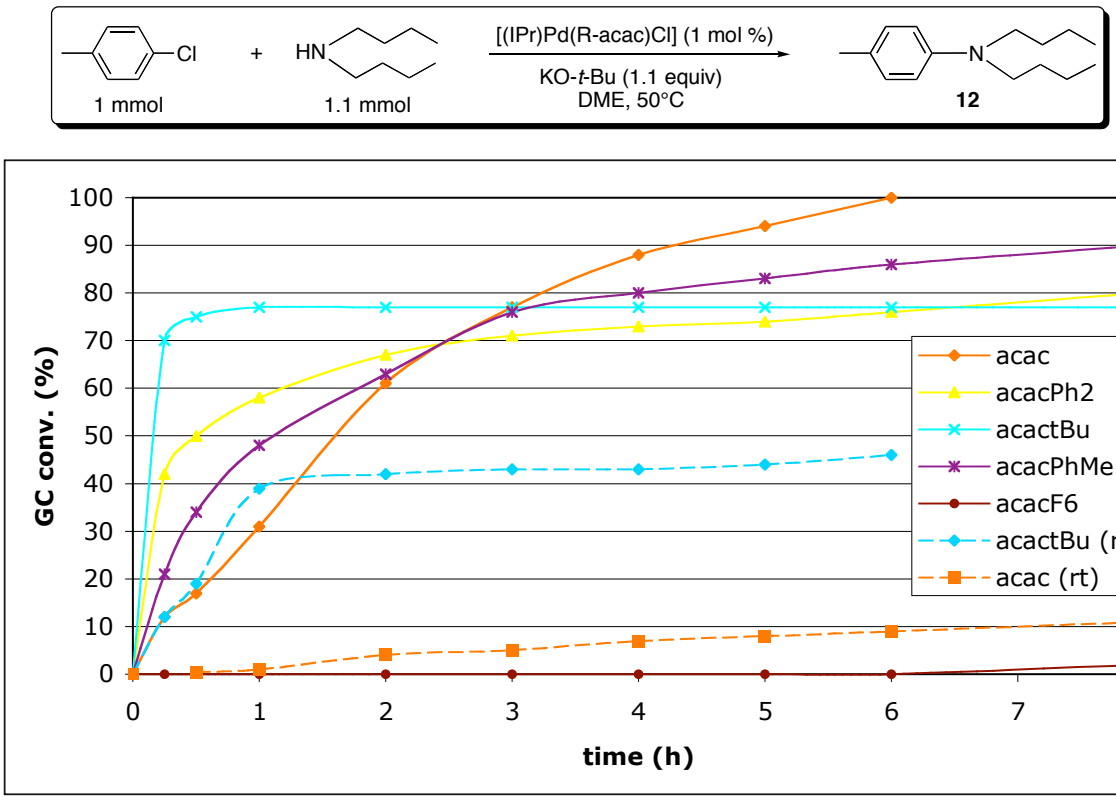

Figure 23. Reaction profile of **Pd8**-**Pd11** in an aryl amination reaction

On the contrary, [(IPr)Pd(acacPhMe)Cl] **Pd9** and [(IPr)Pd(acacPh$_2$)Cl] **Pd8** were quickly activated. After 3 hours, the reaction was almost completed but proceeded more slowly afterwards to eventually reach 70-90% conversion after 8 hours. It is interesting to notice that the activity of [(IPr)Pd(acacPhMe)Cl] **Pd9** was found to reside between that of [(IPr)Pd(acacPh$_2$)Cl] **Pd8** and the unsubstituted acac complex **Pd6**. Thus, changing the nature of the substituents has immediate consequences on the activity of the catalyst. This result is promising and could permit to combine several characteristics we observed in a rationally designed pre-catalyst.

Finally, [(IPr)Pd(acactBu)Cl] **Pd10** was extremely quickly activated. In half an hour, the reaction led to 75% conversion. Nevertheless, we did not observe further conversion after the first 30 minutes. Thus, bulkiness and electron-donating effect seem to be important factors influencing the rate of the activation.

Relevance to the activation mechanism

As discussed in section **III.D.1** of this chapter, two main rationales were envisaged

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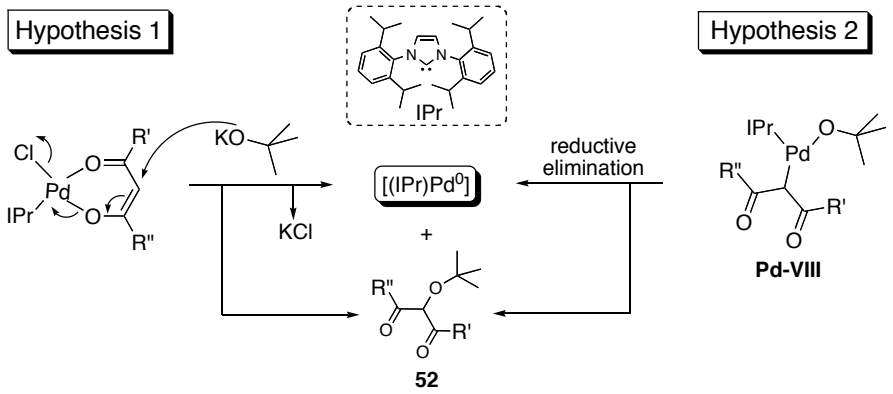
for the activation (i.e. $Pd^{II} \rightarrow Pd^{0}$) of the acac-containing compounds. The information gathered with the acac-derivatized complexes allow for refining our proposal.

Primarily, the fact that catalytic activity was observed in the presence of **Pd8** and **Pd10**, which lack hydrogens at the external position of the acac moiety, permit to exclude the intermediacy of **Pd-VII** and the formation of diketone **53** (see Scheme 27 on p 114, top path).

The steric impact of the acac substitution seems to play an important role on the activation rate. Increasing the steric hindrance, we can consider the following order: acac ≈ $acacF_6$ < acacPhMe < $acacPh_2$ < acactBu. With the exclusion of $acacF_6$, the rate of activation follows the reverse order; the bulkier the R-acac moiety, the faster the activation. This seems to favor hypothesis 2, since steric pressure around the acac would favor the reductive elimination in **Pd-VIII** (Scheme 29) whereas it would be detrimental to a direct nucleophilic attack on the acac, as postulated in hypothesis 1.



Scheme 29. Key steps for the proposed activation of [(NHC)Pd(R-acac)Cl]

Additionally, the inertness of [(IPr)Pd($acacF_6$)Cl] **Pd11**, which exhibits a similar steric environment as [(IPr)Pd(acac)Cl], raise the question of the electronic effects in the present system. Trifluoromethyl groups are clearly electron-withdrawing and therefore render the internal position of the acac moiety in **Pd11** more electrophilic. Hence, considering hypothesis 1, where nucleophilic attack at the acac internal position would occur, the $acacF_6$-containing complex should be activated more easily.

To conclude on the activation pathway for the "acac family", the observation of **52** along with the inertness of [(IPr)Pd($acacF_6$)Cl] and the high activation rate of [(IPr)Pd(acactBu)Cl] strongly support the rationale described by hypothesis 2 (see Scheme 27 on p 114) as the likely activation mechanism for the present catalytic system.

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F. Concluding Remark

In summary, a very straightforward synthesis of a valuable palladium pre-catalyst was achieved. It has allowed us to synthesize several complexes of general formulae [(NHC)Pd(R-acac)Cl], which have proven highly efficient in the Buchwald-Hartwig and the α-ketone arylation reactions. Additionally, preliminary mechanistic studies have permitted to postulate an activation pathway for these compounds.

IV. Conclusion

Overall, this work led to the synthesis of two new families of NHC-containing palladium(II) pre-catalysts, which are both highly efficient in different cross-coupling reactions.

The roots of [(NHC)Pd(R-allyl)Cl] complexes are to be found in their common precursor possessing an unsubstituted η^3-π-allyl moiety, [(NHC)Pd(allyl)Cl]. Relying on previous observations from our laboratory, we hypothesized that, by substituting the allyl moiety, an unbalance would be generated in the Pd–allyl interaction, leading to a more facile activation step. This idea was partially corroborated by the bond length differences observed in the solid-sate structures of the crotyl-, prenyl-, and cinnamyl-containing complexes we synthesized, when compared to the parent allyl. Further comparative trials in the Suzuki-Miyaura and the Buchwald-Hartwig reactions validated an easier activation step, especially at room temperature, for the substituted allyl compounds. Hence, [(SIPr)Pd(cinnamyl)Cl] can notably perform aryl amination reactions of a wide range of amines with aryl chlorides at room temperature in minutes, including heteroaromatic halides.[228] When the reaction temperature was raised to 80°C, this system could be effective with as low as 10 ppm of catalyst, providing the highest turnover numbers to date.

The synthesis of [(NHC)Pd(acac)Cl] arose from the desire of developing a practical catalytic tool for chemists in a wide sense. These studies led to the synthesis of

[228] This enhanced activity notably led to the recent use of [(IPr)Pd(cin)Cl] **Pd3** in the Suzuki-Miyaura coupling of highly functionalized aryl chlorides and perfluorooctylsulfonates at room temperature, see: Lipshutz, B. H.; Petersen, T. B.; Abela, A. R. *Org. Lett.* **2008**, *10*, 1333–1336.

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[(IPr)Pd(acac)Cl] **Pd6** from two commercially available starting materials, employing a synthetic route that requires no precaution and a simple filtration as purification step. The resulting pre-catalyst was further showed to be highly efficient in aryl amination and α-ketone arylation reactions, allowing for the coupling of unactivated chlorides and heteroaromatic halides. Following the idea we applied to the "allyl family", we further derivatized the acac moiety with different types of substitution. Examination of the catalytic activity of these [(IPr)Pd(R-acac)Cl] complexes allowed for the proposal of an activation pathway. Along the way, inert atmosphere MALDI-TOF MS studies, in addition to supporting some hypotheses regarding the activation mode of these pre-catalysts, furnished clear evidence for the existence of the highly unsaturated 12-electron species [(IPr)Pd^0] as true catalyst in these reactions.

V. Experimental section

A. General information

- All aryl halides, amines and boronic acids were used as received (Aldrich, Acros).
- Technical grade isopropanol was used to carry out catalytic reactions (Mallinckrodt Chemicals). Anhydrous 1,2-dimethoxyethane (DME), potassium *tert*-butoxide (Acros) and $[Pd(crotyl)Cl]_2$ (Strem) were stored under argon in a MBraun glovebox.
- IPr·HCl, SIPr·HCl, IMes·HCl and their corresponding free carbenes were synthesized according to literature procedures.[229]
- Dry THF was distilled over Ph_2CO/Na.
- Elemental analyses were performed at Robertson Microlit Laboratories, Inc., Madison, NJ, USA.
- ^1H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian-300 or Varian-400 MHz spectrometer at ambient temperature in $CDCl_3$, C_6D_6 or DMSO-d_6 (Cambridge Isotope Laboratories, Inc). Assignments of some ^1H and ^{13}C NMR signals rely on COSY and/or HMBC experiments.
- Flash chromatography was performed on silica gel 60 (230-400 mesh, Silicycle).

[229] For synthesis of carbenes, see: Arduengo, A. J., III; Calabrese, J. C.; Davidson, F.; Rasika Dias, H. V.; Goerlich, J. R.; Krafczyk, R.; Marshall, W. J.; Tamm, M.; Schmutzler, R. *Helv. Chim. Acta* **1999**, *82*, 2348–2364, and references therein. See also ref. 97.

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- Crystallographic data for **Pd1**-**Pd6** and **Pd8**-**Pd10** can be downloaded free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax (+44) 1223-336-033.

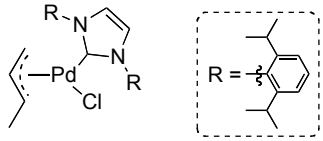
B. Synthesis of Pd complexes

1. [(NHC)Pd(R-allyl)Cl] (Pd1-Pd4)

Synthesis of [Pd(R-allyl)Cl]$_2$. *General procedure:* A 250 mL double-necked round-bottom flask, equipped with a magnetic bar, was charged with 250 mL of distilled water in which argon was bubbled for 30 min. After this time, the flask was opened under argon flow and $PdCl_2$ (10 mmol, 1.77 g, 1 equiv) and KCl (20 mmol, 1.42 g, 2 equiv) were added in turn and the flask was sealed with a rubber septum. The mixture was allowed to stir for 1 hour and an excess of the corresponding (R-allyl)Cl (30 mmol, 3 equiv) was then injected through the septum. The mixture was allowed to stir for 24 hours. Then, the reaction mixture was extracted with three portions of chloroform and the organic layers gathered, dried over $MgSO_4$, filtered and reduced to yield the corresponding dimer. The identity and purity of the dimers were confirmed by comparison with data reported in the literature. [169,230]

Synthesis of [(NHC)Pd(R-allyl)Cl] Complexes.[195] *General Procedure:* In a glovebox, a scintillation vial with a stirring bar was charged with 2.2 mmol of IPr or SIPr carbene and 15 mL of dry THF. Once dissolved, 1 mmol of the corresponding palladium dimer $[Pd(R\text{-allyl})Cl_2]_2$ was added and the mixture stirred at room temperature for 1.5 hours. Outside of the glovebox, the solvent was evaporated *in vacuo* and the remaining solid triturated with pentane and collected by filtration on a sintered frit in air. The complex was then recrystallized from DCM/pentane.

[(IPr)Pd(crotyl)Cl] (Pd1). The general procedure yielded 1.09 g (92%) of the title complex.



Pd1

[230] Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033–2046.

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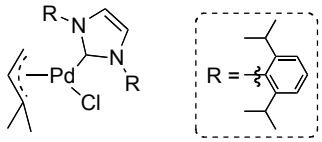
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 1.6 Hz, 4H), 7.14 (s, 2H), 4.49 (dt, *J* = 6.8, 4.8 Hz, 1H), 3.46 (sextet, *J* = 6.4 Hz, 1H), 3.06 (q, *J* = 6.8 Hz, 2H), 2.89 (q, *J* = 6.8 Hz, 2H), 2.71 (d, *J* = 6.4 Hz, 1H), 1.41 (d, *J* = 8.0 Hz, 1H), 1.35 (d, *J* = 6.8 Hz, 12H), 1.15 (d, *J* = 6.8 Hz, 6H), 1.11 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 187.0, 146.3, 146.2, 136.2, 130.0, 124.2, 124.0, 113.3, 90.2, 44.9, 28.7, 26.5, 26.0, 23.1, 17.1. **Elemental analysis** calcd. (%) for $C_{31}H_{43}ClN_2Pd$ (MW 585.56): C, 63.59; H, 7.40; N, 4.78. Found: C, 63.42; H, 7.53; N, 4.63. **CCDC-27868** contains the supplementary crystallographic data for this complex.

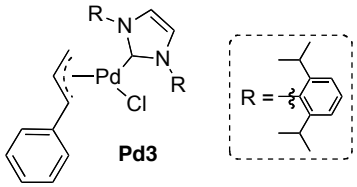
[(IPr)Pd(prenyl)Cl] (**Pd2**). The general procedure yielded 1.13 g (95%) of the title complex.



Pd2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (t, *J* = 8 Hz, 2H), 7.32 (d, *J* = 8 Hz, 4H), 7.20 (s, 2H), 4.42 (dd, *J* = 12.4, 7.2 Hz, 1H), 3.23 (q, *J* = 6.8 Hz, 2H), 2.85 (q, *J* = 6.8 Hz, 2H), 2.70 (dd, *J* = 7.2, 1.6 Hz, 1H), 1.58 (d, *J* = 8.4 Hz, 1H), 1.49 (s, 3H), 1.46 (d, *J* = 6.8 Hz, 6H), 1.36 (d, *J* = 6.8 Hz, 6H), 1.23 (d, *J* = 6.8 Hz, 6H), 1.11 (d, *J* = 6.8 Hz, 6H), 0.78 (s, 3H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 187.1, 146.4, 146.1, 136.4, 130.0, 124.1, 124.0, 123.8, 106.6, 105.7, 41.6, 28.8, 28.6, 26.8, 26.0, 23.7, 20.0. **Elemental analysis** calcd. (%) for $C_{32}H_{45}ClN_2Pd$ (MW 599.59): C, 64.10; H, 7.56; N, 4.67. Found: C, 64.36; H, 7.66; N, 4.34. **CCDC-27869** contains the supplementary crystallographic data for this complex.

[(IPr)Pd(cinnamyl)Cl] (**Pd3**). The general procedure yielded 1.10 g (85%) of the title complex.



Pd3

^{1}H NMR (C_6D_6, 400 MHz): δ 7.16 (m, 9H), 6.98 (d, *J* = 7.2 Hz, 2H), 6.64 (s, 2H), 5.07 (dd, *J* = 18.8, 6.8 Hz, 1H), 4.30 (d, *J* = 12.8 Hz, 1H), 3.31 (t, *J* = 6.4 Hz, 2H), 3.13 (t, *J* = 6.4 Hz, 2H), 3.02 (d, *J* = 6.4 Hz, 1H), 1.80 (d, *J* = 11.6, 1H), 1.46 (d, *J* = 6.4 Hz, 6H), 1.39 (d,

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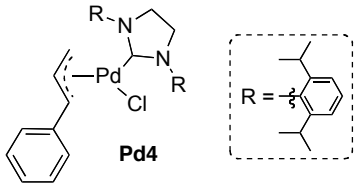
J = 6.4 Hz, 6H), 1.03 (d, *J* = 4 Hz, 12H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 185.2, 146.2, 138.1, 136.1, 130.1, 128.4, 127.5, 126.8, 124.4, 124.0, 123.9, 109.0, 90.4, 28.8, 26.2, 23.1, 46.3. **Elemental analysis** calcd. (%) for $C_{36}H_{45}ClN_2Pd$ (MW 647.63): C, 66.76; H, 7.00; N, 4.33. Found: C, 67.03; H, 7.25; N, 4.03. **CCDC-27870** contains the supplementary crystallographic data for this complex.

[(SIPr)Pd(cinnamyl)Cl] (**Pd4**). The general procedure yielded 1.06 mg (82%) of the title complex.

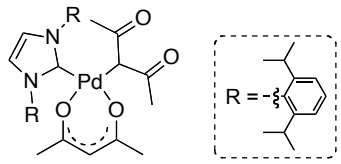


Pd4

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 8 Hz, 4H), 7.15-7.11 (m, 5H), 5.05 (dt, *J* = 12.4, 9.2, 1H), 4.34 (d, *J* = 13.2 Hz, 1H), 4.03 (s, 4H), 3.44 (broad s, 4H), 2.89 (broad s, 1H), 1.57 (broad s, 1H), 1.43 (d, *J* = 2.8 Hz, 12H), 1.27 (d, *J* = 6.8 Hz, 12H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 212.3, 147.3, 137.8, 136.6, 129.3, 128.5, 127.5, 126.9, 125.3, 124.5, 109.3, 91.9, 54.2, 46.2, 28.7, 26.8, 24.0. **Elemental analysis** calcd. (%) for $C_{36}H_{47}ClN_2Pd$ (MW 649.64): C, 66.56; H, 7.29; N, 4.31. Found: C, 66.27; H, 7.09; N, 4.13. **CCDC-27871** contains the supplementary crystallographic data for this complex.

2. [(NHC)Pd(R-acac)Cl] Pd5-Pd11

[(IPr)Pd(acac)$_2$] (**Pd5**). In a glovebox, a Schlenk flask equipped with a magnetic bar was loaded with free carbene IPr (855 mg, 2.2 mmol), [Pd(acac)$_2$] (609 mg, 2 mmol) and dry toluene (30 mL), and sealed with a rubber cap. The mixture was stirred at room temperature for two hours. Outside the glovebox, the solvent was evaporated *in vacuo* and THF (25 mL) was added. The solution was filtered and the solid washed with THF (2x5 mL). The solvent was evaporated *in vacuo*; the remaining solid was then triturated with cold pentane (25 mL) and filtered out the solution. Recrystallization in a chloroform/pentane mixture (25/75) yielded 1.28 g (93%) of the desired compound.



Pd5

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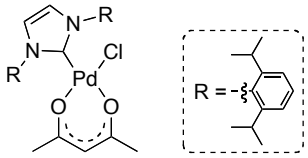
^{1}H NMR (400 MHz, C_6D_6): δ 7.28-7.24 (m, 2H), 7.18 (d, *J* = 8.0 Hz, 4H), 6.47 (s, 2H), 5.90 (s, 1H), 4.78 (s, 1H), 2.88 (q, *J* = 6.8 Hz, 4H), 2.63 (d, *J* = 0.8 Hz, 3H), 2.01 (d, *J* = 0.8 Hz, 3H), 1.63 (s, 3H), 1.35 (d, *J* = 6.8, 12H), 1.31 (s, 3H), 0.97 (d, *J* = 6.8, 12H). **^{13}C NMR (100 MHz, C_6D_6):** δ 207.5, 192.9, 188.1, 185.6, 183.3, 161.2, 146.9, 135.9, 131.2, 130.4, 125.7, 125.2, 124.7, 124.5, 104.8, 100.3, 47.2, 31.9, 31.5, 29.3, 29.0, 28.9, 28.1, 27.0, 26.5, 26.2, 25.1, 24.0, 23.8, 23.4. **Elemental analysis** calcd. (%) for $C_{37}H_{50}N_2O_4Pd$ (MW 693.22): C, 64.11; H, 7.27; N, 4.04. Found: C, 63.89; H, 7.06; N, 3.86. **CCDC-263919** contains the supplementary crystallographic data for this complex.

One-pot/free NHC synthesis of [(NHC)Pd(acac)Cl]. *General procedure:* In a glovebox, a Schlenk flask equipped with a magnetic bar was loaded with the desired free carbene (7 mmol, 1.4 equiv), [Pd(acac)$_2$] (1.53 g, 5 mmol) and dry dioxane (50 mL), and sealed with a rubber cap. The mixture was stirred at room temperature for two hours. Then, 1.25 mL of HCl 4M in dioxane were added to the solution and the mixture allowed to stir at room temperature for another 2 hours. The solvent was then evaporated *in vacuo* and diethyl ether was added until no more solid dissolved (20 mL). The mixture was filtered and the solid washed with diethyl ether (2 x 10 mL). The solvent was evaporated *in vacuo* and the powder obtained kept under vacuum overnight to yield the desired product.

[(IPr)Pd(acac)Cl] (**Pd6**). The general procedure yielded 2.80 g (90%) of the title complex.



Pd6

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (t, *J* = 7.8 Hz, 2H, H^{Ar}), 7.35 (d, *J* = 7.8 Hz, 4H, H^{Ar}), 7.12 (s, 2H, N–CH), 5.12 (s, 1H, C(O)–CH), 2.95 (septet, *J* = 6.4 Hz, 4H, C*H*$(CH_3)_2$), 1.84 (s, 3H, C(O)–CH_3), 1.82 (s, 3H, C(O)–CH_3), 1.34 (d, *J* = 6.4 Hz, 12H, CH(C*H*$_3)_2$), 1.10 (d, *J* = 6.4 Hz, 12H, CH(C*H*$_3)_2$). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 187.1 (C, C=O), 184.1 (C, C=O), 156.4 (C, N–C–N), 147.0 (C, N–C^{Ar}), 135.5 (C, C^{Ar}), 134.8 (C, C^{Ar}), 130.9 (C, C^{Ar}), 125.7 (C, C^{Ar}), 124.7 (C, C^{Ar}), 124.6 (CH, N–CH), 99.9 (CH, C(O)–*C*H), 30.0 (CH, *C*H$(CH_3)_2$), 29.1 (CH, *C*H$(CH_3)_2$), 27.6 (CH_3, C(O)–*C*H_3), 26.8 (CH_3, C(O)–*C*H_3), 23.7 (CH_3, CH(*C*H$_3)_2$), 23.5 (CH_3, CH(*C*H$_3)_2$). **Elemental analysis** calcd. (%) for

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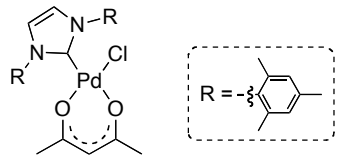
$C_{32}H_{43}ClN_2O_2Pd$ (MW 629.57): C, 61.05; H, 6.88; N, 4.45. Found: C, 60.78; H, 7.15; N, 4.29. **CCDC-263920** contains the supplementary crystallographic data for this complex.

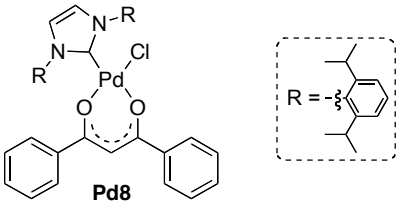
[(IMes)Pd(acac)Cl] (**Pd7**). The general procedure yielded 2.37 g (87%) of the title complex.



Pd7

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06 (s, 2H, N–CH), 7.01 (s broad, 2H, H^{Ar}), 6.97 (s broad, 2H, H^{Ar}), 5.10 (s, 1H, C(O)–CH), 2.34 (s, 6H, CH_3), 2.30 (s broad, 6H, CH_3), 2.14 (s broad, 6H, CH_3), 1.75 (s, 3H, C(O)–CH_3), 1.74 (s, 3H, C(O)–CH_3). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 187.5 (C, C=O), 183.6 (C, C=O), 154.1 (C, N–C–N), 139.6 (C, N–C^{Ar}), 137.4 (C, C^{Ar}), 136.1 (C, C^{Ar}), 135.3 (C, C^{Ar}), 130.1 (CH, C^{Ar}), 129.2 (CH, C^{Ar}), 124.2 (CH, N–CH), 100.1 (CH, C(O)–*C*H), 27.5 (CH_3, C(O)–*C*H_3), 26.0 (CH_3, C(O)–*C*H_3), 21.6 (CH_3), 19.2 (CH_3), 18.2 (CH_3). **Calcd. HRMS** for $C_{28}H_{34}N_3O_2Pd$ (M+MeCN-Cl^-): 550.1707. Found: 550.1686. **Elemental analysis** calcd. (%) for $C_{26}H_{31}ClN_2O_2Pd$ (MW 545.41): C, 57.26; H, 5.73; N, 5.14. Found: C, 57.21; H, 5.87; N, 5.11.

[(IPr)Pd(acacPh$_2$)Cl] (**Pd8**). The general procedure, using 1/3 of the reagents, yielded 1.15 g (91%) of the title complex.



Pd8

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.90 (m, 2H, H^{Ar}), 7.86-7.80 (m, 2H, H^{Ar}), 7.60-7.54 (m, 4H, H^{Ar}), 7.50-7.30 (m, 10H, H^{Ar}), 6.70 (s, 1H, C(O)–CH–C(O)), 3.42 (s broad, 2H, C*H*(CH_3)$_2$), 2.76 (s broad, 2H, C*H*(CH_3)$_2$), 1.52 (s broad, 6H, CH(C*H*$_3$)$_2$), 1.19 (d, *J* = 6.8 Hz, 12H, CH(C*H*$_3$)$_2$), 0.88 (s broad, 6H, CH(C*H*$_3$)$_2$). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 181.3 (C, C=O), 178.5 (C, C=O), 156.1 (C, N–C–N), 147.3 (C, N–C^{Ar}), 145.6 (C, N–C^{Ar}), 139.0 (C, C^{Ar}), 138.3 (C, C^{Ar}), 135.0 (C, C^{Ar}), 131.0 (CH, C^{Ar}), 130.9 (CH, C^{Ar}), 130.4 (CH, C^{Ar}), 128.1 (CH, C^{Ar}), 127.9 (CH, C^{Ar}), 127.14 (CH, C^{Ar}), 127.07 (CH, C^{Ar}), 125.6 (CH, C^{Ar}), 124.5 (CH, N–CH), 124.0 (CH, N–CH), 93.2 (CH, C(O)–*C*H–C(O)), 28.9 (CH, *C*H(CH_3)$_2$),

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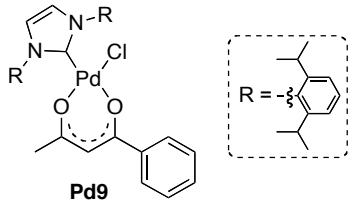
28.3 (CH, *C*H(CH_3)$_2$), 26.4 (CH_3, CH(*C*H_3)$_2$), 25.9 (CH_3, CH(*C*H_3)$_2$), 23.0 (CH_3, CH(*C*H_3)$_2$), 22.4 (CH_3, CH(*C*H_3)$_2$). **Elemental analysis** calcd. (%) for $C_{42}H_{47}ClN_2O_2Pd$ (MW 753.71): C, 66.93; H, 6.29; N, 3.72. Found: C, 66.78; H, 6.15; N, 3.79.

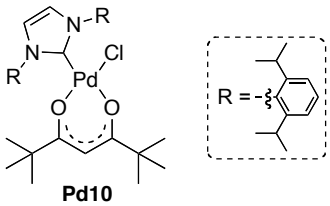
[(IPr)Pd(acacPhMe)Cl] (**Pd9**). The general procedure, using 1/3 of the reagents, yielded 1.00 g (87%) of the title complex.



Pd9

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (t, *J* = 7.8 Hz, 2H, H^{Ar}), 7.35 (d, *J* = 7.8 Hz, 4H, H^{Ar}), 7.12 (s, 2H, N–C*H*), 5.12 (s, 1H, C(O)–C*H*), 2.95 (septet, *J* = 6.4 Hz, 4H, C*H*(CH_3)$_2$), 1.84 (s, 3H, C(O)–CH_3), 1.82 (s, 3H, C(O)–CH_3), 1.34 (d, *J* = 6.4 Hz, 12H, CH(CH_3)$_2$), 1.10 (d, *J* = 6.4 Hz, 12H, CH(CH_3)$_2$). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 187.1 (C, *C*=O), 184.1 (C, *C*=O), 156.4 (C, N–*C*–N), 147.0 (C, N–*C*^{Ar}), 135.5 (C, C^{Ar}), 134.8 (C, C^{Ar}), 130.9 (C, C^{Ar}), 125.7 (C, C^{Ar}), 124.7 (C, C^{Ar}), 124.6 (CH, N–*C*H), 99.9 (CH, C(O)–*C*H), 30.0 (CH, *C*H(CH_3)$_2$), 29.1 (CH, *C*H(CH_3)$_2$), 27.6 (CH_3, C(O)–*C*H_3), 26.8 (CH_3, C(O)–*C*H_3), 23.7 (CH_3, CH(*C*H_3)$_2$), 23.5 (CH_3, CH(*C*H_3)$_2$). **Elemental analysis** calcd. (%) for $C_{37}H_{45}ClN_2O_2Pd$ (MW 691.64): C, 64.25; H, 6.56; N, 4.05. Found: C, 64.03; H, 6.35; N, 3.82.

[(IPr)Pd(acactBu)Cl] (**Pd10**). The general procedure, using 1/3 of the reagents, yielded 1.12 g (94%) of the title complex.



Pd10

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (t, *J* = 7.7 Hz, 2H, *p*-H^{Ar}), 7.37-7.33 (m, 4H, *m*-H^{Ar}), 7.09 (s, 2H, N–CH), 5.46 (s, 1H, C(O)–CH–C(O)), 3.33 (septet, *J* = 6.6 Hz, 2H, C*H*(CH_3)$_2$), 2.78 (septet, *J* = 6.1 Hz, 2H, C*H*(CH_3)$_2$), 1.44-1.31 (m, 12H, CH(CH_3)$_2$), 1.15-0.95 (m, 30H, CH(CH_3)$_2$ + C(CH_3)$_3$). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 195.2 (C, C=O), 193.4 (C, C=O), 158.0 (C, N–C–N), 147.5 (C, N–C^{Ar}), 144.9 (C, N–C^{Ar}), 135.5 (CH, C^{Ar}), 130.1 (CH, C^{Ar}), 125.6 (CH, N–CH), 124.8 (C, C^{Ar}), 123.8 (C, C^{Ar}), 91.0 (CH, C(O)–*C*H–C(O)), 41.0 (C,

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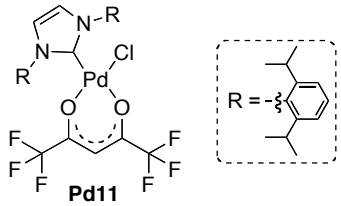
C(CH_3)$_3$), 40.6 (C, *C*(CH_3)$_3$), 28.9 (CH_3, C(*C*H_3)$_3$), 28.7 (CH, *C*H(CH_3)$_2$), 28.4 (CH_3, C(*C*H_3)$_3$), 28.0 (CH, *C*H(CH_3)$_2$), 26.4 (CH_3, CH(*C*H_3)$_2$), 25.7 (CH_3, CH(*C*H_3)$_2$), 23.5 (CH_3, CH(*C*H_3)$_2$), 23.3 (CH_3, CH(*C*H_3)$_2$). **Elemental analysis** calcd. (%) for $C_{38}H_{55}ClN_2O_2Pd$ (MW 713.73): C, 63.95; H, 7.77; N, 3.92. Found: C, 63.99; H, 7.55; N, 3.81.

[(IPr)Pd(acacF_6)Cl] (**Pd11**). The general procedure, using 1/3 of the reagents, yielded 1.16 g (92%) of the title complex.



Pd11

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1H, C(O)–CH–C(O)), 7.73 (s, 2H, N–CH), 7.58 (t, *J* = 7.8 Hz, 2H, *p*-H^{Ar}), 7.36 (d, *J* = 7.8 Hz, 4H, *m*-H^{Ar}), 2.39 (septet, *J* = 6.8 Hz, 4H, C*H*(CH_3)$_2$), 1.25 (d, *J* = 6.8 Hz, 12H, CH(C*H*$_3$)$_2$), 1.18 (d, *J* = 6.8 Hz, 12H, CH(C*H*$_3$)$_2$). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 149.2, 146.8, 144.8, 137.9, 137.3, 134.9, 132.4, 129.4, 126.0, 124.8, 49.4, 29.1, 26.9, 24.3, 23.6. **Elemental analysis** calcd. (%) for $C_{32}H_{37}ClF_6N_2O_2Pd$ (MW 737.51): C, 52.11; H, 5.06; N, 3.80. Found: C, 52.18; H, 5.15; N: 4.09.

One-pot/NHC·HCl synthesis of [(NHC)Pd(acac)Cl].

[(IPr)Pd(acac)Cl] (**Pd6**): In a round-bottom flask equipped with a magnetic stir bar and a condenser, [Pd(acac)$_2$] (0.716 g, 2.35 mmol), IPr·HCl (1.10 g, 2.59 mmol) and technical grade 1,4-dioxane (15 mL) were loaded and the reaction mixture was refluxed for 44 hours. The solvent was then evaporated *in vacuo* and diethyl ether was added. The resulting mixture was filtered over a plug of Celite to afford a clear yellow solution. Ether was removed and the orange/yellow powder obtained was washed with pentane and dried under vacuum, affording the desired complex as a pale yellow powder. Yield: 1.36 g (90%).

Large-scale synthesis of [(IPr)Pd(acac)Cl] (**Pd6**): In a round-bottom flask equipped with a magnetic stir bar and a condenser, [Pd(acac)$_2$] (7.16 g, 23.50 mmol), IPr·HCl (11.00 g, 25.85 mmol) and technical grade 1,4-dioxane (150 mL) were loaded and the reaction mixture was refluxed for 44 hours. The solvent was then evaporated *in vacuo* and diethyl ether was added. The resulting mixture was filtered over a plug of Celite to afford a clear yellow solution. Ether was removed and the orange/yellow powder obtained was washed

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with pentane and dried under vacuum, affording the desired complex as a pale yellow powder. Yield: 14.1 g (93%).

[(IMes)Pd(acac)Cl] (**Pd7**): In a round-bottom flask equipped with a magnetic stir bar and a condenser, [Pd(acac)$_2$] (0.89 g, 2.93 mmol), IMes·HCl (1.00 g, 2.93 mmol) and technical grade 1,4-dioxane (15 mL) were loaded and the reaction mixture was refluxed for 24 hours. 1,4-Dioxane was then evaporated in vacuo and cold diethyl ether was added leading to the formation of a yellow precipitate. The mixture was filtered over a plug of silica (immobilizing the precipitate) and washed with cold diethylether until the solvent came through colorless. The filtrate was discarded and the plug of silica was washed with dichloromethane affording a bright yellow solution. After evaporation of the DCM, the desired complex was obtained as a yellow powder. Yield: 1.34 g (81%).

C. Cross-coupling reactions using [(NHC)Pd(R-allyl)Cl]

1. Comparative study of [(NHC)Pd(R-allyl)Cl]

General procedure for the Suzuki-Miyaura reactions: In a glovebox, a [Pd] pre-catalyst (0.01 mmol), potassium *tert*-butoxide (1.1 mmol, 124 mg), boronic acid (1.05 mmol) and aryl halide (if solid, otherwise *vide infra*) were added in turn to a vial equipped with a magnetic bar, and closed with a screw cap fitted with a septum. Outside the glovebox, degassed technical grade 2-propanol (1 mL) was added. The mixture was then stirred at room temperature unless indicated otherwise. After 15 min, the aryl halide (1 mmol) was injected (if liquid) and the reaction was monitored by gas chromatography. Reported GC conversions are the average of at least two runs.

General procedure for the Buchwald-Hartwig reactions: In a glovebox, a [Pd] pre-catalyst (0.01 mmol), potassium *tert*-butoxide (1.1 mmol, 124 mg) and anhydrous dimethoxyethane (DME) (1 mL) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the glovebox, the amine (1.1 mmol) and the aryl halide (1 mmol) were injected in turn through the septum. If one of the two starting materials was a solid, it was added to the vial inside the glovebox and DME and the second starting material were added outside the glovebox. The reaction mixture was then stirred at the room temperature unless indicated otherwise and the conversion of the reaction

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followed by gas chromatography. Reported GC conversions are the average of at least two runs.

2. General procedure for the Buchwald-Hartwig reactions using [(SIPr)Pd(cin)Cl]

General procedure: In a glovebox, [(SIPr)Pd(cin)Cl] **Pd4** (0.01 mmol, 6.5 mg), potassium *tert*-butoxide (1.1 mmol, 124 mg) and anhydrous DME (1 mL) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the glovebox, the amine (1.1 mmol) and the aryl halide (1 mmol) were injected in turn through the septum. If one of the two starting materials was a solid, it was added to the vial inside the glovebox and DME and the second starting material were added outside the glovebox. The reaction mixture was then stirred at the required temperature. When the reaction reached completion, or no further conversion could be observed by gas chromatography, water was added to the reaction mixture, the organic layer was extracted with *tert*-butylmethyl ether (MTBE), dried over magnesium sulfate and the solvent was evaporated *in vacuo*. When necessary the product was purified by flash chromatography on silica gel. The reported yields are the average of at least two runs.

3. General procedure for the Buchwald-Hartwig reactions at low catalyst loadings

Preparation of catalyst solutions: In a glovebox, in a scintillation vial, 6.5 mg (0.01 mmol) of [(SIPr)Pd(cinnamyl)Cl] **Pd4** were dissolved in 10 mL of DME, providing solution A. In another vial, 9 mL of DME were added to 1 mL of solution A, providing solution B. A third vial containing 1 mL of solution B and 9 mL of DME provided solution C.

General procedure: In a glovebox, potassium *tert*-butoxide (1.1 mmol, 124 mg), hexamethylbenzene (1 mmol, 162 mg) and 1 mL of catalyst solution (solution A for 0.1 mol % of **Pd4**, solution C for 0.001 mol % of **Pd4**) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the glovebox, the amine (1.1 mmol) and the aryl halide (1 mmol) were injected in turn through the septum. The reaction mixture was then stirred at room temperature unless otherwise indicated. The reaction was monitored by gas chromatography and the yields given using hexamethylbenzene as internal standard.

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D. Cross-coupling reactions using [(NHC)Pd(R-acac)Cl]

1. Comparative study of [(NHC)Pd(R-acac)Cl]

General procedure for the Buchwald-Hartwig reactions: In a glovebox, a [Pd] pre-catalyst (0.01 mmol), potassium *tert*-butoxide (1.1 mmol, 124 mg) and anhydrous dimethoxyethane (DME) (1 mL) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the glovebox, the amine (1.1 mmol) and the aryl halide (1 mmol) were injected in turn through the septum. If one of the two starting materials was a solid, it was added to the vial inside the glovebox and DME and the second starting material were added outside the glovebox. The reaction mixture was then stirred at the required temperature and the reaction was monitored by gas chromatography.

General procedure for the α-ketone arylation reactions: In a glovebox, a [Pd] pre-catalyst (0.01 mmol), sodium *tert*-butoxide (1.5 mmol, 144 mg) and anhydrous toluene (1 mL) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the glovebox, the ketone (1.1 mmol) and the aryl halide (1 mmol) were injected in turn through the septum. If one of the two starting materials was a solid, it was added to the vial inside the glovebox and toluene and the second starting material were added outside the glovebox. The reaction mixture was then stirred at the required temperature, and the reaction was monitored by gas chromatography.

2. General procedure for the Buchwald-Hartwig reactions using [(IPr)Pd(acac)Cl]

General procedure: In a glovebox, [(IPr)Pd(acac)Cl] **Pd6** (0.01 mmol, 6.3 mg), potassium *tert*-butoxide (1.1 mmol, 124 mg) and anhydrous dimethoxyethane (DME) (1 mL) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the glovebox, the amine (1.1 mmol) and the aryl halide (1 mmol) were injected in turn through the septum. If one of the two starting materials was a solid, it was added to the vial inside the glovebox and DME and the second starting material were added outside the glovebox under argon. The reaction mixture was then stirred at 50ºC. When the reaction reached completion, or no further conversion could be observed by gas chromatography, water was added to the reaction mixture, the organic layer was extracted with *tert*-butylmethyl ether (MTBE), dried over magnesium sulfate and the solvent was evaporated *in vacuo*. When necessary the product was purified by flash chromatography on silica gel. The reported yields are the average of at least two runs.

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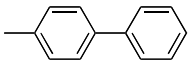
3. General procedure for the α-ketone-arylation reactions using [(IPr)Pd(acac)Cl]

General procedure: In a glovebox, [(IPr)Pd(acac)Cl] **Pd6** (0.01 mmol, 6.3 mg), sodium *tert*-butoxide (1.5 mmol, 144 mg) and anhydrous toluene (1 mL) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the glovebox, the ketone (1.1 mmol) and the aryl halide (1 mmol) were injected in turn through the septum. If one of the two starting materials was a solid, it was added to the vial inside the glovebox and toluene and the second starting material were added outside the glovebox. The reaction mixture was then stirred at 60ºC. When the reaction reached completion, or no further conversion could be observed by gas chromatography, water was added to the reaction mixture, the organic layer was extracted with *tert*-butylmethyl ether (MTBE), dried over magnesium sulfate and the solvent was evaporated *in vacuo*. When necessary the product was purified by flash chromatography on silica gel. The reported yields are the average of at least two runs.

E. Characterization of cross-coupling products 1-51

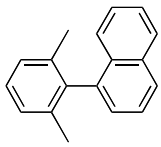
4-Methylbiphenyl (1)[231]



1

The general procedure, using **Pd3** and the aryl chloride, afforded, after flash chromatography on silica gel (hexanes/EtOAc, 90/10), 303 mg (90%) of the title compound.

1-(2,4,6-Trimethylphenyl)-naphthalene (2)[232]



2

The general procedure, using **Pd3** and the aryl chloride, afforded, after flash chromatography on silica gel (hexanes/EtOAc, 90/10), 438 mg (89%) of the title compound.

[231] Rao, M. S. C.; Rao, G. S. K. *Synthesis* **1987**, 231–233.
[232] Adjabeng, G.; Brenstrum, T.; Frampton, C. S.; Robertson, A. J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 5082–5086.

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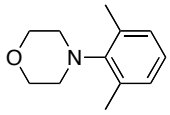
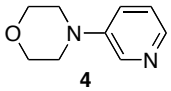
_N_-(2,6-Dimethylphenyl)morpholine (3)[233]



3

A) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 178 mg (93%) of the title compound.
B) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 170 mg (90%) of the title compound.

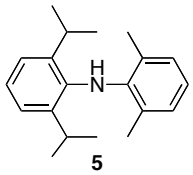
_N_-(3-Pyridyl)morpholine (4)[234]



4

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 80/20), 148 mg (90%) of the title compound.
B) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 80/20), 141 mg (86%) of the title compound.
C) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 80/20), 143 mg (87%) of the title compound.

_N_-(2,6-Diisopropylphenyl)-2',6'-dimethylaniline (5)[178]



5

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 245 mg (87%) of the title compound.
B) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 273 mg (97%) of the title compound.
C) The general procedure, using **Pd6** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/DCM, 90/10), 264 mg (94%) of the title compound.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13-7.09 (m, 3H, H^{Ar}), 6.91 (d, J = 7.5 Hz, 2H, H^{Ar}), 6.69 (t, J = 7.5 Hz, 1H, H^{Ar}), 3.15 (septet, J = 6.6 Hz, 2H, CH(CH_3)$_2$), 1.97 (s, 6H, C^{Ar}–CH_3),

[233] Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158–1174.
[234] Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *61*, 7240–7241.

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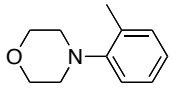
1.11 (d, J = 6.6 Hz, 12H, CH(CH_3)$_2$). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 144.3 (C, C^{Ar}), 143.3 (C, C^{Ar}), 139.0 (C, C^{Ar}), 129.7 (CH, C^{Ar}), 125.8 (C, C^{Ar}), 125.0 (CH, C^{Ar}), 123.4 (CH, C^{Ar}), 119.8 (CH, C^{Ar}), 28.2 (CH, *C*H(CH_3)$_2$), 23.7 (CH_3, CH(*C*H_3)$_2$), 19.5 (CH_3, C^{Ar}–*C*H_3).

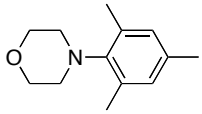
_N_-(_o_-Tolyl)morpholine (6)[235]



6

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 170 mg (96%) of the title compound.
B) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 163 mg (92%) of the title compound.
C) The general procedure, using **Pd6** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 170 mg (96%) of the title compound.

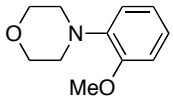
_N_-(2,4,6-Trimethylphenyl)morpholine (7)[133]



7

The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 193 mg (94%) of the title compound.

_N_-(2-Methoxyphenyl)morpholine (8)[236]



8

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 170 mg (88%) of the title compound.
B) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 178 mg (92%) of the title compound.
C) The general procedure, using **Pd6** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 186 mg (96%) of the title compound.

[235] Barluengua, J.; Aznar, F.; Fernandez, M. *Chem.–Eur. J.* **1997**, *3*, 1629–1637.
[236] Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560–2565.

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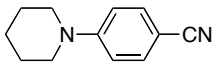
_N_-(4-Cyanophenyl)piperidine (9)[237]



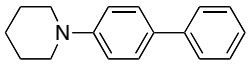
9

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 168 mg (90%) of the title compound.

B) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 80/20), 179 mg (96%) of the title compound.

C) The general procedure, using **Pd6** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 95/5), 168 mg (90%) of the title compound.

_N_-(4-Biphenylyl)piperidine (10)[238]

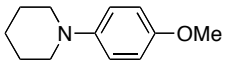


10

The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/DCM, 90/10), 197 mg (83%) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 7.2 Hz, 2H, H^{Ar}), 7.48 (d, J = 8.4 Hz, 2H, H^{Ar}), 7.40-7.35 (m, 2H, H^{Ar}), 7.25 (t, J = 7.2 Hz, 1H, H^{Ar}), 6.98 (d, J = 8.4 Hz, 2H, H^{Ar}), 3.19 (t, J = 4.8 Hz, 4H, CH_2–N), 1.74-1.67 (m, 4H, CH_2–CH_2–N), 1.61-1.56 (m, 2H, CH_2(CH_2)$_2$–N). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 151.6 (C, N–C^{Ar}), 141.2 (C, C^{Ar}), 131.8 (C, C^{Ar}), 128.8 (CH, C^{Ar}), 127.8 (CH, C^{Ar}), 126.6 (CH, C^{Ar}), 126.4 (CH, C^{Ar}), 116.6 (CH, C^{Ar}), 50.6 (CH_2, CH_2–N), 26.0 (CH_2, CH_2–CH_2–N), 24.5 (CH_2, CH_2(CH_2)$_2$–N). **Elemental analysis** calcd. (%) for $C_{17}H_{19}N$ (MW 237.34): C, 86.03; H, 8.07; N, 5.90. Found: C, 86.28; H, 7.78; N, 5.87.

_N_-(4-Methoxyphenyl)piperidine (11)[239]



11

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 95/5), 178 mg (93%) of the title compound.

[237] Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157.
[238] This compound has already been reported but our spectroscopic data were not in accordance with the literature. Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268–1273.
[239] Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829–12842.

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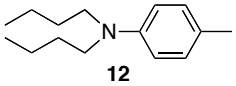
B) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 95/5), 182 mg (95%) of the title compound.

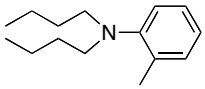
***N,N*-Dibutyl-*N*-(*p*-tolyl)amine (12)**[240]



12

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 215 mg (98%) of the title compound.
B) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 191 mg (87%) of the title compound.
C) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 207 mg (95%) of the title compound.

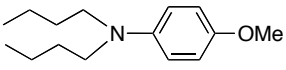
***N,N*-Dibutyl-*N*-(*o*-tolyl)amine (13)**[240]



13

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 193 mg (88%) of the title compound.
B) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 197 mg (90%) of the title compound.
C) The general procedure, using **Pd6** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/DCM, 90/10), 210 mg (96%) of the title compound.

***N,N*-Dibutyl-*N*-(4-methoxyphenyl)amine (14)**[125e]



14

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 222 mg (94%) of the title compound.
B) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 224 mg (95%) of the title compound.

[240] Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem* **1999**, *64*, 5575–5580.

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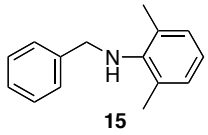
C) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 95/5), 203 mg (86%) of the title compound.

***N*-(2,6-Dimethylphenyl)benzylamine (15)**[237]

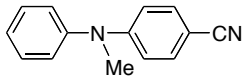


15

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after filtration through Celite, 209 mg (99%) of crude product that was estimated pure enough (> 95%) by NMR and GC.

B) The general procedure, using **Pd4** and the aryl chloride, yielded, after filtration through Celite, 190 mg (90%) of crude product that was estimated pure enough (> 98%) by NMR and GC.

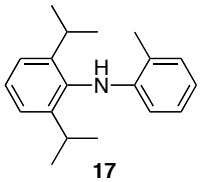
***N*-Methyl-*N*-(4-cyanophenyl)aniline (16)**[174]



16

The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 202 mg (97%) of the title compound.

***N*-(2,6-Diisopropylphenyl)-*N*-(*o*-tolyl)amine (17)**[178]



17

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 257 mg (96%) of the title compound.

B) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 249 mg (93%) of the title compound.

C) The general procedure, using **Pd6** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/DCM, 90/10), 246 mg (92%) of the title compound.

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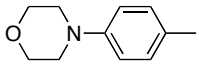
D) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 90/10), 237 mg (89%) of the title compound.

***N*-(*p*-Tolyl)morpholine (18)**[241]

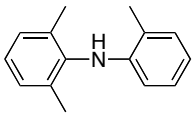


18

A) The general procedure, using **Pd4** and the aryl chloride, yielded, after filtration through Celite, 168 mg (95%) of crude product that was estimated pure enough (> 95%) by NMR and GC.

B) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 171 mg (97%) of the title compound.

***N*-(2,6-Dimethylphenyl)-*N*-(*o*-tolyl)amine (19)**[174]

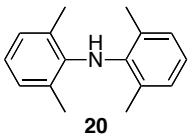


19

A) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 190 mg (90%) of the title compound.

B) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 95/5), 180 mg (85%) of the title compound.

***N*-(2,6-Dimethylphenyl)-2',6'-dimethylaniline (20)**[242]



20

The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 194 mg (86%) of the title compound.

[241] Tsuji, Y.; Huh, K. T.; Ohsugi, Y.; Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 1365–1370.
[242] Ehrentraut, A.; Zapf, A.; Beller, M. *J. Mol. Catal. A: Chem.* **2002**, *182–183*, 515–523.

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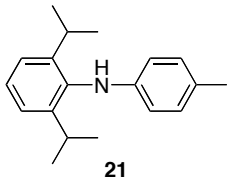
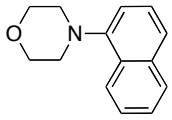
***N*-(2,6-Diisopropylphenyl)-*N*-(*p*-tolyl)amine (21)**[241]



21

A) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 233 mg (87%) of the title compound.
B) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 90/10), 259 mg (97%) of the title compound.

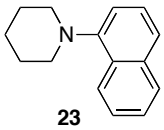
***N*-(1-Naphthyl)morpholine (22)**[243]



22

A) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 90/10), 194 mg (91%) of the title compound.
B) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 90/10), 183 mg (86%) of the title compound.

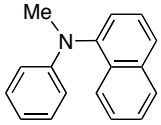
***N*-(1-Naphthyl)piperidine (23)**[194]



23

The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 90/10), 184 mg (87%) of the title compound.

***N*-Methyl-*N*-(1-naphthyl)aniline (24)**[244]



24

[243] Guinot, S. G. R.; Hepworth, J. D.; Wainwright, M. J. *Chem. Soc., Perkin Trans. 2* **1998**, 297–304.
[244] Odedra, A.; Wu, C.-J.; Pratap, T. B.; Huang, C.-W.; Ran, Y.-F.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 3406–3412.

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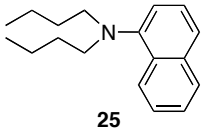
A) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 90/10), 208 mg (89%) of the title compound.
B) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 95/5), 222 mg (95%) of the title compound.

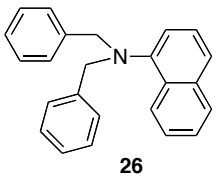
***N,N*-Dibutyl-*N*-(1-naphthyl)amine (25)**



25

The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 95/5), 243 mg (95%) of the title compound.
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, *J* = 9.0 Hz, 1H, H^{Ar}), 7.76 (d, *J* = 9.0 Hz, 1H, H^{Ar}), 7.50 (d, *J* = 10.8 Hz, 1H, H^{Ar}), 7.46-7.33 (m, 3H, H^{Ar}), 7.13 (d, *J* = 7.5 Hz, 1H, H^{Ar}), 3.10 (t, *J* = 7.2 Hz, 4H, N–CH_2), 1.51-1.42 (m, 4H, N–CH_2–CH_2), 1.33-1.20 (m, 4H, N–$(CH_2)_2$–CH_2), 0.83 (t, *J* = 7.5 Hz, 6H, CH_3). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 148.9 (C, N–C^{Ar}), 135.2 (C, C^{Ar}), 131.5 (C, C^{Ar}), 128.3 (CH, C^{Ar}), 125.8 (CH, C^{Ar}), 125.7 (CH, C^{Ar}), 125.2 (CH, C^{Ar}), 124.5 (CH, C^{Ar}), 123.4 (CH, C^{Ar}), 118.2 (CH, C^{Ar}), 54.3 (CH_2, N–CH_2), 29.6 (CH_2, N–CH_2–CH_2), 20.8 (CH_2, N–$(CH_2)_2$–CH_2), 14.2 (CH_3). **Elemental analysis** calcd. (%) for $C_{18}H_{25}N$ (MW 255.40): C, 84.65; H, 9.87; N, 5.48. Found: C, 84.63; H, 9.83; N, 5.20.

***N,N*-Dibenzyl-*N*-(1-naphthyl)amine (26)**[245]



26

The general procedure yielded, after flash chromatography on silica gel (pentane/DCM, 90/10), 239 mg (74%) of the title compound.

[245] Buzniak, J.; Skulski, L.; Wybraniec-Bugaj, J. *Polish J. Chem.* **1991**, *55*, 1923–1927.

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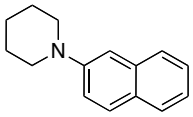
***N*-(2-Naphthyl)piperidine (27)**[246]



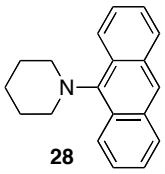
27

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 192 mg (92%) of the title compound.

B) The general procedure, using **Pd6** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/DCM, 95/5), 186 mg (88%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.65 (m, 3H, H^{Ar}), 7.39-7.35 (m, 1H, H^{Ar}), 7.28-7.23 (m, 2H, H^{Ar}), 7.11 (s, 1H, H^{Ar}), 3.23 (t, J = 4.8 Hz, 4H, CH_2-N), 1.77-1.71 (m, 4H, CH_2–CH_2–N), 1.62-1.58 (m, 2H, C$H_2(CH_2)_2$–N). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 150.3 (C, N–C^{Ar}), 134.9 (C, C^{Ar}), 128.7 (CH, C^{Ar}), 128.5 (C, C^{Ar}), 127.6 (CH, C^{Ar}), 126.9 (CH, C^{Ar}), 126.3 (CH, C^{Ar}), 123.3 (CH, C^{Ar}), 120.4 (CH, C^{Ar}), 110.5 (CH, C^{Ar}), 51.2 (CH_2, CH_2–N), 26.1 (CH_2, CH_2–CH_2–N), 24.6 (CH_2, $CH_2(CH_2)_2$–N).

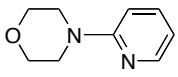
***N*-(9-Anthryl)piperidine (28)**[247]



28

The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 90/10), 248 mg (95%) of the title compound.

***N*-(2-Pyridyl)morpholine (29)**[234]



29

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after filtration through Celite, 154 mg (94%) of crude product that was estimated pure (> 95%) by NMR and GC.

B) The general procedure, using **Pd4** and the aryl chloride, yielded, after filtration through Celite, 146 mg (89%) of crude product that was estimated pure enough (> 95%) by NMR and GC.

[246] Carmack, M.; Behforouz, M.; Berchtold, G. A.; Berkowitz, S. M.; Wiesler, D.; Barone, R. J. *Heterocycl. Chem.* **1989**, *26*, 1305–1318.
[247] Sweger, R. W.; Czarnik, A. W. *J. Am. Chem. Soc.* **1991**, *113*, 1523–1530.

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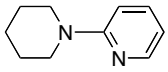
C) The general procedure, using **Pd6** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 85/15), 141 mg (86%) of the title compound.
D) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 85/15), 160 mg (98%) of the title compound.

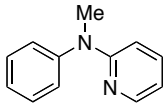
***N*-(2-Pyridyl)piperidine (30)**[248]



30

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 156 mg (96%) of the title compound.
B) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 159 mg (98%) of the title compound.
C) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 154 mg (95%) of the title compound.

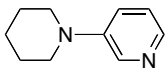
***N*-Methyl-*N*-(2-pyridyl)aniline (31)**[249]



31

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 169 mg (92%) of the title compound.
B) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 169 mg (92%) of the title compound.
C) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane, DCM, 90/10), 168 mg (91%) of the title compound.

***N*-(3-Pyridyl)piperidine (32)**[250]



32

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 80/20), 117 mg (72%) of the title compound.

[248] Thomas, S.; Roberts, S.; Pasumanski, L.; Gamsey, S.; Singaram, B. *Org. Lett.* **2001**, *5*, 3867–3870.
[249] Hauser, C. H.; Weiss, M. J. *J. Org. Chem.* **1949**, *14*, 310–321.
[250] Jamart-Gregoire, B.; Léger, C.; Caubère, P. *Tetrahedron Lett.* **1990**, *31*, 7599–7602.

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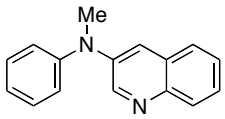
B) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 80/20), 133 mg (82%) of the title compound.
C) The general procedure, using **Pd6** with the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 80/20), 128 mg (79%) of the title compound.
D) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 80/20), 141 mg (87%) of the title compound.
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (s, 1H, H^{Ar}), 8.05 (d, *J* = 4.5 Hz, 1H, H^{Ar}), 7.19-7.10 (m, 2H, H^{Ar}), 3.18 (t, *J* = 5.1 Hz, 4H, CH_2–N), 1.75-1.67 (m, 4H, C*H*$_2$–CH_2–N), 1.63-1.57 (m, 2H, C*H*$_2$(CH_2)$_2$–N). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 147.9 (C, N–C^{Ar}), 140.2 (CH, C^{Ar}), 139.1 (CH, C^{Ar}), 123.5 (CH, C^{Ar}), 122.7 (CH, C^{Ar}), 50.0 (CH_2, CH_2–N), 25.7 (CH_2, *C*H_2–CH_2–N), 24.2 (CH_2, *C*H_2(CH_2)$_2$–N).

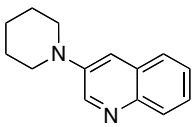
***N*-Methyl-*N*-phenylquinolin-3-amine (33)**[234]



33

A) The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 85/15), 216 mg (92%) of the title compound.
B) The general procedure, using **Pd6** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/DCM, 95/5), 225 mg (96%) of the title compound.

***N*-(3-Quinolinyl)piperidine (34)**[251]



34

The general procedure, using **Pd4** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 70/30), 185 mg (87%) of the title compound.
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.78 (d, *J* = 2.7 Hz, 1H, H^{Ar}), 7.97 (d, *J* = 7.8 Hz, 1H, H^{Ar}), 7.63 (d, *J* = 9.3 Hz, 1H, H^{Ar}), 7.49-7.38 (m, 2H, H^{Ar}), 7.28 (d, *J* = 2.7 Hz, 1H, H^{Ar}), 3.21 (t, *J* = 5.1 Hz, 4H, CH_2–N), 1.77-1.70 (m, 4H, C*H*$_2$–CH_2–N), 1.62-1.55 (m, 2H, C*H*$_2$(CH_2)$_2$–N). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 145.6 (CH, N–CH^{Ar}), 142.7 (C, C^{Ar}), 129.1 (C, C^{Ar}), 128.9

[251] Blanchard, S.; Guillaumet, P.; Caubère, P. *Tetrahedron Lett.* **2001**, *42*, 7037–7039.

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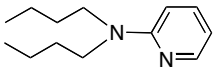
(CH, C^{Ar}), 127.8 (C, C^{Ar}), 126.8 (CH, C^{Ar}), 126.5 (CH, C^{Ar}), 126.0 (CH, C^{Ar}), 116.6 (CH, C^{Ar}), 50.6 (CH_2, CH_2–N), 25.7 (CH_2, *C*H_2–CH_2–N), 24.1 (CH_2, *C*H_2(CH_2)$_2$–N).

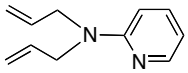
***N,N*-Dibutyl-*N*-(2-pyridyl)amine (35)**[252]



35

A) The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 194 mg (94%) of the title compound.
B) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/DCM, 90/10), 178 mg (86%) of the title compound.

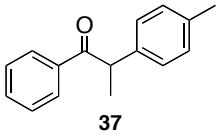
***N,N*-Diallyl-*N*-(2-pyridyl)amine (36)**[192]



36

The general procedure, using **Pd4** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 159 mg (92%) of the title compound.
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, *J* = 3.3 Hz, 1H, H^{Ar}), 7.43-7.37 (m, 1H, H^{Ar}), 6.55-6.51 (m, 1H, H^{Ar}), 6.47 (d, *J* = 8.7 Hz, 1H, H^{Ar}), 5.91-5.82 (m, 2H, –C*H*=CH_2), 5.17-5.12 (m, 4H, –CH=C*H*$_2$), 4.11 (d, *J* = 5.1 Hz, 4H, CH_2–N). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 158.9 (C, N–C^{Ar}), 148.1 (CH, C^{Ar}), 137.3 (CH, *C*H=CH_2), 134.2 (CH, C^{Ar}), 116.2 (CH_2, –CH=*C*H_2), 115.1 (CH, C^{Ar}), 106.3 (CH, C^{Ar}), 50.3 (CH_2, CH_2–N).

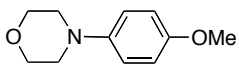
2-(4-Methylphenyl)-1-phenyl-1-propanone (37)[253]



37

The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 216 mg (97%) of the title compound.

4-(4-Methoxyphenyl)morpholine (38)[125e]



38

[252] Watanabe, Y.; Morisaki, Y.; Kondo, T.; Mitsudo, T. *J. Org. Chem.* **1996**, *61*, 4214–4218.
[253] Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816–5817.

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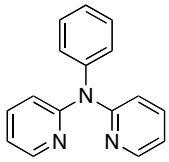
The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 190 mg (99%) of the title compound.

***N*-Phenyl-*N*-(pyridin-2-yl)pyridin-2-amine (39)**[254]

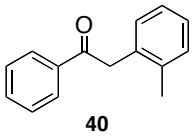


39

The general procedure, using 2-chloropyridine (2.1mmol, 197 μL), aniline (1 mmol, 93 μL), KO-*t*-Bu (2.2 mmol, 248 mg), [(IPr)Pd(acac)Cl] **Pd6** (1 mol %, 12.6 mg) and DME (2 mL), yielded, after flash chromatography on silica gel (pentane/EtOAc, 80/20), 230 mg (93%) of the title compound.

^{1}H NMR (400 MHz, acetone-d_6): δ 8.22 (d, *J* = 4.0 Hz, 2H), 7.61 (m, 2H), 7.38 (t, *J* = 8.1 Hz, 2H), 7.24-7.16 (m, 3H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.97-6.94 (m, 2H). **^{13}C NMR (100 MHz, ($(CD_3)_2CO$):** δ 159.5 (C), 149.4 (CH), 146.6 (C), 138.6 (CH), 130.7 (CH), 128.9 (CH), 126.6 (CH), 119.3 (CH), 118.0 (CH). **Elemental analysis** calcd. (%) for $C_{16}H_{13}N_3$ (MW 247.29): C, 77.71; H, 5.30; N, 16.99. Found: C, 77.79; H, 5.57; N, 16.93.

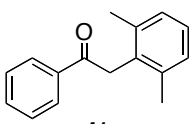
1-Phenyl-2-*o*-tolylethanone (40)[255]



40

A) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 187 mg (89%) of the title compound.
B) The general procedure, using **Pd6** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 189 mg (90%) of the title compound.

2-(2,6-Dimethylphenyl)-1-phenylethanone (41)



41

[254] Mann, F. G.; Watson, J. *J. Org. Chem.* **1948**, *13*, 502–509.
[255] Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478.

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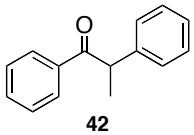
The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 202 mg (90%) of the title compound. **^{1}H NMR (400 MHz, CD_2Cl_2):** δ 8.09 (d, *J* = 7.2 Hz, 2H, H^{Ar}), 7.64 (t, *J* = 7.2 Hz, 1H, H^{Ar}), 7.54 (t, *J* = 8.0 Hz, 2H, H^{Ar}), 7.14-7.06 (m, 3H, H^{Ar}), 4.40 (s, 2H, C(O)–CH_2), 2.21 (s, 6H, Me). **^{13}C NMR (100 MHz, CD_2Cl_2):** δ 197.5 (C, C=O), 137.7 (C, C^{Ar}), 133.7 (CH, C^{Ar}), 133.4 (C, C^{Ar}), 129.2 (CH, C^{Ar}), 128.5 (CH, C^{Ar}), 128.3 (CH, C^{Ar}), 127.3 (CH, C^{Ar}), 114.0 (C, C^{Ar}), 40.2 (CH_2, C(O)–*C*H_2), 20.6 (CH_3). **Elemental analysis** calcd. (%) for $C_{16}H_{16}O$ (MW 224.30): C, 85.68; H, 7.19. Found: C, 85.36; H, 7.23.

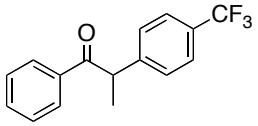
1,2-Diphenylpropan-1-one (**42**)[255]



42

The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 80/20), 206 mg (98%) of the title compound.

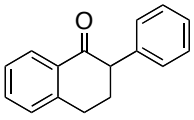
1-Phenyl-2-[4-(trifluoromethyl)phenyl]propan-1-one[256] (**43**)



43

The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/EtOAc, 90/10), 259 mg (93%) of the title compound.

2-Phenyl-α-tetralone (**44**)[257]



44

A) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 138 mg (62%) of the title compound.
B) The general procedure, using **Pd6** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 160 mg (72%) of the title compound.

[256] Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258.
[257] Wang, D. Z.; Kim, Y.-J.; Streitwieser, A. *J. Am. Chem. Soc.* **2000**, *122*, 10754–10760.

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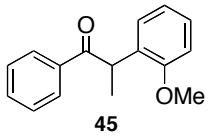
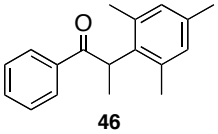
2-(2-Methoxyphenyl)-1-phenylpropan-1-one (45)[258]



45

A) The general procedure, using **Pd6** and the aryl chloride, yielded, after flash chromatography on silica gel (pentane/MTBE, 85/15), 219 mg (91%) of the title compound.
B) The general procedure, using **Pd6** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 85/15), 199 mg (83%) of the title compound.

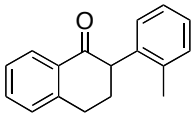
1-Phenyl-2-(2,4,6-trimethylphenyl)propan-1-one (46)[259]



46

The general procedure, using **Pd6** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 212 mg (84%) of the title compound.

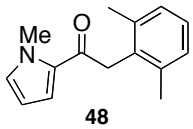
2-(*o*-Tolyl)-α-tetralone (47)[259]



47

The general procedure, using **Pd6** and the aryl bromide, yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 206 mg (87%) of the title compound.

2-(2,6-Dimethyl-phenyl)-1-(1-methyl-1*H*-pyrrol-2-yl)-ethanone (48)



48

The general procedure, using **Pd6** and the aryl chloride, yielded, after a pentane wash, 218 mg (96%) of the title compound.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12-7.10 (m, 1H, H^{Ar}), 7.04-7.02 (m, 3H, H^{Ar}), 6.75 (s, 1H, H^{Ar}), 6.14-6.12 (m, 1H, H^{Ar}), 4.28 (s, 2H, C(O)–CH_2), 3.96 (s, 3H, N–CH_3), 2.32 (s, 6H, C^{Ar}–CH_3). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 188.0 (C, C=O), 137.3 (C, C^{Ar}), 132.9 (C, C^{Ar}),

[258] Bell, H. C.; Pinhey, J. T.; Sternhell, S. *Aust. J. Chem.* **1982**, *35*, 2237–2245.
[259] Wagner, P. J.; Zhou, B. *J. Am. Chem. Soc.* **1988**, *110*, 611–612.

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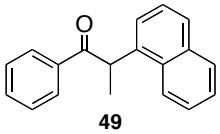
131.0 (CH, C^{Ar}), 130.7 (C, C^{Ar}), 128.0 (CH, C^{Ar}), 126.8 (CH, C^{Ar}), 118.8 (CH, C^{Ar}), 108.0 (CH, C^{Ar}), 39.7 (CH_2, C(O)–*C*H_2), 37.8 (CH_3, N–CH_3), 20.6 (CH_3, C^{Ar}–*C*H_3). **Elemental analysis** calcd. (%) for $C_{15}H_{17}NO$ (MW 227.30): C, 79.26; H, 7.54; N, 6.16. Found: C, 79.39; H, 7.24; N, 5.74.

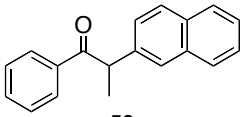
2-(Naphthalen-1-yl)-1-phenyl-propan-1-one (49)[218a]



49

The general procedure, using **Pd6** and the aryl chloride, yielded, after a pentane wash, 250 mg (96%) of the title compound.

2-(Naphthalen-2-yl)-1-phenylpropan-1-one (50)

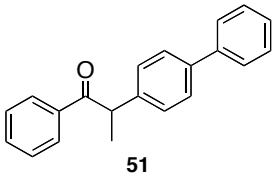


50

The general procedure, using **Pd6** and the aryl bromide, yielded, after a pentane wash, 253 mg (97%) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, *J* = 5.7 Hz, 2H, H^{Ar}), 7.73-7.69 (m, 4H, H^{Ar}), 7.39-7.31 (m, 4H, H^{Ar}), 7.26 (t, *J* = 5.7 Hz, 2H, H^{Ar}), 4.77 (q, *J* = 5.1 Hz, 1H, C*H*–CH_3), 1.58 (d, *J* = 5.1 Hz, 3H, CH–C*H*$_3$). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 200.3 (C, C=O), 139.1 (C, C^{Ar}), 136.5 (C, C^{Ar}), 133.7 (C, C^{Ar}), 132.9 (CH, C^{Ar}), 132.4 (C, C^{Ar}), 128.9 (CH, C^{Ar}), 128.8 (CH, C^{Ar}), 128.5 (CH, C^{Ar}), 127.8 (CH, C^{Ar}), 127.7 (CH, C^{Ar}), 126.5 (CH, C^{Ar}), 125.2 (CH, C^{Ar}), 126.0 (CH, C^{Ar}), 125.8 (CH, C^{Ar}), 48.0 (CH, *C*H–CH_3), 19.6 (CH_3, CH–*C*H_3). **Elemental analysis** calcd. (%) for $C_{19}H_{16}O$ (MW 260.33): C, 87.66; H, 6.19. Found: C, 87.90; H, 6.35.

2-(Biphenyl-4-yl)-1-phenylpropan-1-one (51)[218c]



51

The general procedure, using **Pd6** and the aryl bromide, yielded, after a pentane wash, 272 mg (95%) of the title compound.

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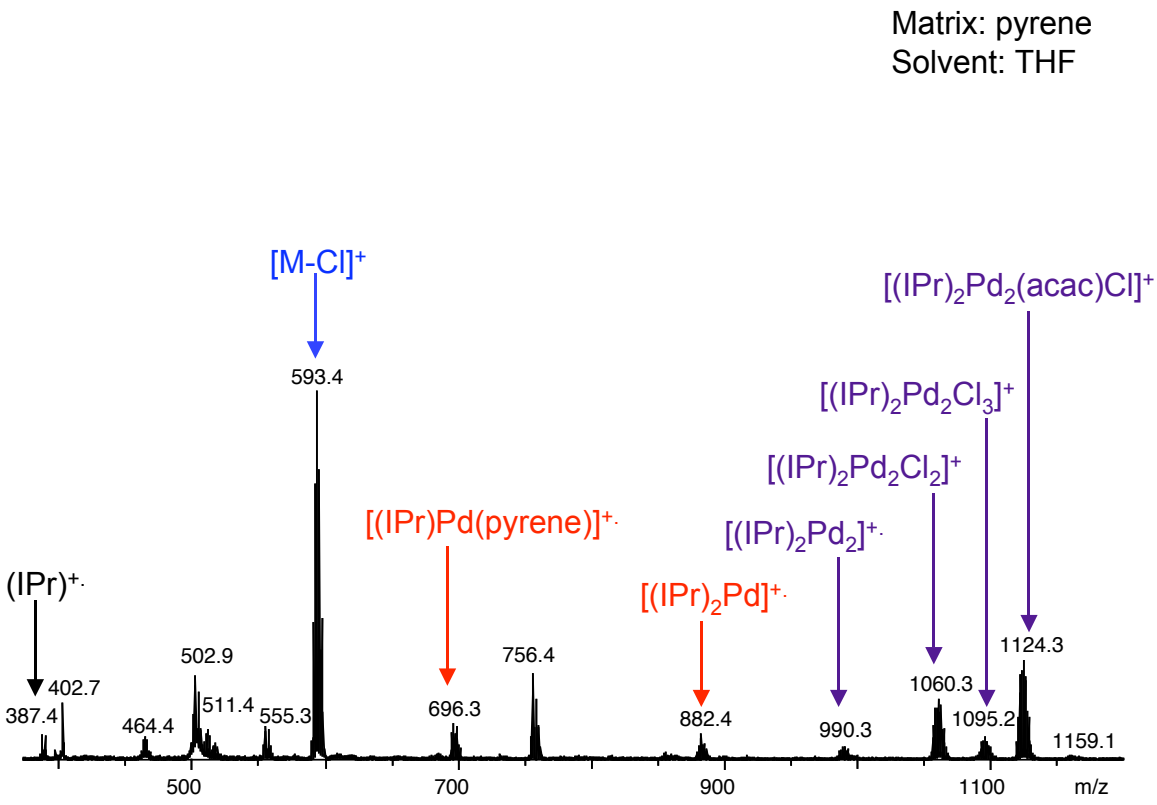
F. Inert atmosphere MALDI-TOF MS analyses

Representative procedure: Inert-atmosphere MALDI MS analyses were performed using a Bruker OmniFlex® MALDI-TOF mass spectrometer equipped with a nitrogen laser (337 nm) and interfaced to an MBraun Labmaster 130® glovebox. Data were collected in positive reflection mode, with the accelerating voltage held at 20 kV for all experiments. Reaction mixtures for MALDI analyses were prepared by treating pre-catalyst [(IPr)Pd(acac)Cl] **Pd6** (9.1 mg, 0.0145 mmol) with KO-*t*-Bu (1.6 mg, 1 equiv or 16.0 mg, 10 equiv) in 2 mL THF and stirring at 22°C. The reaction mixtures were periodically sampled by mixing 100 μL with 0.5 mL of a solution of pyrene (25 mg.mL^{-1}) in THF.

MS 1: {[(IPr)Pd(acac)Cl]} collected immediately



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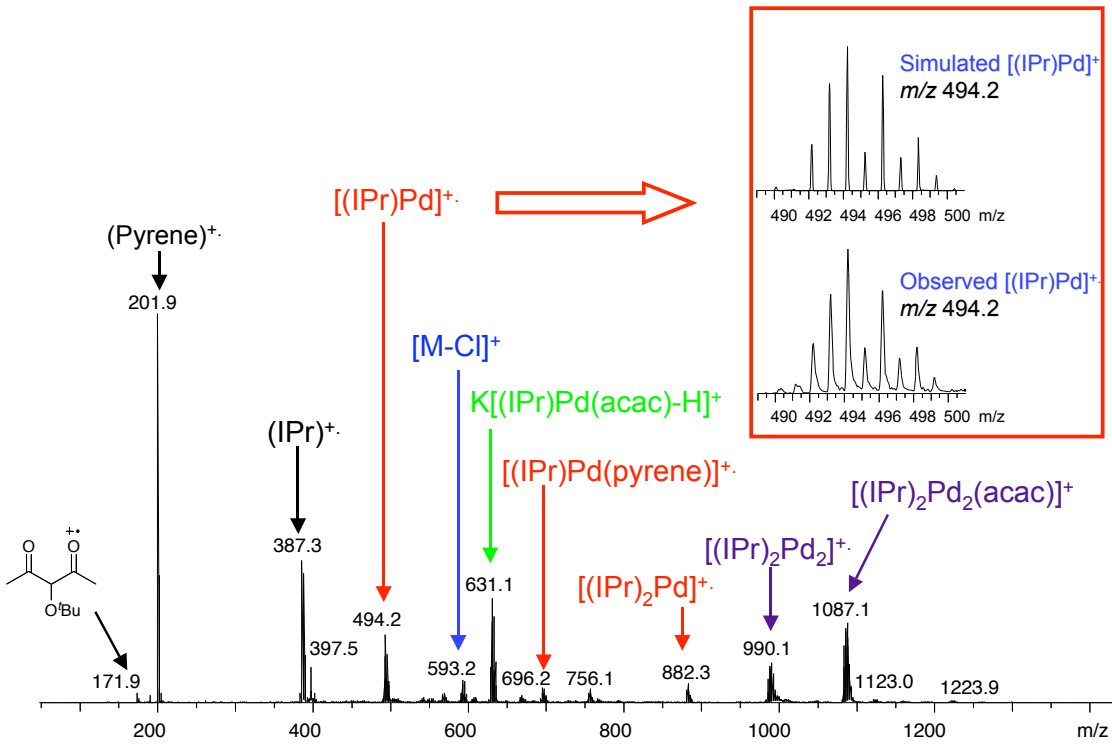
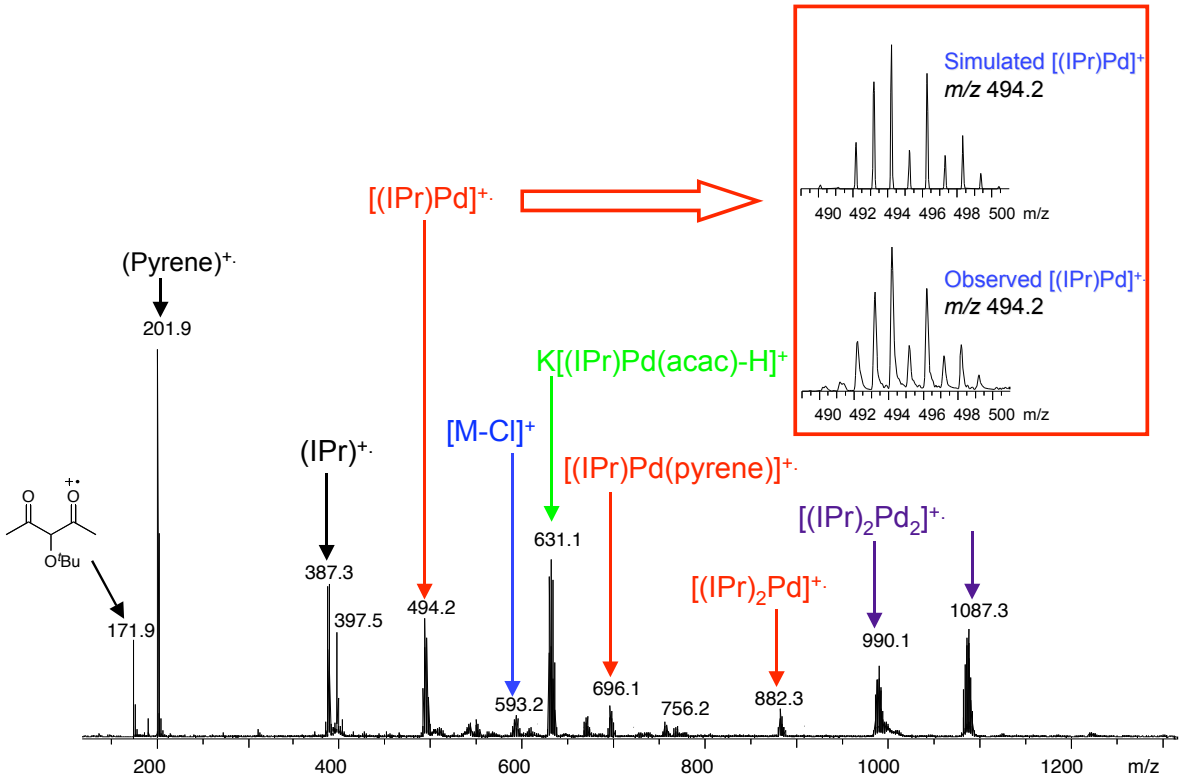
MS 2: {[(IPr)Pd(acac)Cl] + 1 equiv KO-*t*-Bu} collected immediately



MS 3: {[(IPr)Pd(acac)Cl] + 1 equiv KO-*t*-Bu} collected after 15 min stirring at rt



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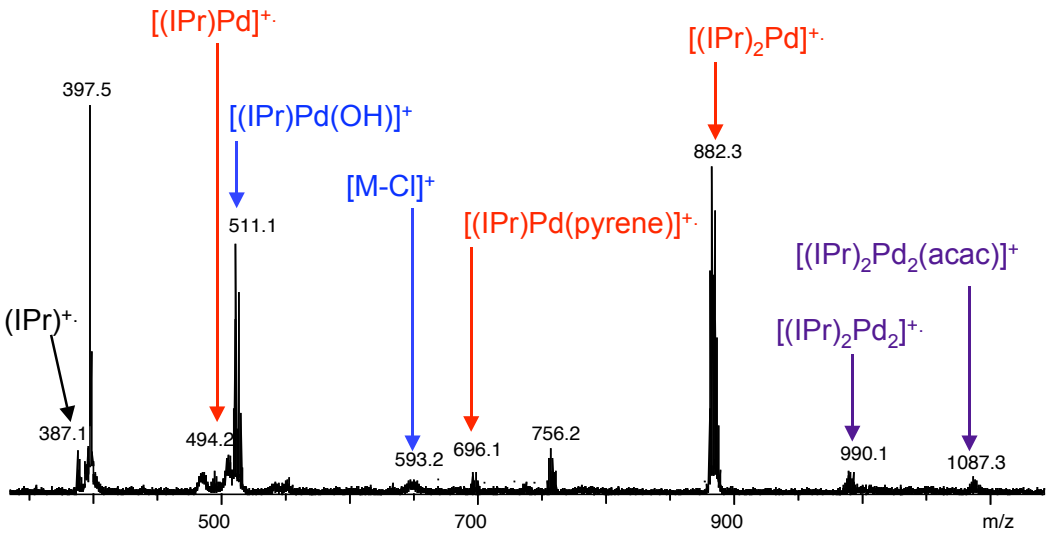
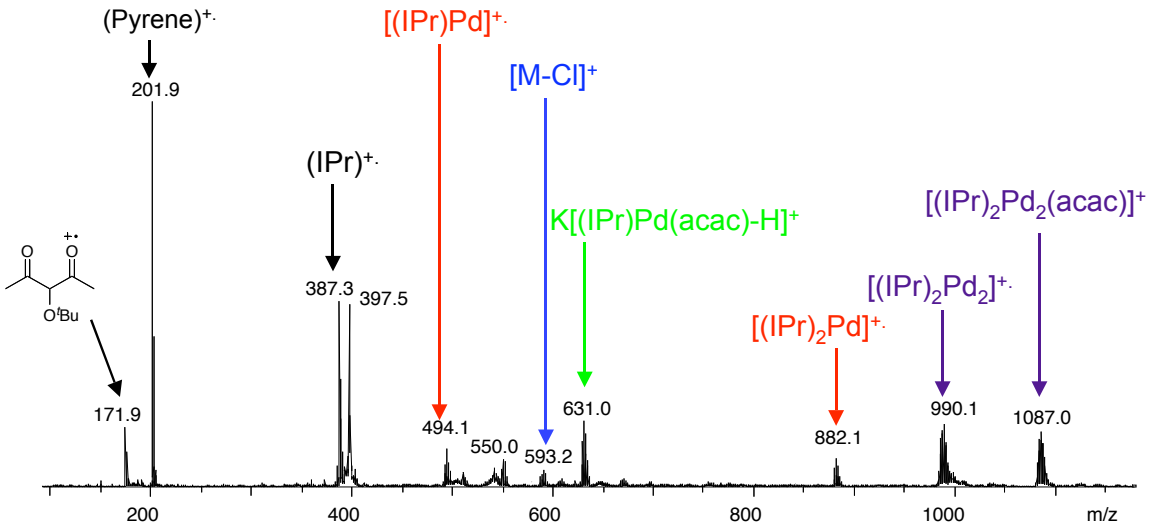
MS 4: {[(IPr)Pd(acac)Cl] + 1 equiv KO-*t*-Bu} collected after overnight stirring at rt



MS 5: {[(IPr)Pd(acac)Cl] + 10 equiv KO-*t*-Bu} collected immediately



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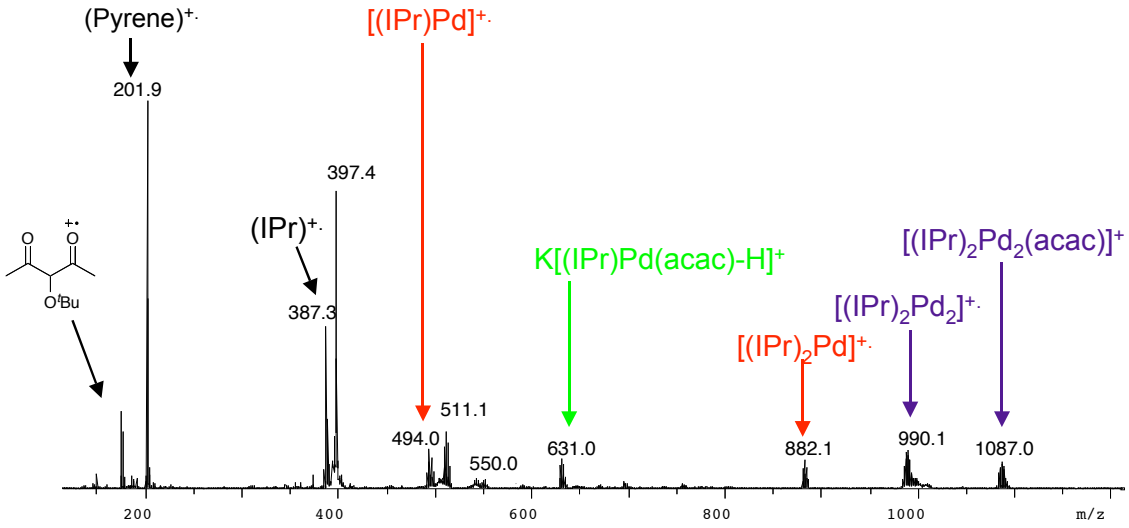
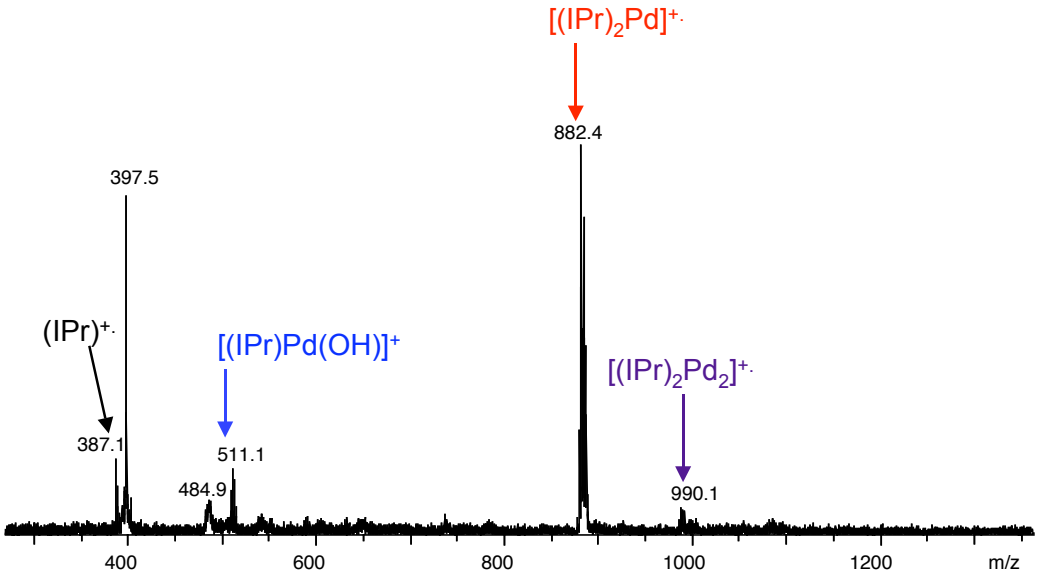
MS 6: {[(IPr)Pd(acac)Cl] + 10 equiv KO-*t*-Bu} collected after 15 min stirring at rt



MS 7: {[(IPr)Pd(acac)Cl] + 10 equiv KO-*t*-Bu} collected after overnight stirring at rt



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CHAPTER II

Ga

Synthesis of Well-Defined [(NHC)Ga^{III}] Complexes

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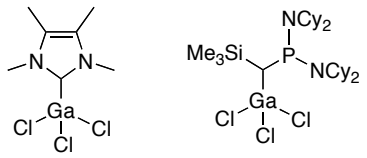
I. Introduction

Because of their excellent σ-donor properties,[260] N-heterocyclic carbenes have notably permitted the synthesis of a number of monomeric group 13 compounds since the seminal isolation and characterization of [(IMes)AlH_3] (IMes = *N*,*N*'-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) by Arduengo.[66] Surprisingly, while similar adducts of NHC-group 13 trihydride ([(NHC)MH_3]) and trimethyl ([(NHC)MMe_3]) have been isolated,[261,262] little attention has been paid to the corresponding trihalide adducts.[263,264,265] Thus, to the best of our knowledge, only two heteroatom carbene-containing $GaCl_3$ adducts (**LXVII** and **LXVIII**, Figure 24) have been reported to date.[266]



LXVII **LXVIII**

Figure 24. Previously reported carbene-$GaCl_3$ adducts

Furthermore, the only NHC-containing $GaCl_3$ adduct, [(ITM)$GaCl_3$] **LXVII**, could not be crystallized and studied by X-ray analysis,[266b] the structural nature of [(NHC)$GaCl_3$] adducts therefore remains elusive.

Additionally, the identity of the NHC in **LXVII** is quite peculiar, as it is a NHC with very small steric hindrance; a feature that precludes any generalization about the synthetic route for bulkier N-heterocyclic carbenes.

---

[260] See sections **III** and **IV** of the Introduction.

[261] For a review on group 13 hydride chemistry, see: Gardiner, M. G.; Raston, C. L. *Coord. Chem. Rev*. **1997**, *166*, 1–34.

[262] For studies on NHC-group 13 trihydride adducts, see: (a) Francis, M. D.; Hibbs, D. E.; Hursthouse, M. B.; Jones, C.; Smithies, N. A. *J. Chem. Soc., Dalton Trans*. **1998**, 3249–3254. (b) Baker, R. J.; Cole, M. L.; Jones, C.; Mahon, M. F. *J. Chem. Soc., Dalton Trans*. **2002**, 1992–1996, see also ref. 65a. For studies on NHC-group 13 trimethyl adducts, see ref. 68.

[263] (a) Black, S. J.; Hibbs, D. E.; Hursthouse, M. B.; Jones, C.; Abdul Malik, K. M.; Smithies, N. A. *J. Chem. Soc., Dalton Trans*. **1997**, 4313–4319. (b) Cole, M. L.; Davies, A. J.; Jones, C. *J. Chem. Soc., Dalton Trans*. **2001**, 2451–2452.

[264] For a rare mixed hydride-halide compound, see: Abernethy, C. D.; Cole, M. L.; Jones, C. *Organometallics* **2000**, *19*, 4852–4857.

[265] For a theoretical study of group 13 trihalide, see: Beste, A.; Krämer, O.; Gerhard, A.; Frenking, G. *Eur. J. Inorg. Chem*. **1999**, 2037–2045.

[266] (a) Cowley, A. H.; Gabbaï, F. P.; Carrano, C. J.; Mokry, L. M.; Bond, M. R.; Bertrand, G. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 578–580. (b) Stasch, A.; Singh, S.; Roesky, H. W.; Noltemeyer, M.; Schmidt, H.-G. *Eur. J. Inorg. Chem*. **2004**, 4052–4055.

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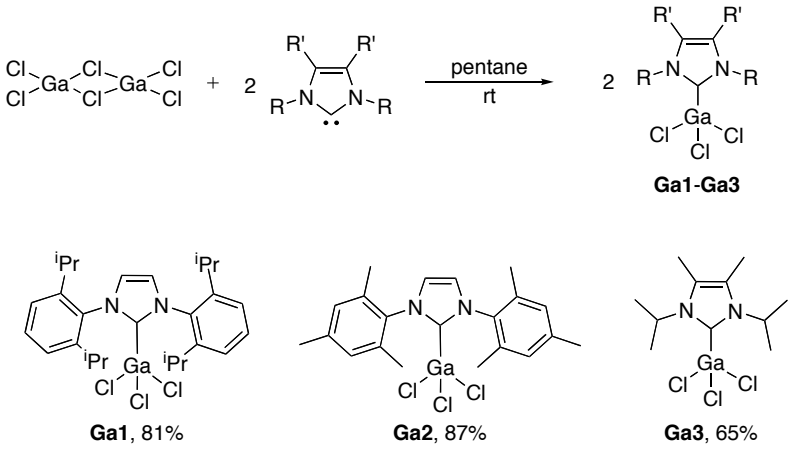
This is somewhat surprising since gallium trichloride is arguably the most utilized species in Ga^{III}-catalyzed organic transformations,[267] and NHCs attached to the gallium center could enhance and/or modulate the catalytic activity. Furthermore, we envisaged that sterically encumbering NHC would provide increased stability to tetracoordinated Ga^{III} complexes and therefore simplify their use under aerobic conditions.

II. Synthesis of [(NHC)$GaCl_3$] complexes[268]

Gallium(III) trichloride was treated with one equivalent of free N-heterocyclic carbene ligand in pentane to cleanly yield, after one hour at room temperature, adducts of the type [(NHC)$GaCl_3$] (Scheme 30).



Scheme 30. Synthesis of [(NHC)$GaCl_3$] **Ga1**, **Ga2** and **Ga3**

We first reacted IPr (*N,N'*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) with $GaCl_3$, leading to complex **Ga1**. The air- and moisture-stable white powder obtained presented the

[267] For recent selected references, see: (a) Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* **2002**, *67*, 1414–1417. (b) Kobayashi, K.; Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2002**, *124*, 8528–8529. (c) Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294–10295. (d) Viswanathan, G. S.; Wang, M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2138–2141. (e) Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 7812–7813. (f) Yonehara, F.; Kido, Y.; Sugimoto, H.; Morita, S.; Yamaguchi, M. *J. Org. Chem.* **2003**, *68*, 6752–6759. (g) Amemiya, R.; Fujii, A.; Yamaguchi, M. *Tetrahedron Lett.* **2004**, *45*, 4333–4335. (h) Yadav, J. S.; Reddy, B. V. S.; Padmavani, B.; Gupta, M. K. *Tetrahedron Lett.* **2004**, *45*, 7577–7579. (i) Oshita, M.; Yamashita, K.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 761–766. (j) Oshita, M.; Okazaki, T.; Ohe, K.; Chatani, N. *Org. Lett.* **2005**, *7*, 331–334. (k) Simmons, E. M.; Sarpong, R. *Org. Lett.* **2006**, *8*, 2883–2886. (l) Prajapati, D.; Gohain, M.; Gogoi, B. J. *Tetrahedron Lett.* **2006**, *47*, 3535–3539. (m) Huang, Z.-H.; Zou, J.-P.; Jiang, W.-Q. *Tetrahedron Lett.* **2006**, *47*, 7965–7968.

[268] Marion, N.; Escudero-Adán, E. C.; Benet-Buchholz, J.; Stevens, E. D.; Fensterbank, L.; Malacria, M.; Nolan, S. P. *Organometallics* **2007**, *26*, 3256–3259.

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characteristic ^{1}H NMR signals for the isopropyl chains of IPr ligand (septet at δ = 2.63 ppm and 2 doublets at δ = 1.38 ppm and δ = 1.18 ppm). No signal attributable to an imidazolium salt was observed. Interestingly, the resonance for the protons at C4/C5 positions of the imidazole ring was particularly downfield (δ = 8.15 ppm). The ^{13}C NMR spectrum did not bring more valuable information since we could not observe the resonance of the carbenic carbon (even with prolonged ^{13}C NMR sequence and increased relaxation time d1), a feature previously reported by Roesky for compound **LXVII**.[266b] We believe this is due to the high quadruple moment of the coordinated gallium center that broadens the signal to such an extent that it is not observable. To unambiguously confirm the structure, single crystals suitable for X-ray diffraction study were grown from a saturated acetone solution. Compound **Ga1**, which crystallizes in the monoclinic space group $P2_1/c$, exhibited the expected atom connectivity (Figure 25). Selected bond lengths and angles are presented in Table 22.

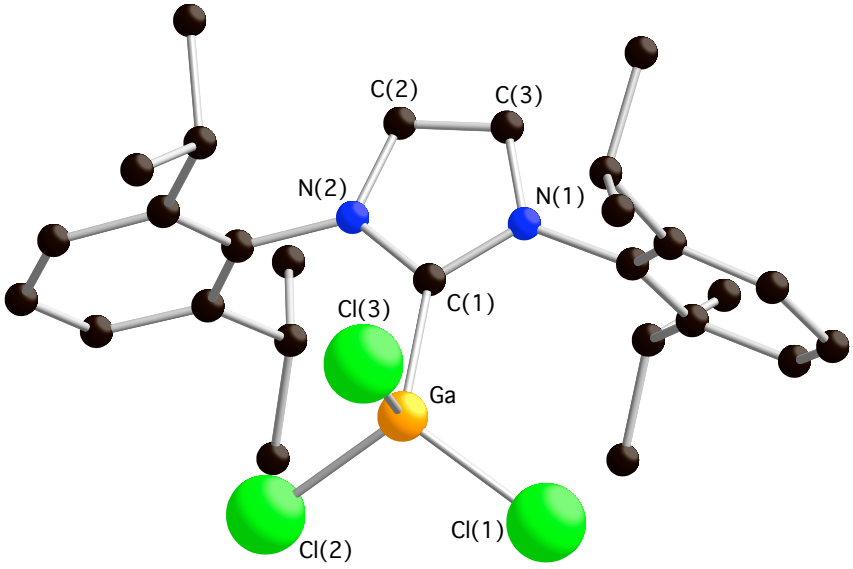

Figure 25. Ball-and-stick representation of [(IPr)GaCl$_3$] **Ga1** (hydrogen atoms are omitted for clarity)

Using a comparable synthetic route, adducts **Ga2** and **Ga3** were synthesized in moderate to good yields. The [(NHC)GaCl$_3$] compounds precipitated in pentane and were washed with methanol. They were found soluble in most organic solvents but not in hydrocarbons.

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Table 22. Selected bond lengths (Å) and angles (degree) of [$GaCl_3$(NHC)] **Ga1**-**Ga3**

	[(IPr)$GaCl_3$] Ga1	**[(IMes)$GaCl_3$] Ga2**	**[(IPrMe)$GaCl_3$] Ga3**
Ga–C(1)	2.016(2)	1.954(4)	2.011(4)
Ga–Cl(1)	2.173(5)	2.1674(8)	2.203(10)
Ga–Cl(2)	2.179(5)	2.1674(10)	2.197(11)
Ga–Cl(3)	2.177(6)	2.1910(8)	2.198(11)
C(2)–C(3)	1.339(3)	1.356(4)	1.373(5)
C(1)–N(1)	1.348(2)	1.376(4)	1.353(5)
C(1)–N(2)	1.351(2)	1.368(5)	1.366(5)
N(1)–C(3)	1.379(2)	1.389(5)	1.408(5)
N(2)–C(2)	1.380(3)	1.394(6)	1.401(5)
C(1)–Ga–Cl(1)	112.01(5)	113.26(8)	109.66(11)
N(1)–C(1)–N(2)	105.00(4)	102.9(3)	106.3(3)
Cl(1)–Ga–Cl(2)	107.00(2)	107.86(4)	108.40(4)
N(1)–C(3)–C(2)	106.8(2)	106.1(3)	106.6(3)

The proposed structure for compound **Ga2** could be elucidated unambiguously by single crystal X-ray structure analysis. [(IMes)$GaCl_3$] presented the expected atom connectivity (see Figure 26). Selected bond lengths and angles are presented in Table 22.

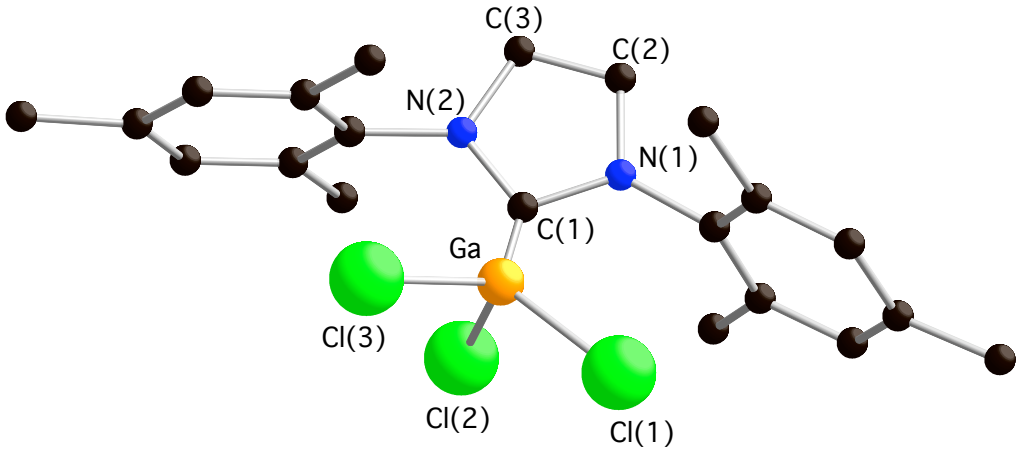

Figure 26. Ball-and-stick representation of [(IMes)$GaCl_3$] **Ga2** (hydrogen atoms are omitted for clarity)

As a special feature, compound **Ga2** presents, in the solid-state, two different positions of the main molecule with an occupation ratio of 50%. These positions of the

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molecule are shifted with respect to each other along the *c*-axis by 0.96 Å. Probably, layers of molecules along the *c*-axes are shifted back and forwards in the solid framework presenting the final overlapped structure model. This particular crystal packing with the overlapped structures is presented in Figure 27. The obtained model refined in the orthorhombic polar space group $Pca2_1$ (a: 17.0210 Å, b: 16.8034 Å, c: 7.9054 Å) with excellent statistics and presented only few correlations of atoms sitting of near positions. Structures solved in smaller (*a*: 11.9750 Å, *b*: 11.9750 Å, *c*: 7.8980 Å) and larger (*a*: 17.0295 Å, *b*: 7.9029 Å, *c*: 33.5977 Å) orthorhombic crystal cells did not refine successfully and the R_1-factor did not converge to lower values than 20%.

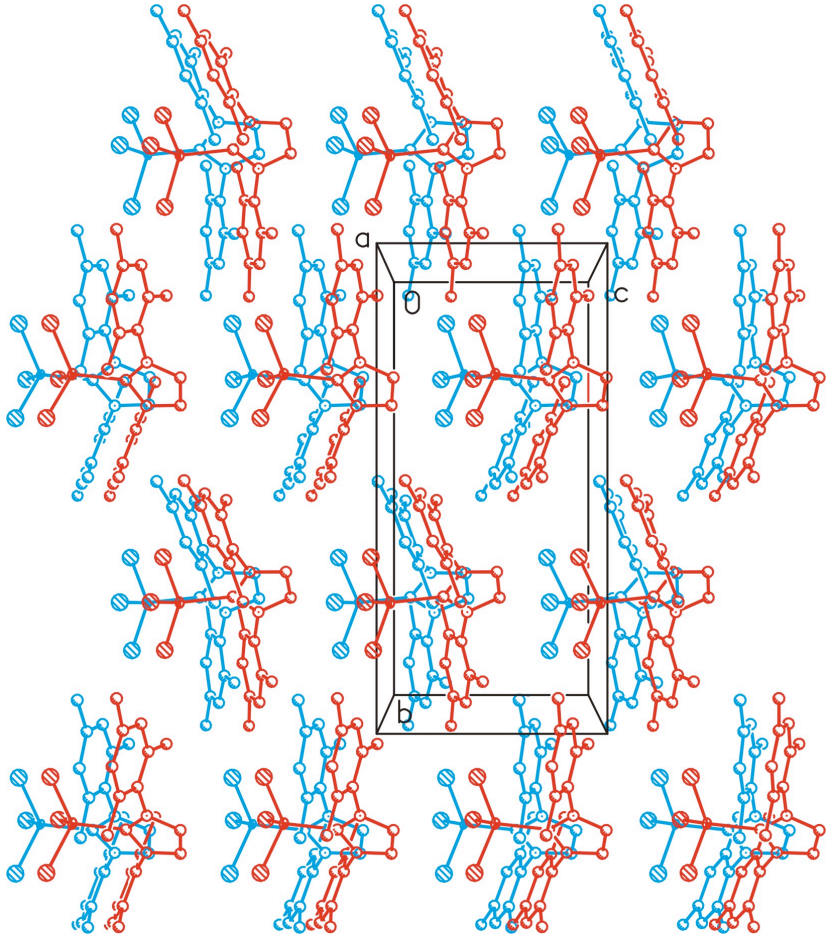

Figure 27. Crystal packing of **Ga2** with view along the *a*-axis showing the shifted position of the molecules. Hydrogen atoms are omitted for clarity

Interestingly, [(IPrMe)$GaCl_3$] **Ga3** (IPrMe = 1,3-diisopropyl-4,5-dimethyl-imidazol-2-ylidene), that crystallizes in the triclinic space group $P\bar{1}$ (see Figure 28, selected bond lengths and angles are given in Table 21), presented a much shorter Ga–C(1) bond than its

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known trihydride and trimethyl congeners, 2.011(4) Å, 2.071(5) Å and 2.13(2) Å respectively. This is probably due to a stronger interaction between the NHC and the electron-poor gallium bearing three chloride ligands.

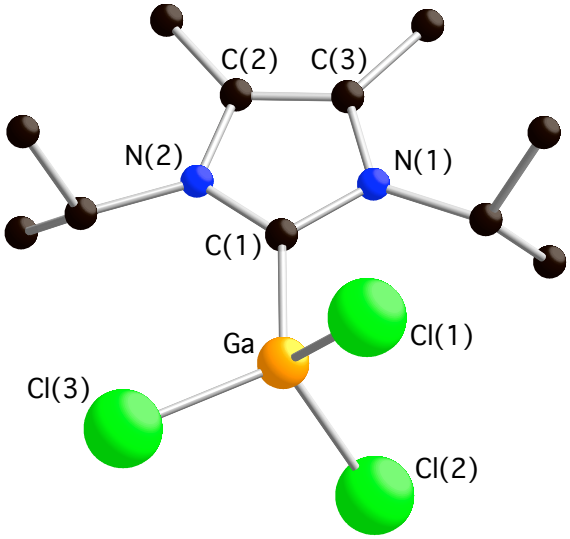

Figure 28. Ball-and-stick representation of [(IPrMe)$GaCl_3$] **Ga3** (hydrogen atoms are omitted for clarity)

All three complexes adopt a slightly distorted tetragonal pyramid geometry around the gallium center. In all cases, the gallium-carbene bond, Ga–C(1), was much shorter than the Ga–Cl bonds by 0.18 Å on average, with the IMes-containing adduct presenting the shortest of all Ga–C(1) bonds, 1.954(4) Å. A consequence of this feature could be observed in the wider carbene–gallium–chloride angle when compared to the Cl–Ga–Cl angle, which is believed to be an effect of the steric pressure of the NHC substituents onto the chlorides. Remarkably, this effect was significant only in **Ga1** and **Ga2**, both possessing bulky aryl substituted moieties on the NHC nitrogens. The structure of **Ga3**, translating the slight hindrance of the IPrMe ligand, presented a near-perfect tetragonal pyramid arrangement with C–Ga–Cl and Cl–Ga–Cl angles very close to 109º.

It is noteworthy that regardless of the steric hindrance brought about by the NHC ligand, the [(NHC)$GaCl_3$] adducts described here are indefinitely air- and moisture-stable and do not decompose in solution, even in polychlorinated solvents.[269]

[269] As a testimony to their stability, samples of **Ga1**, **Ga2**, and **Ga3** retrieved from our laboratories in New Orleans showed no signs of decomposition by ^{1}H and ^{13}C NMR after being subjected for three months to harsh environmental conditions (≈35°C, high humidity and high level of volatile chemicals) imposed by hurricane Katrina.

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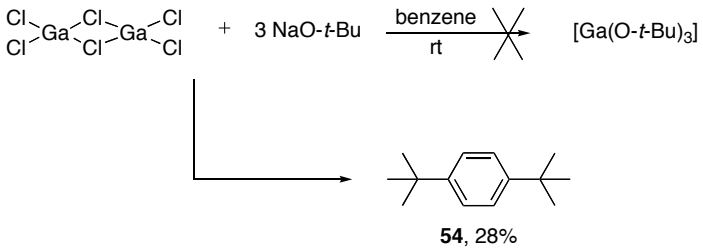
Finally, it should be noted that we envisaged synthesizing the corresponding alkoxide complexes, namely [(NHC)Ga(OR)$_3$]. Therefore, we primarily carried out the reaction between $GaCl_3$ and NaO-*t*-Bu in benzene in order to obtain [Ga(O-*t*-Bu)$_3$].[270] Unexpectedly, we only observed the formation of aryl derivative **54** (Scheme 31).



Scheme 31. Attempted synthesis of [Ga(O-*t*-Bu)$_3$]

The formation of *p*-di-*tert*-butylphenyl **54** is likely the result of a double Friedel-Crafts reaction promoted by the gallium center. Further attempts using NaO-*t*-Am instead of NaO-*t*-Bu resulted in the formation of a complex mixture, as evidenced by ^{1}H and ^{13}C NMR.

III. Preliminary catalytic trials

A. Enyne cycloisomerization

Since Ga^{III} salts are known to be good activators of π-bonds,[267,271] we first attempted to use complex **Ga1** in an enyne cycloisomerization reaction. Notably, we sought a precursor for which a reactivity profile was known in the literature, so that we could compare catalytic activities if needed. Hence, enyne **55**, which leads to interesting cycloisomerized products in the presence of $PtCl_2$,[272] was reacted in the presence of 5 mol % of [(IPr)$GaCl_3$] in toluene (Eq 32). After several hours of stirring, first at room temperature, then at 80ºC, no reaction could be observed. We then added 1 equivalent of $AgBF_4$, in order to abstract a chloride on the gallium and liberate a coordination site. The starting enyne was consumed in 30 min but led to a complex mixture of unidentified products.

[270] (a) Mehrotra, R. C.; Mehrotra, R. K. *Curr. Science* **1964**, *33*, 241. (b) Bindal, S. R.; Mathur, V. K.; Mehrotra, R. C. *J. Chem. Soc. A: Inorg. Phys. Theor.* **1969**, 863–867.
[271] For a review, see: Yamaguchi, M.; Nishimura, Y. *Chem. Commun.* **2008**, 35–48.
[272] Mainetti, E.; Mouriès, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132–2135.

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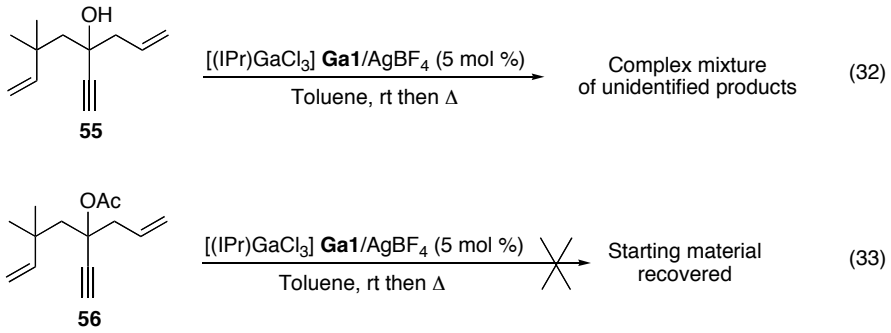
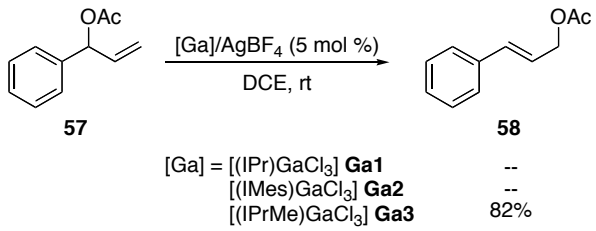


The corresponding acetate of **55**, **56**, was similarly subjected to 5 mol % of **Ga1** but returned mainly starting material even upon addition of $AgBF_4$ (Eq 33).

B. Allylic rearrangement

Pursuing our efforts to uncover catalytic applications for the $[(NHC)GaCl_3]$ complexes synthesized, we turned our attention to alkene activation. We notably looked at a possible catalytic activity in the allylic rearrangement reaction. We chose the easily accessible allylic acetate **57** for preliminary tests. Whereas the use of **Ga1** and **Ga2** resulted in the formation of complex mixtures of unidentified products, 5 mol % of **Ga3** cleanly produced, at room temperature and in one hour, 82% of the rearranged acetate (Scheme 32).



Scheme 32. $[(NHC)GaCl_3]$-Catalyzed allylic rearrangement

IV. Conclusion

In conclusion, we have described the very straightforward synthesis of three air- and moisture-stable NHC-containing Ga^{III} complexes. These $[(NHC)GaCl_3]$ adducts were fully characterized and the first X-ray structures of $[(NHC)GaCl_3]$ adducts could be obtained. We therefore have demonstrated that the presence of a NHC, possessing indifferently aryl or alkyl groups, clearly has a stabilizing effect on $GaCl_3$.

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The catalytic activity of these complexes was tested in two different organic transformations. While they failed to efficiently catalyze the enyne cycloisomerization reaction, examination of an allylic rearrangement reaction proved more successful. Interestingly, the latter transformation was found to be efficiently catalyzed by [(IPrMe)$GaCl_3$] whereas [(IPr)$GaCl_3$] and [(IMes)$GaCl_3$] led only to oligomerization of the substrate. This last result indicates that these group 13 adducts can indeed lead to catalytic applications and that the nature of the NHC bound to the gallium center is key for fine-tuning their activity.

V. Experimental section

A. General information

- $GaCl_3$ was purchased as a crystalline solid from Aldrich, used as received and stored in a glove box.
- All NHCs were synthesized according to literature procedures.[97,230]
- Dry THF was distilled over Ph_2CO/Na. Anhydrous pentane was used as purchased.
- Flash chromatography was performed on silica gel 60 (230-400 mesh, Silicycle).
- ^1H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian-300 or Varian-400 MHz spectrometer at ambient temperature in $CDCl_3$, C_6D_6 or acetone-d_6 (Cambridge Isotope Laboratories, Inc). Assignments of some ^1H and ^{13}C NMR signals rely on COSY and/or HMBC experiments.
- Infrared spectra were recorded on a Bruker TENSOR 27 equipped with an ATR Diamond.
- HRMS analyses were performed by the Mass Spectrometry Facility at the Institute of Chemical Research of Catalonia (ICIQ), Tarragona (Spain).
- Elemental analyses were performed at Robertson Microlit Laboratories, Inc., Madison, NJ, USA.

B. Synthesis of [(NHC)$GaCl_3$] Ga1-Ga3

General procedure: In a glovebox, in a 250 mL round-bottom flask, NHC (1 equiv) was mixed with 70 mL of pentane and stirred for 30 min in order to solubilize it. $GaCl_3$ (1

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equiv), as a crystalline solid, was then added in one portion, resulting in the immediate appearance of a white precipitate. The solution was stirred for one hour and then filtered in air. The white solid collected was then washed with MeOH and dried.

[(IPr)GaCl$_3$] Ga1. The general procedure, using IPr (400 mg, 1.023 mmol) and $GaCl_3$ (180 mg, 1.023 mmol), yielded 467 mg (81%) of the title compound.
^{1}H NMR (400 MHz, acetone-d_6): δ 8.15 (s, 2H, =CH^{NHC}), 7.57 (t, *J* = 7.6 Hz, 2H, *p*-H^{Ar}), 7.40 (d, *J* = 7.6 Hz, 4H, *m*-H^{Ar}), 2.63 (sept, *J* = 6.8 Hz, 4H, C*H*(CH$_3$)$_2$), 1.38 (d, *J* = 6.8 Hz, 12H, Me), 1.18 (d, *J* = 6.8 Hz, 12H, Me). **^{13}C NMR (100 MHz, CD_2Cl_2):** δ 145.7 (C, C^{Ar}), 132.5 (C, C^{Ar}), 131.4 (CH, =CH^{NHC}), 126.4 (CH, C^{Ar}), 124.2 (CH, C^{Ar}), 29.1 (CH, *C*H(CH$_3$)$_2$), 25.6 (CH$_3$, CH(*C*H$_3$)$_2$), 22.3 (CH$_3$, CH(*C*H$_3$)$_2$). **Calcd. HRMS** for $C_{29}H_{39}Cl_3GaN_3Na$ (M+Na+MeCN): 626.1363. Found: 626.1358. **Elemental analysis** calcd. (%) for $C_{27}H_{36}Cl_3GaN_2$ (MW 564.65): C, 57.43; H, 6.43; N, 4.96. Found: C, 57.78; H, 6.15; N, 4.99. **CCDC-628373** contains the supplementary crystallographic data for this complex.

[(IMes)GaCl$_3$] Ga2. The general procedure, using IMes (800 mg, 2.632 mmol) and $GaCl_3$ (465 mg, 2.634 mmol), yielded 1.101 g (87%) of the title compound.
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.71 (s, 4H, H^{Ar}), 5.78 (s, 2H, =CH^{NHC}), 2.05 (s, 6H, *p*-Me), 2.00 (s, 12H, *o*-Me). **^{13}C NMR (100 MHz, acetone-d_6):** δ 146.6 (C, C^{Ar}), 136.3 (CH, =CH^{NHC}), 134.4 (C, C^{Ar}), 130.2 (CH, C^{Ar}), 127.1 (C, C^{Ar}), 21.2 (CH$_3$, *p*-Me), 17.9 (CH$_3$, *o*-Me). **Calcd. HRMS** for $C_{23}H_{27}Cl_2GaN_3$ (M-Cl+MeCN): 484.0838. Found: 484.0851. **Elemental analysis** calcd. (%) for $C_{21}H_{24}Cl_3GaN_2$ (MW 480.49): C, 52.49; H, 5.03; N, 5.83. Found: C, 52.48; H, 5.15; N, 5.99. **CCDC-631974** contains the supplementary crystallographic data for this complex.

[(IPrMe)GaCl$_3$] Ga3. The general procedure, using IPrMe (364 mg, 2.00 mmol) and $GaCl_3$ (352 mg, 2.00 mmol), yielded 463 mg (65%) of the title compound.
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.73 (sept, *J* = 7.6 Hz, 2H, C*H*(CH$_3$)$_2$), 1.35 (s, 6H, Me^{NHC}), 0.98 (d, *J* = 7.6 Hz, 12H, CH(C*H*$_3$)$_2$). **^{13}C NMR (100 MHz, C_6D_6):** δ 127.4 (C, C^{NHC}), 53.4 (CH, *C*H(CH$_3$)$_2$), 21.6 (CH$_3$, CH(*C*H$_3$)$_2$), 10.4 (CH$_3$, Me^{NHC}). **Calcd. HRMS** for $C_{13}H_{23}Cl_2GaN_3$ (M-Cl+MeCN): 360.0525. Found: 360.0533. **Elemental analysis** Calcd. (%) for $C_{11}H_{20}Cl_3GaN_2$ (MW 356.36): C, 37.07; H, 5.66; N, 7.86. Found: C, 37.23; H, 5.85; N, 7.71. **CCDC-628372** contains the supplementary crystallographic data for this complex.

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C. Crystallographic data for [(NHC)$GaCl_3$] Ga1-Ga3

Crystallographic data are summarized in Table S1. CCDC-628373 ([(IPr)$GaCl_3$] **Ga1**), CCDC-631974 ([(IMes)$GaCl_3$] **Ga2**) and CCDC-628372 ([(IPrMe)$GaCl_3$] **Ga3**) contain the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336 033; E-mail: deposit@ccdc.cam.ac.uk).

Table S1. Crystallographic data for **Ga1**, **Ga2**, and **Ga3**

	[(IPr)$GaCl_3$] Ga1	**[(IMes)$GaCl_3$] Ga2**	**[(IPrMe)$GaCl_3$] Ga3**
Chemical formula	$C_{27}H_{36}Cl_3GaN_2$	$C_{21}H_{24}Cl_3GaN_2$	$C_{11}H_{20}Cl_3GaN_2$
M (g.mol^{-1})	564.65	480.49	356.36
T (K)	150(2)	100(2)	273(2)
Crystal system	Monoclinic	Orthorhombic	Triclinic
Space group	$P2_1/c$	$Pca2_1$	$P\bar{1}$
a (Å)	18.3566(8)	17.021(2)	9.3044(14)
b (Å)	16.1415(7)	16.803(2)	9.5428(14)
c (Å)	20.1819(8)	7.9054(11)	10.4460(16)
α (°)	90.00	90.00	100.038(3)
β (°)	103.0580(10)	90.00	94.926(3)
γ (°)	90.00	90.00	117.304(2)
V (Å^3)	5825.3(4)	2261.0(5)	796.8(2)
Z	8	4	2
Density calcd. (g.cm^{-3})	1.288	1.412	1.485
Absorb. coeff. (mm^{-1})	1.237	1.580	2.212
F(000)	2352	984	364
Crystal size (mm)		0.40 x 0.05 x 0.03	0.50 x 0.30 x 0.15
θ (°)	2.12–22.50	2.70–37.58	2.475–30.851
Index range *hkl*	-19–19, -17–17, -21–21	-29–29, -28–28, -7–13	-11–11, -11–11, -12–12
Data/Restraints/Parameter	7614/548/611	9569/25/500	2795/140/160
Goodness-of-fit on F^2	0.923	1.053	1.134
R values (all data)	R_1 = 0.0264 wR_2 = 0.0687	R_1 = 0.0647 wR_2 = 0.1174	R_1 = 0.0486 wR_2 = 0.1236

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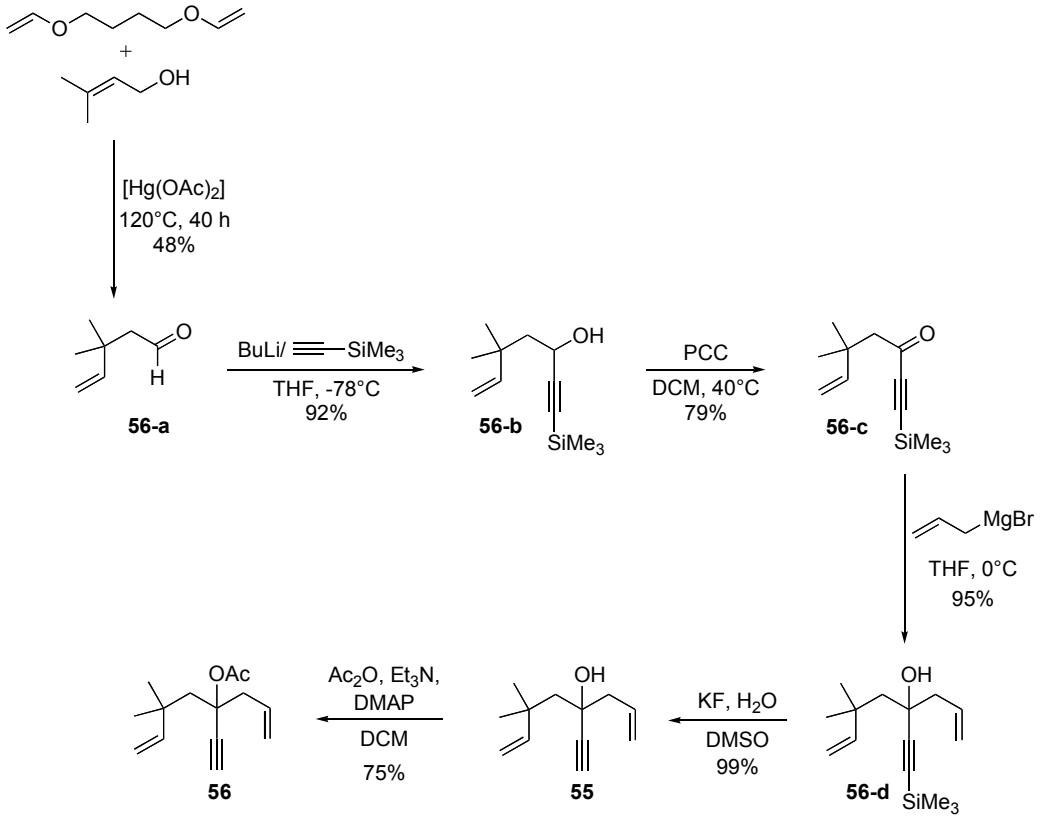
D. Catalytic trials in enyne cycloisomerization

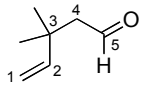
1. Synthesis of enynes 55 and 56

General synthetic scheme



Procedures and characterization

3,3-Dimethyl-pent-4-enal (56-a)[273]



56-a

4-Butanediol divinyl ether (13.86 g, 97 mmol, 1 equiv), 3-methyl-2-butane-1-ol (9.76 mL, 97 mmol, 1 equiv) and mercury(II) acetate (0.56 g, 1.75 mmol, 0.018 equiv) were introduced in a round-bottom flask under nitrogen. The mixture was heated up to 120°C. After 40 hours, the flask was allowed to cool down to room temperature. Then, water (40 mL) was added and the organic layer was extracted with diethyl ether. The combined organic layers were washed with water, dried over magnesium sulfate and evaporated. The residue was distilled under reduced pressure (b.p. 35°C, 20 mm Hg) to give 5.2 g (47 mmol) of **56-a** (48% yield) as a colorless oil.

[273] Ang, K. H.; Bräse, S.; Steinig, A. G.; Meuer, F. E.; Llebaria, A.; Voigt K.; de Meijere, A. *Tetrahedron* **1996**, *52*, 11503–11528.

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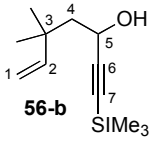
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H, H^5), 5.90 (dd, *J* = 16.9, 10.8 Hz, 1H, H^2), 5.01 (m, 2H, H^1), 2.34 (s, 2H, $2H^4$), 1.15 (s, 6 H, $2CH_3$). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 203.2 (CH, C^5), 152.0 (CH, C^2), 112.0 (CH_2, C^1), 54.8 (CH_2, C^4), 35.9 (C, C^3), 29.4 ($2CH_3$). **IR (neat):** ν 3085, 2963, 2875, 1721, 1638 cm^{-1}.

5,5-Dimethyl-1-trimethylsilanyl-hept-6-en-1-yn-3-ol (**56-b**)

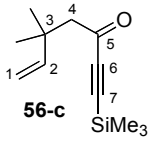


56-b

A 50 mL flask, containing 10 mL of dry THF, was cooled at -78°C, under argon atmosphere. First trimethylsilylacetylene (2.55 mL, 18 mmol, 1.5 equiv) and then BuLi (2.3 M in hexanes, 6.15 mL, 14.4 mmol, 1.2 equiv) were added. After 20 min, aldehyde **56-a** (1.5 g, 12 mmol, 1 equiv) diluted in 8 mL of dry THF, was transferred. The mixture was kept 30 min at -78°C and then allowed to warm up to room temperature. The mixture was then quenched with saturated NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give crude **56-b**, which was engaged in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (dd, *J* = 17.4, 10.6 Hz, 1H, H^2), 4.97 (m, 2H, H^1), 4.37 (m, 1H, H^5), 1.77 (d, *J* = 6.8 Hz, 2H, $2H^4$), 1.07 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 0.14 (s, 9H, TMS). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 148.1 (CH, C^2), 111.6 (CH_2, C^1), 108.1 (C, C^6), 89.3 (C, C^7), 60.9 (CH, C^5), 50.6 (CH_2, C^4), 36.5 (C, C^3), 28.2 (CH_3), 26.5 (CH_3), 0.13 (CH_3, TMS). **IR (neat):** ν 3352, 3084, 2961, 2172, 1637 cm^{-1}.

5,5-Dimethyl-1-trimethylsilanyl-hept-6-en-1-yn-3-one (**56-c**)



56-c

PCC (3.9 g, 18 mmol, 1.5 equiv) was mixed with 19.4 g of neutral alumina in CH_2Cl_2 (45 mL). A solution of **56-b** (2.3 g, 11 mmol, 1 equiv) in CH_2Cl_2 (30 mL) was then added. The resulting suspension was stirred at room temperature overnight. The mixture was then filtered over Celite and concentrated to yield a yellow oil which was engaged in the next step without further purification.

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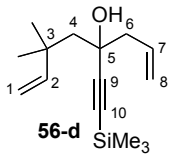
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (dd, *J* = 17.4, 10.6 Hz, 1H, H^2), 4.95 (m, 2H, H^1), 2.56 (s, 2H, $2H^4$), 1.14 (s, 6H, $2CH_3$), 0.21 (s, 9H, TMS). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 186.8 (C, C^5), 146.8 (CH, C^2), 111.4 (CH_2, C^1), 103.9 (C, C^6), 97.9 (C, C^7), 57.0 (CH_2, C^4), 37.2 (C, C^3), 27.2 (CH_3), -0.50 (CH_3, TMS). **IR (neat):** ν 3085, 2962, 2930, 2116, 1739, 1640 cm^{-1}.

6,6-Dimethyl-4-trimethylsilanylethynyl-octa-1,7-dien-4-ol (**56-d**)

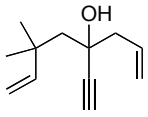


56-d

At 0°C, allyl magnesium bromide (1 M in Et_2O, 12 mL, 12 mmol, 2 equiv) was added to a solution of **56-c** (1.25 g, 6 mmol, 1 equiv) in dry THF (10 mL). The mixture was then allowed to warm up to room temperature, quenched with saturated NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give the crude oil **56-d**, which was engaged without further purification in the next step.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.06 (dd, *J* = 17.7, 10.8 Hz, 1H, H^2), 5.90 (m, 1H, H^7), 5.14-4.94 (m, 4H, $2H^1$ + $2H^8$), 2.39-2.28 (m, 2H, $2H^6$), 1.71 (s, 2H, $2H^4$), 1.25 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 0.12 (s, 9H, TMS). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 149.4 (CH, C^2), 133.6 (CH, C^7), 119.2 (CH_2, C^1), 111.3 (CH_2, C^8), 109.3 (C, C^9), 90.3 (C, C^{10}), 69.8 (C, C^5), 52.8 (CH^2, C^6), 49.6 (CH_2, C^4), 37.2 (C, C^3), 30.2 (CH_3), 27.1 (CH_3), 0.00 (CH_3, TMS). **IR (neat):** ν 3430, 3081, 2961, 2931, 2166, 1639 cm^{-1}.

4-Ethynyl-6,6-dimethylocta-1,7-dien-4-ol (**55**)



55

Crude alcohol **56-d** (5 mmol, 1 equiv) was diluted with 20 mL of DMSO. KF (435 mg, 7.5 mmol, 1.5 equiv) and a few drops of water were added. After 45 min the reaction mixture was quenched with water and extracted with diethyl ether. The combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated to give a yellow oil, which, after flash chromatography on silica gel (pentane/Et_2O, 90/10), yielded 609 mg (57% over 4 steps) of the title compound. Spectroscopic data were in accordance with the literature.[272]

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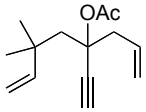
4-Ethynyl-6,6-dimethylocta-1,7-dien-4-yl acetate (56)



56

Alcohol **55** (356 mg, 2 mmol, 1 equiv), DCE (6 mL), DMAP (52 mg, 0.6 mmol, 0.3 equiv), Et_3N (1.3 mL, 8 mmol, 4 equiv), and Ac_2O (0.36 mL, 4 mmol, 2 equiv) were added in turn in a round-bottom flask equipped with a condenser. The reaction mixture was heated overnight at 80°C, quenched with a saturated aqueous NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and evaporated to give a crude oil that was purified by flash chromatography on silica gel (pentane/MTBE, 90/10) affording 413 mg (94%). Spectroscopic data were in accordance with the literature.[272]

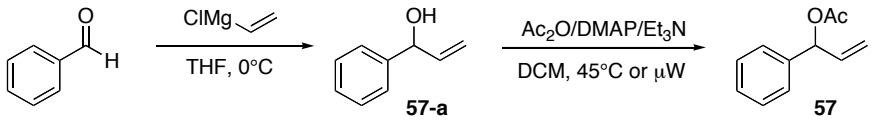
2. General procedure for the cycloisomerization reactions using [(IPr)GaCl$_3$]

To a solution of [(IPr)$GaCl_3$] (14 mg, 0.025 mmol, 5 mol %) in toluene (15 mL) in a scintillation vial equipped with a stirring bar, $AgBF_4$ (2.5 mg, 0.025 mmol, 5 mol %) was added. Then, a 5 mL toluene solution of dienyne **55** or **56** (0.5 mmol) was added. The reaction was monitored by TLC. As no conversion was observed by TLC, the mixture was then heated up at 80ºC. When no starting material remained, the solvent was removed and the residue was dissolved in pentane, filtered through Celite and concentrated.

E. Catalytic trials in allylic rearrangement

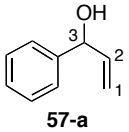
1. Synthesis of allylic acetate 57

General synthetic scheme



Procedures and characterization

1-Phenylprop-2-en-1-ol (57-a)



57-a

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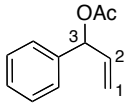
In an oven-dried round-bottom flask, a solution of the benzaldehyde (1.06 g, 10 mmol, 1 equiv) in THF (20 mL) was stirred for 10 minutes under nitrogen at 0ºC. To this reaction mixture, vinyl magnesium chloride 1.6 M (9.4 mL, 15 mmol, 1.5 equiv) was added and the reaction was stirred for 20 minutes. The reaction was then allowed to warm up to room temperature, quenched with a saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and evaporated to give the crude allylic alcohol **57-a** that was engaged in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.31 (m, 5H, H^{Ar}), 6.06 (ddd, *J* = 16.4, 10.3, 6.0 Hz, 1H, H^2), 5.35 (dd, *J* = 16.4, 1.5 Hz, 1H, H^1), 5.22-5.15 (m, 2H, H^1 + H^3), 3.18 (s broad, 1H, OH). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 142.6 (C, C^{Ar}), 140.2 (CH, C^2), 128.3 (CH, C^{Ar}), 127.4 (CH, C^{Ar}), 126.2 (CH, C^{Ar}), 114.7 (CH_2, C^1), 74.9 (CH, C^3).

1-Phenylallyl acetate (**57**)



57

Allylic alcohol **57-a** (10 mmol, 1 equiv), 1,2-dichloroethane (DCE) (40 mL), DMAP (0.360 g, 3.0 mmol, 0.3 equiv), Et_3N (5.6 mL, 40 mmol, 4 equiv), and Ac_2O (1.8 mL, 20 mmol, 2 equiv) were added in turn in a round-bottom flask equipped with a condenser. The reaction mixture was heated overnight at 80°C. The reaction was then quenched with a saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and evaporated to give a crude oil that was purified by flash chromatography (pentane/MTBE, 95/5) on silica gel, yielding 1.269 g (72% over 2 steps) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.32 (m, 5H, H^{Ar}), 6.27 (d, *J* = 5.9 Hz, 1H, H^3), 6.00 (ddd, *J* = 17.1, 10.4, 5.9 Hz, 1H, H^2), 5.32-5.21 (m, 2H, H^1), 2.09 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.0 (C, C=O), 139.0 (C, C^{Ar}), 136.4 (CH, C^2), 128.7 (CH, C^{Ar}), 128.3 (CH, C^{Ar}), 127.3 (CH, C^{Ar}), 117.0 (CH_2, C^1), 76.3 (CH, C^3), 21.3 (CH_3, OAc). **Calcd. HMRS** for $C_{11}H_{12}O_2Na$ (M+Na): 199.0735. Found: 199.0739.

2. Procedure for the allylic rearrangement reactions using [(NHC)$GaCl_3$]

To a DCE solution (4 mL) of [(NHC)$GaCl_3$] (5 mol %) in a scintillation vial, $AgBF_4$ (5 mol %) was added. The solution instantly became cloudy and the reaction mixture was stirred for

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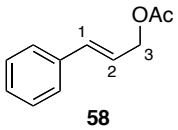
1 min before a DCE solution (1 mL) of allylic acetate **57** (44 mg, 0.25 mmol) was added. The reaction mixture was monitored by TLC. The resulting mixture was concentrated, dissolved in pentane, filtered through Celite and concentrated.

Cinnamyl acetate[274] **(58)**



58

The general procedure, using **Ga3** yielded, as determined by ^{1}H NMR, 82% of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.37 (m, 2H, H^{Ar}), 7.35-7.22 (m, 3H, H^{Ar}), 6.65 (d, *J* = 15.9 Hz, 1H, H^{1}), 6.65 (dt, *J* = 15.9, 6.5 Hz, 1H, H^{2}), 4.73 (dd, *J* = 6.5, 1.3 Hz, 2H, H^{3}), 2.10 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 171.0 (C, C=O), 136.3 (C, C^{Ar}), 134.4 (CH, C^{1}), 128.8 (CH, C^{Ar}), 128.2 (CH, C^{Ar}), 126.8 (CH, C^{Ar}), 123.3 (CH, C^{2}), 65.3 (CH_2, C^{3}), 21.2 (CH_3, OAc). **Calcd. HMRS** for $C_{11}H_{12}O_2Na$ (M+Na): 199.0735. Found: 199.0737.

[274] Cinnamyl acetate is a commercially available product, CAS # [103-54-8].

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CHAPTER III

Au

Well-Defined [(NHC)Au^{I}] Pre-Catalysts in Homogeneous Catalysis

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I. Introduction

As presented in the Objectives section of this work (Introduction chapter, **VI.B.3**), a major goal of this work was the use in homogeneous catalysis of new NHC–gold(I) complexes previously synthesized in the laboratory. We began this research project in September 2004, at a time where only one report,[275] disclosed in 2003, using NHCs as ligands in gold catalysis had appeared. In the following introduction section, we present the main achievements to date with this type of compounds.

A. Generalities

Gold catalysis, notably in its homogeneous catalysis incarnation, has emerged from a mere curiosity to a now very frequently publicized source of novel catalytic transformation of interest to the organic community.[276] Even though the use of simple gold(I) and gold(III) salts – such as AuCl, $AuCl_3$ and $NaAuCl_4$ – has been reported, most studies employ gold(I) chloride complexes bearing a monodentate ancillary ligand, [(PPh_3)AuCl] certainly being the most frequently encountered catalyst.[276] These linear dicoordinated gold compounds, upon activation by a chloride "abstractor" such as a silver(I) salt, generate a mono-ligated cationic catalyst, which requires strong electronic and steric stabilization from its ancillary ligand. Therefore, it comes as no surprise that N-heterocyclic carbenes, commonly described as excellent σ-donors, are becoming increasingly employed in this field.

The first NHC–gold(I) complex was isolated in 1973,[277] but it is only recently that these compounds, mainly as Au^I species of formulae [(NHC)AuCl], have gained popularity, taking advantage of straightforward synthetic routes developed recently.[278] Notably, NHC–gold complexes have encountered successes as potential drugs,[279] luminescent

[275] Schneider, S. K.; Herrmann, W. A.; Herdtweck, E. *Z. Anorg. Allg. Chem.* **2003**, *629*, 2363–2370.
[276] For recent general reviews on homogeneous Au-catalysis, see: (a) Muzard, J. *Tetrahedron* **2008**, DOI: 10.1016/j.tet.2008.04.018. (b) Li, C.-J. *Tetrahedron* **2008**, DOI: 10.1016/j.tet.2008.03.083. (c) Crone, B.; Kirsch, S. F. *Chem–Eur. J.* **2008**, *14*, 3514–3522. (d) Bongers, N.; Krause, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 2178–2181. (e) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885–3903. (f) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (g) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (h) Hashmi, A. S. K. *Catal. Today* **2007**, *122*, 211–214. (i) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403. (j) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346. (k) Patil, N. T.; Yamamoto, Y. *ARKIVOC* **2007**, 6–19. (l) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896–7936. (m) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990–6993. (n) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387–391.
[277] Minghetti, G.; Bonati, F. *J. Organomet. Chem.* **1973**, *54*, C62–C63.
[278] For a review on NHC–gold complexes, see: Lin, I. J. B; Vasam, C. S. *Can. J. Chem.* **2005**, *83*, 812–825.
[279] Baker, M. V.; Barnard, P. J.; Berners-Price, S. J.; Brayshaw, S. K.; Hickey, J. L.; Skelton, B. W.; White, A. H. *Dalton Trans.* **2006**, 3708–3715 and references therein.

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devices,[280] and have permitted to uncover important general features regarding the nature of the metal–NHC bond.[281]

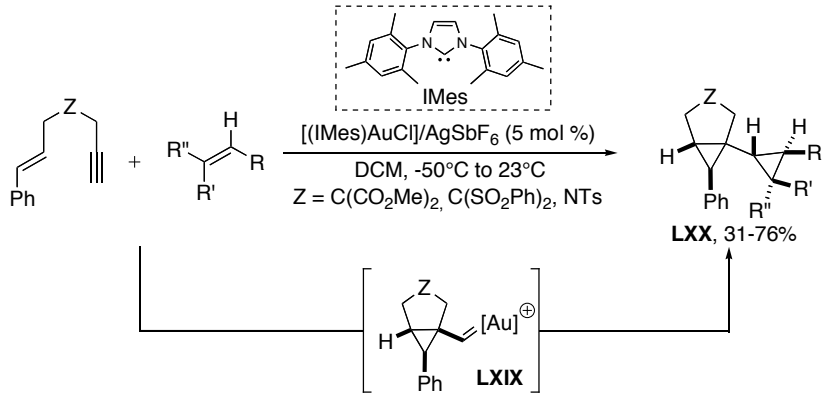
In this introduction, we will focus on the applications of NHC–gold(I) and NHC–gold(III) compounds in homogeneous and heterogeneous catalysis. Their broad reactivity scope will notably be emphasized as well as selectivity issues when compared to other ligands bound to gold centers.

B. Gold–carbene generation from acetylenic substrates

1. Enyne cycloisomerization and related reactions

The skeletal rearrangement of enynes is arguably the most popular reaction in gold catalysis.[276] Nevertheless, only a handful of reports have appeared that use NHC-based gold catalysts, clearly hinting at further studies in this field.

Recently, the efficient use of [(IMes)AuCl] (IMes = *N*,*N*'-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene), in conjunction with $AgSbF_6$, was reported for the intermolecular bis-cyclopropanation of 1,6-enynes with alkenes (Scheme 33).[282,283] In this transformation, the first cyclopropanation occurs intramolecularly, leading to cyclopropylcarbene intermediate **LXIX**, which is trapped by an external alkene to afford bis-cyclopropyl compounds **LXX**.



Scheme 33. [(IMes)AuCl]-Catalyzed intermolecular bis-cyclopropanation of enynes with alkenes

[280] Barnard, P. J.; Wedlock, L. E.; Baker, M. V.; Berners-Price, S. J.; Joyce, D. A.; Skelton, B. W.; Steer, J. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 5966–5970.
[281] Hu, X.; Castro-Rodriguez, I.; Olsen, K.; Meyer, K. *Organometallics* **2004**, *23*, 755–764. See also ref. 82.
[282] López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6029–6032.
[283] As early as 2005, the Echavarren group reported the activity of [(IMes)AuCl] in the methoxycyclization of 1,6-enynes but this NHC–Au complex was only used during the optimization studies, see: Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179.

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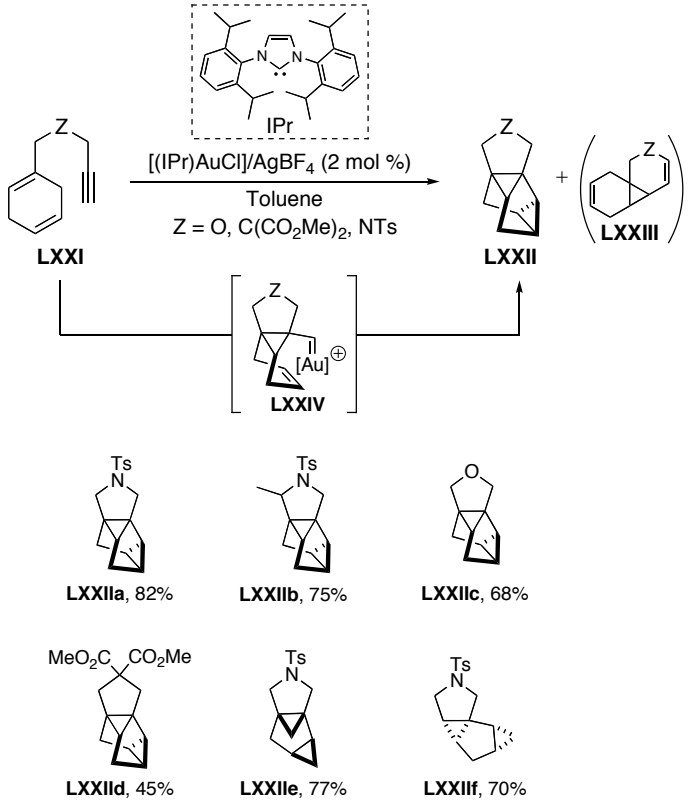
For this specific transformation, the NHC ligand on gold outperformed tertiary phosphine and phosphite ligands both in terms of yield and selectivity. The scope of the reaction was found broad, encompassing cyclic and acyclic alkenes. Interestingly, in the presence of an unsymmetrical diene, the second cyclopropanation occured at the less hindered C=C bond. Subsequent developments by Chung allowed for the synthesis of tetracyclo[3.3.0.0^{2,8}.0^{4,6}]octanes **LXXII** (Scheme 34) using [(IPr)AuCl] (IPr = *N*,*N*'-bis(2,6-diisopropylphenyl)imidazol-2-ylidene).[284] These highly strained compounds were obtained from a double intramolecular cyclopropanation of 1,6-enynes **LXXI**, which possess a 1,4-cyclohexadiene core, *via* cyclopropylcarbene **LXXIV**. Optimization studies revealed the key importance of solvent and of the nature of the silver salt, notably allowing for a better control of the **LXXII**/**LXXIII** selectivity; the architectural scope is shown in Scheme 34. Of note, the use of acyclic 1,4-dienes, instead of the rigid 1,4-cyclohexadiene framework, produced compounds **LXXIIe** and **LXXIIf**, other highly interesting entries into cyclopropyl-rich fused polycyclic structures.



Scheme 34. [(IPr)AuCl]-Catalyzed intramolecular bis-cyclopropanation

Other evidence supporting the involvement of a cyclopropylcarbene species as inter-

[284] Kim, S. M.; Park, J. H.; Choi S. Y.; Chung, Y. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 6172–6175.

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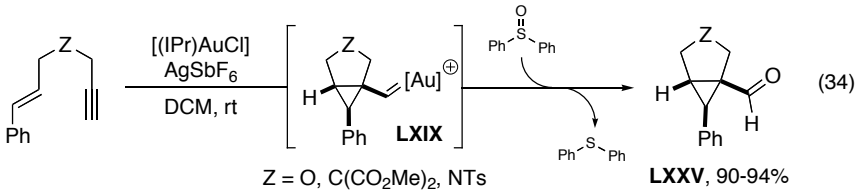
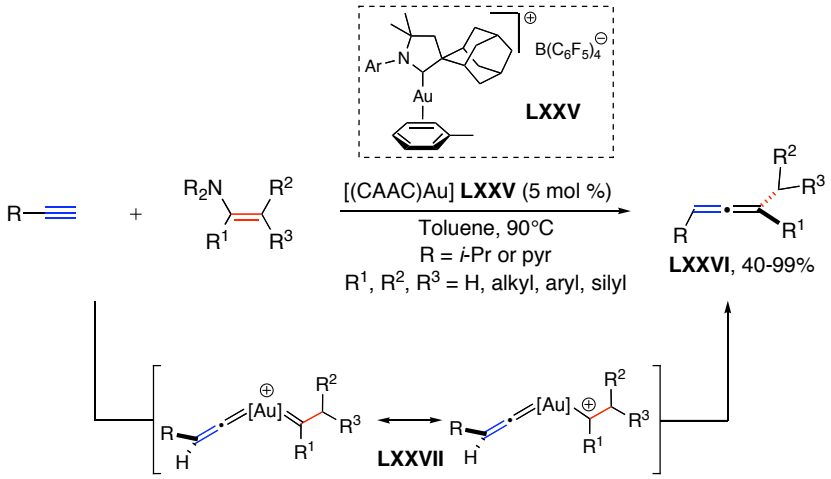
mediate in the isomerization of 1,6-enynes was reported by Toste and co-workers.[285] Different types of Au-catalyzed enyne cycloisomerizations were carried out in the presence of diphenylsulfoxide, which was found to oxidize the carbenic intermediate **LXIX** (Eq 34). The IPr-containing catalyst [(IPr)AuCl] exhibited superior activity in these oxidation reactions when compared to the PPh_3- or IMes-containing analogues.



The authors further showed the generality of the oxidative trapping of a carbenoid intermediate in other gold-promoted reactions such as diazo insertion and acetylenic Schmidt rearrangement. Of note, a series of isolated [(NHC)Au(NTf_2)] have been shown to catalyze a number of previously reported cycloisomerization reactions involving enynes.[286]

Bertrand recently reported the use of cyclic (alkyl)(amino)carbene ligand (CAAC) as highly stabilizing ligand for the synthesis of the η^2-toluene gold(I) adduct **LXXVI** (Scheme 35).[287]



Scheme 35. [(CAAC)Au]-Catalyzed cross-coupling of alkynes and enamines

This stable cationic catalyst was found to selectively form allenes of type **LXXVI** from enamines and terminal alkynes (Scheme 35), a reaction that usually produces propargylic amines. The authors, based on thorough mechanistic studies, proposed that the

[285] Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838–5839.
[286] Ricard, L.; Gagosz, F. *Organometallics* **2007**, *26*, 4704–4707.
[287] Lavallo, V.; Frey, G. D.; Kousar, S.; Donnadieu, B.; Bertrand, G. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 13569–13573.

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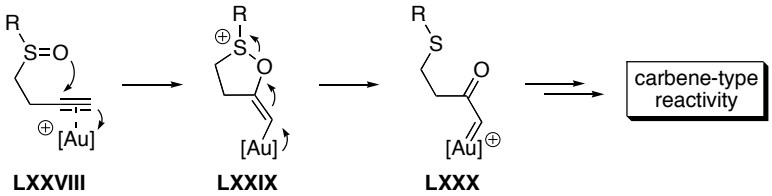
reaction could proceed through a gold acetylide intermediate from which formal coupling between a carbene and a vinylydene, both attached to the gold center (intermediate **LXXVII**), would allow for the formation of the three-carbon allenic core. Importantly, the use of AuCl, $[(PPh_3)AuCl]/KB(C_6F_5)_4$ or the neutral counterpart of **LXXV**, [(CAAC)AuCl], yielded only the previously reported propargyl amine product; stressing the requirement of both a cationic gold center and the presence of the CAAC ligand.

2. Homopropargylic sulfoxides

Homopropargylic sulfoxides exhibit an interesting reactivity, leading to generation of a gold–carbene species that has been investigated recently. The sulfoxide moiety acts as a nucleophile through its oxygen atom (Scheme 36, **LXXVIII** to **LXXIX**) and as a leaving group through its sulfur atom (Scheme 36, **LXXIX** to **LXXX**).



Scheme 36. Au-Promoted rearrangement of homopropargylic sulfoxides

The net result is an intramolecular redox process where the sulfoxide function in **LXXVIII** is converted into a sulfide function and the alkyne into an α-carbonyl gold carbenoid **LXXX**. Further reactivity is a function of the pendant groups. Arylsulfoxides have notably been employed and yielded benzothiepinones after insertion of the gold carbenoid into a C–H aryl bond.[288] Further studies demonstrated that this reaction could be equally performed with sulfimines, with final formation of enamines, and that 5-*exo*-dig versus 6-*endo*-dig attack occurred as a function of the substrate. Interestingly, in the case of a 6-*endo*-dig attack, the carbenoid was trapped by 1,2-migration of the sulfide, leading to α-thio conjugated enones. Alternatively, alkyl or aryl 1,2-migration can take place for substrates bearing a secondary or tertiary propargylic alcohol function such as **LXXXI**, leading to β-hydroxyenone **LXXXII** (Scheme 37).[289] Using unsymmetrical propargylic alcohols, the ability of 1,2-migration, in an intermediate such as **LXXXIII**, was demonstrated to follow the order aryl > alkyl > H. In all cases, it appeared that a NHC-based gold(I) catalyst,

[288] Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160–4161.
[289] (a) Li, G.; Zhang, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5156–5159. Very recently, Zhang further used $[(IPr)Au(NTf_2)]$ in the isomerization of propargylic acetates into 1,3-dienes, see: (b) Li, G.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 3740-3741.

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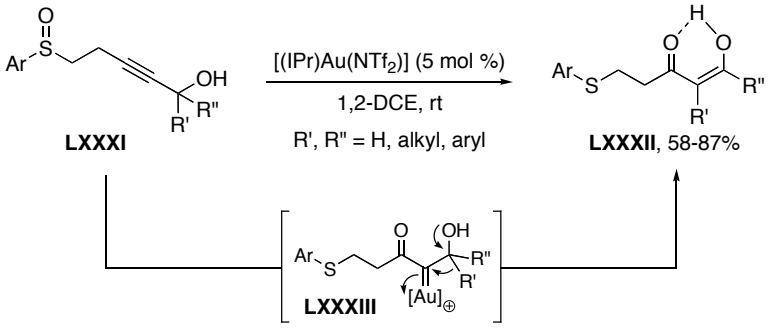
[(IMes)AuCl] for the synthesis of benzothiepinones[20] and [(IPr)Au(NTf$_2$)] for β-hydroxyenone formation,[21] were best suited for these transformations involving alkynylsulfoxides rearrangement.



Scheme 37. Au-Catalyzed formation of β-hydroxyenones

C. Alkene activation

Even though less studied – and less straightforward – than reactions involving alkynes, Au-catalysis can be extended to alkenes. The first report involving NHC–gold complexes in alkene activation only appeared in 2006 by Peris and Fernández who disclosed a reaction of diboration of olefins. They demonstrated that bis-NHC complexes **LXXXIV** and **LXXXV** (Figure 29) efficiently catalyzed the diboration of styrene and vinylcyclohexane at room temperature.[290] It should be added that this is so far the only report of gold catalysis employing complexes of formulae [(NHC)$_2$Au]X.

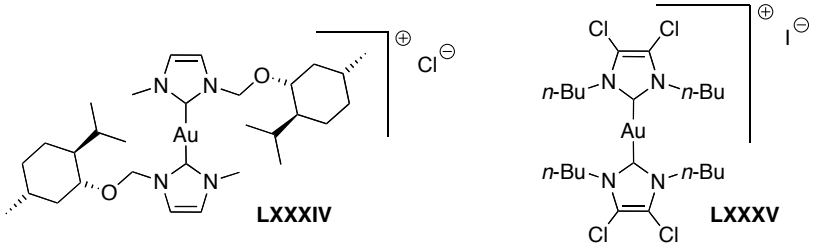


Figure 29. Structures of [(NHC)$_2$Au]$^+$X$^-$ catalytically active in olefin diboration

In seminal work, Widenhoefer showed that [(IPr)AuCl] was highly active in the hydroamination of unactivated alkenes (Scheme 38).[291] The authors found that this catalyst displayed enhanced catalytic activity when compared to sterically hindered, electron-rich *o*-biphenylphosphine-containing gold species. Hence, the room temperature intramolecular

[290] Corberán, R.; Ramírez, J.; Poyatos, M.; Peris, E.; Fernández, E. *Tetrahedron: Asymmetry* **2006**, *17*, 1759–1762.
[291] Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 5303–5305.

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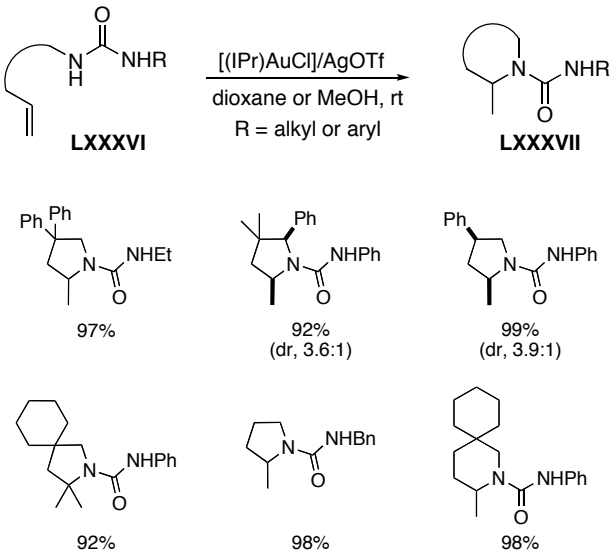
hydroamination of a large array of *N*-alkenyl ureas **LXXXVI** could be effectively carried out (Scheme 38). Additionally, this catalytic system displayed excellent *exo*-selectivity and good diastereoselectivity.



Scheme 38. [(IPr)AuCl]-Catalyzed hydroamination of alkenes

The mechanism is believed to proceed *via* initial π-coordination of the alkene to the cationic gold center. The developing carbocation is then trapped intramolecularly by the nucleophilic amine and proto-deauration completes the catalytic cycle.

Very recently, an example of gold-induced olefin polymerization was reported with NHC–gold(III) compounds.[292] Different styrene-type monomers could be polymerized at room temperature in the presence of [(NHC)$AuBr_3$] **LXXXVIIIa-h** (Figure 30) and $NaBAr'_4$ (BAr'_4 = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate).

The study showed that, contrary to NHC–gold(III), NHC–gold(I) compounds were not effective pre-catalysts. The influence of the NHC ligand was further investigated as well as the possibility of an acid catalyzed polymerization. The authors finally concluded that a cationic, rather than radical, polymerization was at play since both the metal center and the ligand influenced the physical properties of the polymeric material produced. This mechanistic hypothesis is in accordance with the generation, *via* π-alkene activation, of a gold-stabilized carbocation. Even though mechanistically diverse, it should be noted that the

[292] Urbano, J.; Hormigo, A. J.; de Frémont, P.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Commun.* **2008**, 759–761.

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polymerization of L-lactide in the presence of a [(NHC)AuCl] initiator has also been studied.[293]

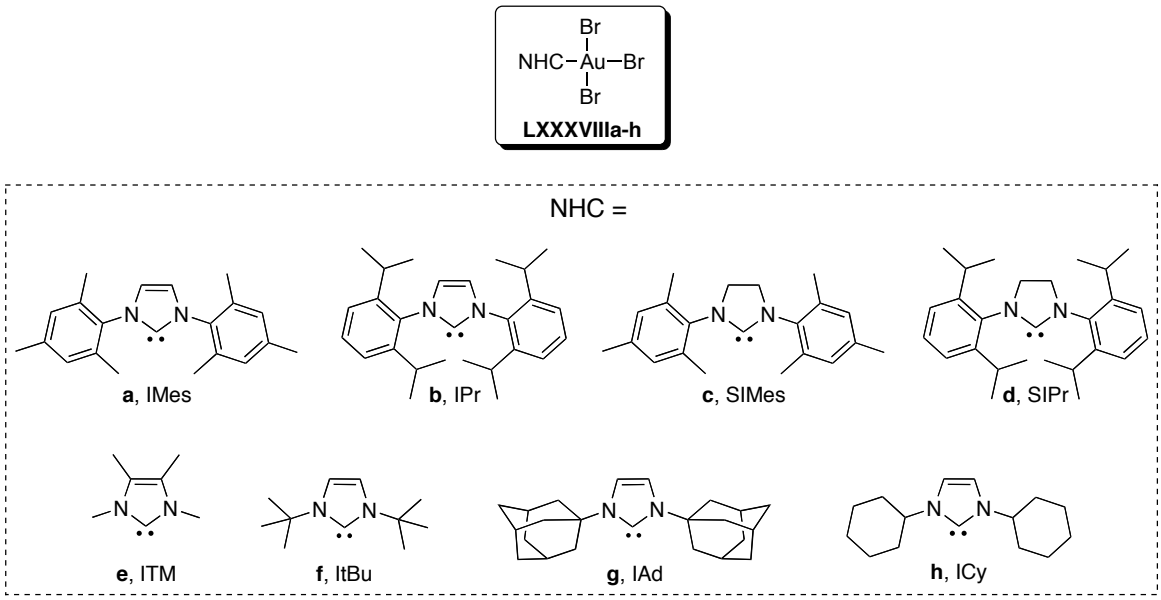
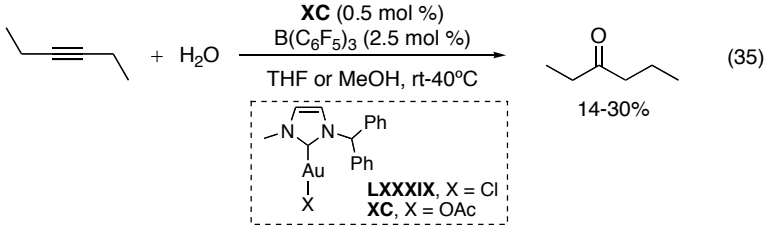


Figure 30. Structure of [(NHC)AuBr$_3$] used for styrene polymerization

D. Alkyne hydration and related reactions

In 2003, Herrmann reported the very first application of a NHC–gold species in catalysis.[275] The authors studied the addition of water to alkynes, a known reaction in the presence of phosphine–gold compounds, leading to ketones. Hence, the conversion of 3-hexyne to 3-hexanone was achieved with 0.5 mol % of [(NHC)Au(OAc)] **XC** (Eq 35). It was notably observed that **LXXXIX** was inactive, but that *in situ* formation of **XC**, from a mixture of **LXXXIX** and AgOAc, provided similar results as reactions performed with well-defined **XC**; highlighting the key role of the coordination of the counteranion in gold(I) chemistry. Even though results were modest, it certainly validated the utilization of NHCs as supporting ligands in gold catalysis.



(35)

[293] (a) Ray, L.; Katiyar, V.; Raihan, M. J.; Nanavati, H.; Shaikh, M. M.; Ghosh, P. *Eur. J. Inorg. Chem.* **2006**, 3724–3730. (b) Ray, L.; Katiyar, V.; Barman, S.; Raihan, M. J.; Nanavati, H.; Shaikh, M. M.; Ghosh, P. *J. Organomet. Chem.* **2007**, *692*, 4259–4269.

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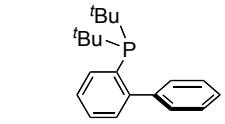
The hydration of alkynes was also a reaction chosen in our laboratory as a benchmark test for the evaluation of the catalytic activity of a series of NHC–gold(III) complexes of formulae [(NHC)AuBr$_3$], **LXXXVIIIa-h** (Figure 30).[294] These compounds, easily obtained by oxidative addition of elemental bromine to [(NHC)AuBr], were the first NHC–gold(III) species shown to display a catalytic behavior. They showed good activity in refluxing methanol, following Markovnikov addition rule, and yielded a number of methyl ketones. The main drawbacks of this catalytic system are the high catalyst loading required (e.g. 10 mol %) and the lack of activity with internal alkynes.

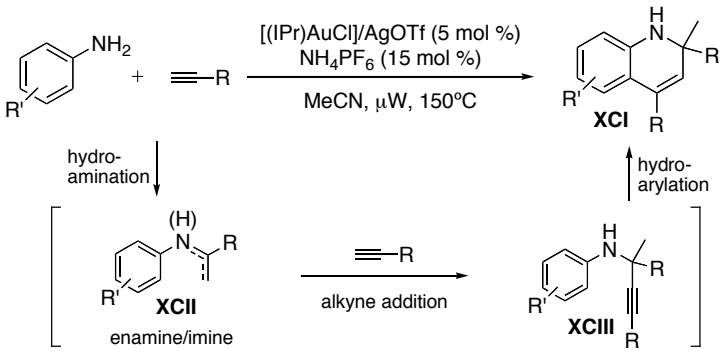
The use of amines instead of water as nucleophile in this reaction leads to the formation of imines or enamines as a function of the substitution degree of the amino group. The newly formed functional group can, in turn, be activated for further reactivity. Following this precept, Che recently reported the formation of 1,2-dihydroquinolines and quinolines from anilines and alkynes catalyzed by [(IPr)AuCl].[295]

As shown in Scheme 39, a number of 1,2-dihydroquinolines **XCI** could be obtained from simple starting material in a tandem process. Experimental evidences were gathered leading to the proposal that enamine **XCII** and propargylic amine **XCIII** were intermediates.



(*o*-biphenyl)di-*tert*-butylphosphine

It is worth noting that during catalyst screening, [(IPr)AuCl] was found more efficient than its IMes counterpart and as active as the [{(*o*-biphenyl)di-*tert*-butylphosphine}AuCl] possessing a bulky and electron-rich phosphine ligand.



Scheme 39. [(IPr)AuCl]-Catalyzed tandem hydroamination/hydroarylation

[294] de Frémont, P.; Singh, R.; Stevens, E. D.; Petersen, J. L.; Nolan, S. P. *Organometallics* **2007**, *26*, 1376–1385.

[295] (a) Liu, X.-Y.; Ding, P.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2007**, *9*, 2645–2648. Of note, Che recently extended this reactivity to the synthesis of pyrrolo[1,2-*a*]quinolines, see: (b) Liu, X.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2008**, *47*, DOI: 10.1002/anie.200800160.

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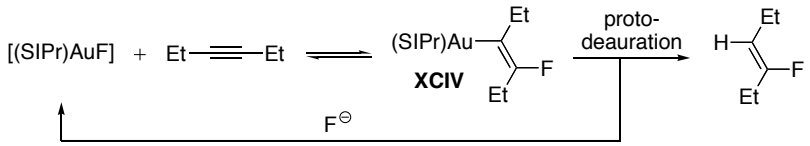
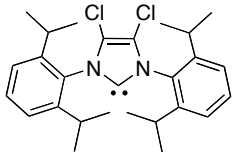
Closely related to the hydration of alkynes, which is formally a hydrohydroxylation reaction, a catalytic hydrofluorination of alkynes was disclosed recently by Sadighi.[296] In a key experiment, the authors observed the formation of vinylgold **XCIV**, a likely hydrofluorination intermediate, resulting from the addition of the Au–F bond across 3-hexyne (Scheme 40).

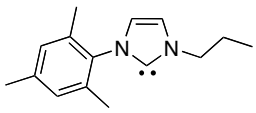


Scheme 40. Au-Catalyzed hydrofluorination of alkynes

Subsequent fine-tuning of the reaction conditions, notably of the fluoride source and of the acidic media, permitted the development of a catalytic transformation using [(NHC)AuCl]/$AgBF_4$ mixtures. Additionally, it should be noted that only *trans*-hydrofluorination was observed and that ^{Cl}IPr (4,5-dichloro-1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) **XCV**, a less electron-rich ligand than IPr, was found more efficient in this reaction than IPr or SIPr.



XCV, ^{Cl}IPr



XCVI, IMesPr

Enlarging the scope of [(NHC)Au]-catalyzed H–X addition across π-bonds, Corma and co-workers recently reported the hydrosilylation of styrene and benzaldehyde by **XCVI**.[297] As acknowledged by the authors, results were modest but promising and further developments are needed – only one NHC was tested – to fully exploit the possibilities offered by Au-catalyzed hydrosilylation.

E. Concluding remarks and perspective

Less than half a decade has passed since the first report on gold catalysis involving N-heterocyclic carbene ligands was disclosed in 2003. Since then, the contributions that have appeared have impressively spanned a wide spectrum of organic transformations. This range encompasses enyne cycloisomerization, in a broad sense, hydroarylation, diboration, hydroamination, hydration and polymerization. Additionally, new areas of research with

[296] Akana, J. A.; Bhattacharyya, K. X.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 7736–7737.
[297] Corma, A.; González-Arellano, C.; Iglesias, M.; Sánchez, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7820–7822.

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promising potential are now being investigated. These include alkane C–H activation,[298] olefin hydrogenation[299] and cross-coupling reactions;[300] remarkably, the latter being catalyzed by a *heterogeneous* NHC-containing gold(I) system. Hence, over a short period of time, it has already been demonstrated that NHC-based gold(I) and gold(III) catalysts can activate alkynes, allenes and alkenes as well as carbonyl and aryl halide compounds. This clearly highlights the important versatility of NHC ligands in the context of Au-catalysis.

II. Preliminary results

A. Synthesis of [(NHC)AuCl] complexes

NHC-Containing gold(I) complexes had already been known for a long time[277] when Lin disclosed a simple and powerful synthetic route using silver(I) oxide and an azolium salt.[103] In our laboratory, the Lin synthesis was employed, along with direct reaction of a free carbene, to synthesize a series of [(NHC)AuCl] complexes with structurally different NHCs (Scheme 41, see next page).[301] All complexes are dicoordinated gold(I) compounds and exhibit an almost perfect linear geometry around the gold center. They are bench-top stable for months and good candidates for catalytic trials.

B. Preliminary catalytic trials

Concomitently with our first catalytic studies with **Au1**-**Au12**, we initiated a collaboration with the research group of Professor Pedro Pérez in Huelva. They notably showed the excellent activity of **Au3** in carbene transfer reactions leading to cyclopropanation and N–H insertion.[302]

It should be added that, even though only one report dealing with NHC–gold compounds in catalysis was available at the time we began this project, the field of gold homogeneous catalysis was on the verge of a true explosion. Early work by the groups of

[298] Fructos, M. R.; de Frémont, P.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Organometallics* **2006**, *25*, 2237–2241.
[299] Corma, A.; Gutiérrez-Puebla, E.; Iglesias, M.; Monge, A.; Pérez-Ferreras, S.; Sánchez, F. *Adv. Synth. Catal.* **2006**, *348*, 1899–1907.
[300] Corma, A.; González-Arellano, C.; Iglesias, M.; Pérez-Ferreras, S.; Sánchez, F. *Synlett* **2007**, 1771–1774.
[301] de Frémont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 2411–2418.
[302] Fructos, M. R.; Belderrain, T. R.; de Frémont, P.; Scott, N. M.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5284–5288.

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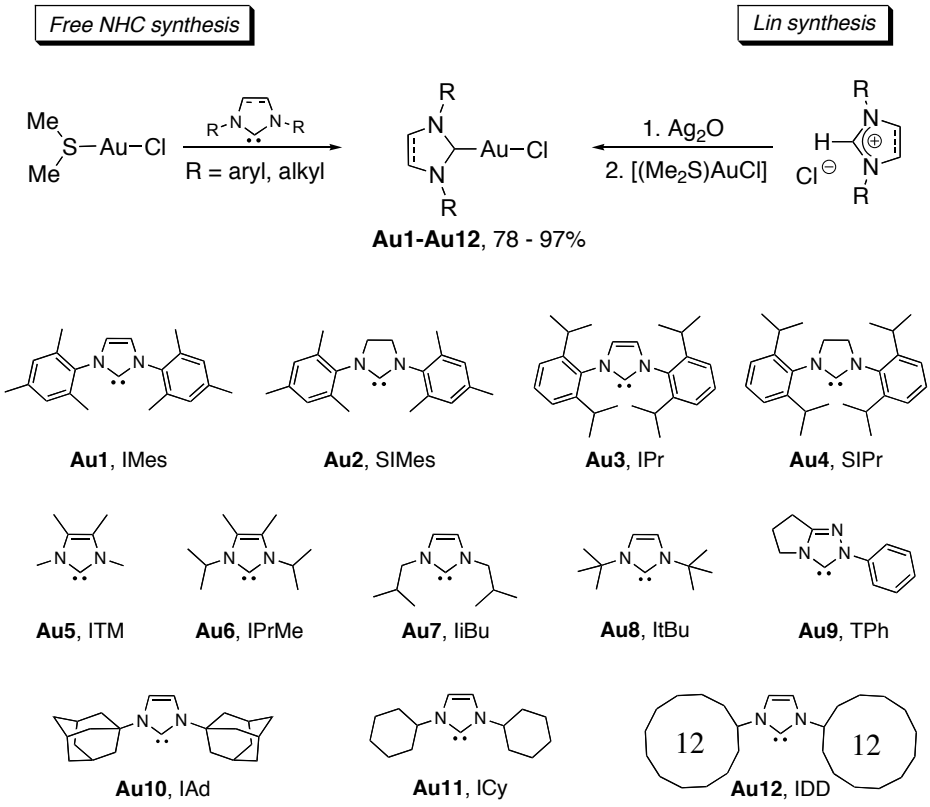
Teles, Krause, and Hashmi notably, set gold(I) and gold(III) salts as viable catalysts,[303] contrary to the common believe of gold inertness. Furthermore, the groundbreaking report from the Echavarren group,[304] rapidly followed by reports from the Toste group,[305] on Au^I-catalyzed enyne cycloisomerization established the superior electrophilicity – and in most cases activity – of gold complexes in cyclization/skeletal rearrangement of polyunsaturated molecules. Subsequent work in this area will be discussed later in the context of our own developments.



Scheme 41. Synthesis of [(NHC)AuCl] **Au1**-**Au12**

Hence, considering the high potential of gold catalysts for alkyne activation, we became interested in examining the activity of the [(NHC)AuCl] series developed in our laboratory in this type of transformations.

[303] (a) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem.* **2004**, *8*, 795–812. (b) Hashmi, A. S. K. *Gold. Bull.* **2004**, *37*, 51–65. (c) Hashmi, A. S. K. *Gold. Bull.* **2003**, *36*, 3–9. (d) Dyker, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4237–4239.
[304] Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402–2406.
[305] (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526–4527. (b) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858–10859. (c) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978–15979.

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III. Enyne cycloisomerization: A branched dienyne as a case study for a novel reactivity pattern[306]

A. Context

Atom economy reactions, as defined by Trost,[307] are of primary importance in modern organic chemistry. In this field, polyunsaturated substrates have become ubiquitous and have notably allowed for the discovery of a number of unprecedented transformations in the presence of late transition metal catalysts.[308] Among the atom economy transformations available to chemists,[309] the cycloisomerization of enynes remains unique because of the increase of molecular complexity brought about in one chemical step.[310] After extensive studies with palladium[311] and platinum,[312] gold(I) and gold(III) salts have emerged lately as powerful catalysts for a myriad of transformations involving enynes.[276,313] The reactivity of gold complexes toward enynes leads notably to the formation of bicyclo[n.1.0] derivatives[314] that are of great synthetic interest as the cyclopropane ring is a widely encountered motif in natural products.[315] It should be noted here that enyne derivatives possessing an ester at the propargylic position have to be considered as a particular class of substrates due to their peculiar reactivity pattern.[316] More specifically, an *O*-ester group adequately placed will perform an internal 1,2- or 1,3-shift upon electrophilic activation of the C≡C bond (Scheme

[306] Marion, N.; de Frémont, P.; Lemière, G.; Stevens, E. D.; Fensterbank, L.; Malacria, M.; Nolan, S. P. *Chem. Commun.* **2006**, 2048–2050.
[307] Trost, B. M. *Science* **1991**, *254*, 1471–1477.
[308] For recent general reviews on the chemistry of polyunsaturated substrates, see: (a) Malacria, M.; Goddard, J.-P.; Fensterbank, L. In *Comprehensive Organometallic Chemistry III*; Crabtree, R.; Mingos, M.; Ojima, I., Eds.; Pergamon Press: Oxford, England, 2006; Vol. 10, Chap. 7, 299–368. (b) Aubert, C.; Fensterbank, L.; Gandon, V.; Malacria, M. *Top. Organomet. Chem.* **2006**, *19*, 259–294.
[309] (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695–705.
[310] For reviews on enyne cycloisomerization, see: (a) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem.–Eur. J.* **2006**, *12*, 5916–5923. (b) Zhang, Z.; Zhu, G.; Tong, X.; Wang, F.; Xie, X.; Wang, J.; Jiang, L. *Curr. Org. Chem.* **2006**, *10*, 1457–1478. (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382. (d) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431–436. (e) Echavarren, A. M.; Méndez, M.; Muñoz, M. P.; Nevado, C.; Martín-Matute, B.; Nieto-Oberhuber, C.; Cárdenas, D. J. *Pure Appl. Chem.* **2004**, *76*, 453–463. (f) Lloyd-Jones, G. *Org. Biomol. Chem.* **2003**, *1*, 215–236. (g) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813–834.
[311] For a review, see: Trost, B. M. *Acc. Chem. Res.* **1990**, *13*, 385–393.
[312] For reviews, see: (a) Añorbe, L.; Domínguez, G.; Pérez-Castells, J. *Chem.–Eur. J.* **2004**, *10*, 4938–4943. (b) Méndez, M.; Mamane, V.; Fürstner, A. *Chemtracts* **2003**, *16*, 397–425.
[313] For reviews focused on enynes in Au-catalysis, see: (a) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296. (b) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200–203.
[314] For a review on LTM-catalyzed formation of cyclopropane from enynes, see: Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328–2334.
[315] For a review on cyclopropane motif in natural products, see: (a) Wessjohann, L. A.; Brandt W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625–1648. (b) Salaun, J. *Curr. Med. Chem.* **1995**, *2*, 511-542.
[316] For reviews on propargylic esters in Pt- and Au-catalysis, see: (a) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750–2752. (b) Marco-Contelles, J.; Soriano, E. *Chem.–Eur. J.* **2007**, *13*, 1350–1357.

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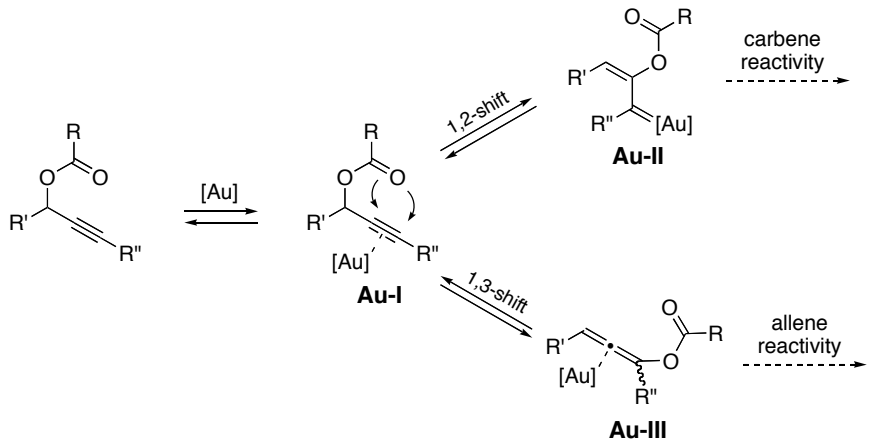
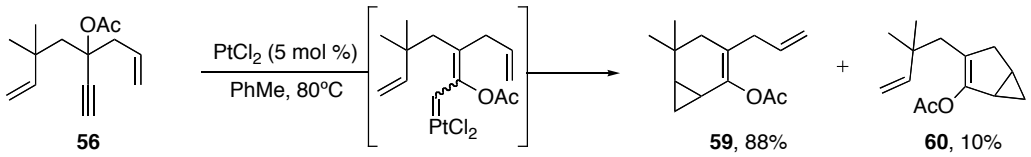
42, **Au-I**), leading to rearranged products **Au-II** and **Au-III** respectively, which can then further evolve as a function of the remaining pendant groups (Scheme 42).



Scheme 42. Reactivity of propargylic acetates in the presence of gold

We primarily focused our attention on the specific dienyne **56**, which bears an acetate at the propargylic position, since its reactivity in the presence of $PtCl_2$ had been previously reported (Scheme 43).[272]



Scheme 43. Pt-Catalyzed cycloisomerization of **56**

Substrate **56** formally contains a 1,6- and a 1,5-enyne cores that lead, after 1,2 migration of the acetate, to **59** and **60** respectively. With $PtCl_2$, the bicyclo[4.1.0]heptene **59** is formed preferentially while the bicyclo[3.1.0]hexene compound **60** is only a minor product. Fürstner showed that this transformation with simple enynes was catalyzed equally well by Pt^{II} or Au^{I}.[317] Since ligand effects have been studied only scathingly in this chemistry, it was of interest to examine whether Au^{I} would provide a similar selectivity as Pt^{II} in this specific system, and furthermore if ligands such as NHCs could support such a transformation. This work was conducted in collaboration with the research groups of Professors Max Malacria and Louis Fensterbank for the experimental part and of Professor Luigi Cavallo for the theoretical part.

[317] Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655.

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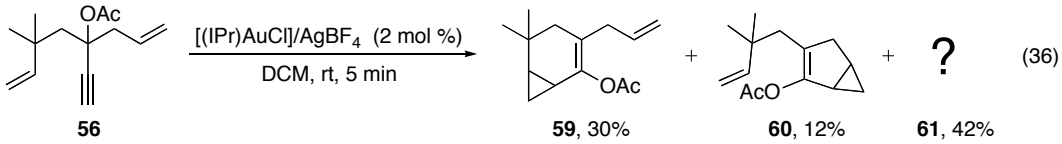
B. Initial studies

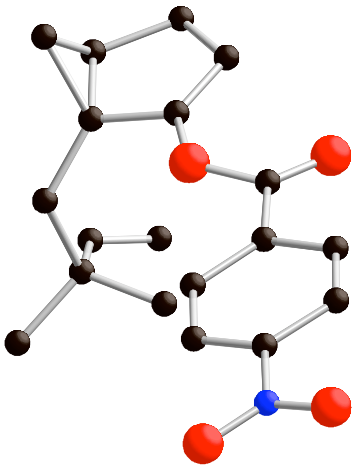
1. Observation of an unprecedented type of enyne cycloisomerization

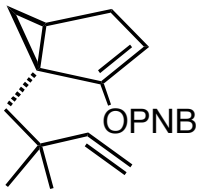
We subjected dienyne **56** to an equimolar mixture of [(IPr)AuCl] **Au3** and $AgBF_4$ (2 mol %) in CH_2Cl_2 at room temperature. After 5 min, no starting material remained; isolation and purification yielded **59** and **60** in moderate yields and a novel compound **61** as the major product (Eq 36).



56 **59**, 30% **60**, 12% **61**, 42% (36)

The ^{1}H NMR data suggested **61** to be a cycloisomerized product displaying three propanoid and one extra vinylic protons. ^{1}H-^{1}H and ^{1}H-^{13}C HSQC NMR experiments did not permit to unequivocally assign the structure of this new product. To determine unambiguously the atom connectivity in **61**, we prepared **56'**, the *p*-nitrobenzoate analogue of **56**, and subjected it to cycloisomerization conditions.[318] Suitable crystals of the purified product were grown and the structure was elucidated by X-ray diffraction (Figure 31).





61'

Figure 31. Ball-and-stick representation of **61'** (Carbon atoms are depicted in black, oxygen in red, and nitrogen in blue; hydrogen atoms are omitted for clarity). Crystal data: $C_{19}H_{21}NO_4$; M = 327.37; triclinic; space group P-1; a = 7.194(1), b = 8.756(2), c = 13.875(3) Å; α = 82.241(4), β = 81.536(4), γ = 80.279(4) º; V = 846.6(3) Å^3; T = 273(2) K; Z = 2; μ = 0.090 mm^{-1}; 1018 reflections measured using a Bruker SMART 1 K CCD diffractometer, 301 unique, (R_{int} = 0.0587); wR_2 = 0.1612, R_1 = 0.0668 for all data. CCDC 267108.

Surprisingly, in **61'** the cyclopropane ring has migrated to the former propargylic position, making **61** a formal vinylcyclopropane rearrangement of **60**.

To gain insights on the active catalytic species in this unprecedented transformation,

[318] Similar distribution as for **56** was observed; **59'/60'/61'**, 27%:8%:46%.

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two control reactions were performed with [(IPr)AuCl] **Au3** and $AgBF_4$, separately. The former was inactive toward dienyne **56**. The latter afforded allene **62**, corresponding to a [3,3]-transposition of the propargylic acetate.[319] These experiments support a cationic gold complex as an active catalytic species. To obtain such a complex, we reacted [(IPr)AuCl] **Au3** with $AgPF_6$ in acetonitrile and were able to isolate [(IPr)Au(NCMe)]PF_6 **Au13** whose structure was confirmed by X-ray diffraction studies (Figure 32).[320]

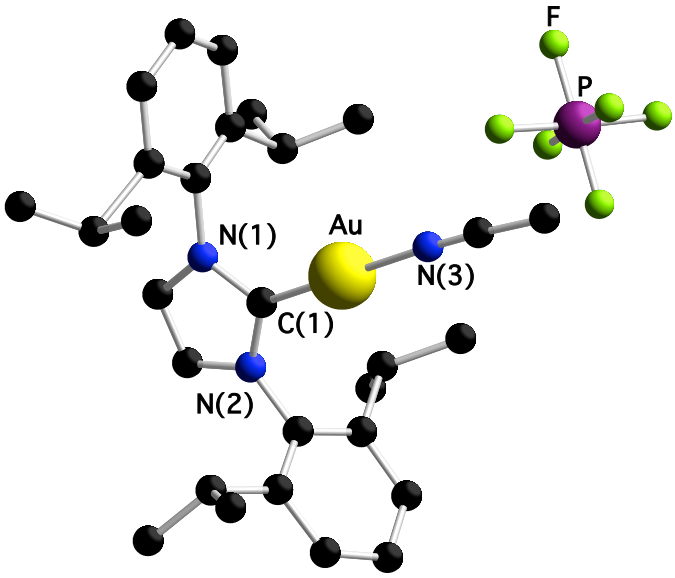
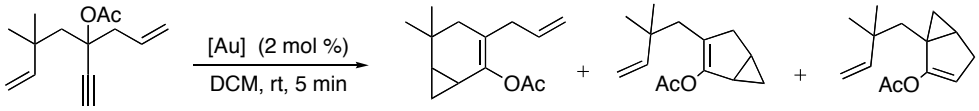


Figure 32. Ball-and-stick representation of [(IPr)Au(NCMe)]PF_6 **Au13** (Hydrogen atoms are omitted for clarity). Crystal data: $C_{31}H_{42}AuN_4PF_6$; M = 812.62; monoclinic; space group $P2_1/n$; a = 8.9662(6), b = 18.347(1), c = 21.693(2) Å; β = 96.841(1) º; V = 3544.0(4) Å^3; T = 298(2) K; Z = 4; μ = 4.254 mm^{-1}; 53909 reflections measured using a Bruker SMART 1K CCD diffractometer, 4626 unique (R_{int} = 0.062); R_1 = 0.0493, wR_2 = 0.1101 for all data. CCDC 296436.

Next, we performed the isomerization of **56** with this cationic species (Scheme 44).



	56	**59**	**60**	**61**
[(IPr)Au(NCMe)]PF_6		**30%**	**15%**	**41%**
[(IPr)AuCl]/$AgPF_6$		30%	12%	42%

Scheme 44. Cationic **Au13**-catalyzed cycloisomerization of **56**

[319] For the formation of allenyl esters from propargylic esters using silver(I) salts, see: (a) Saucy, G.; Marbet, R.; Lindlar, H.; Isler, O. *Helv. Chim. Acta* **1959**, *42*, 1945–1955. (b) Benn, W. R. *J. Org. Chem.* **1968**, *33*, 3113–3118. (c) Schlossarczyk, H.; Sieber, W.; Hesse, M.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 875–944.

[320] For details on the synthesis and characterization of several cationic [(NHC)Au(NCMe)]X complexes, see: de Frémont, P.; Stevens, E. D.; Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J.; Nolan, S. P. *Chem. Commun.* **2006**, 2045–2047.

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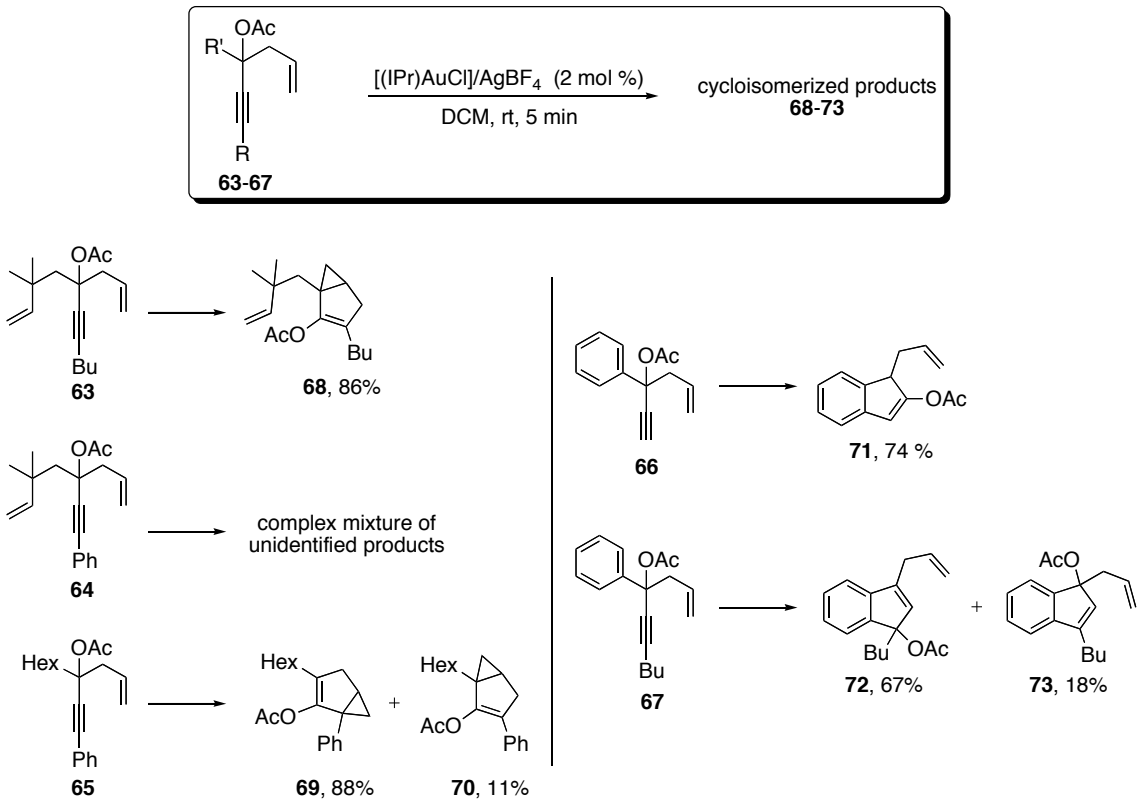
Without the need for silver additives, that are usually very hygroscopic and light-sensitive, we obtained similar results as with an equimolar mixture of [(IPr)AuCl] and $AgPF_6$ (Scheme 44).

This result supports the cationic nature of the catalytically active species. Furthermore, $[(IPr)Au(NCMe)]PF_6$ **Au13** allowed to decrease the catalyst loading to 1 mol % without increasing the reaction time and to 0.1 mol % if the mixture was stirred for 1 h.

2. A general feature for 1,5-enynes?

In order to evaluate the scope of this novel reactivity, we synthesized different 1,5-enynes (**63**-**66**) and subjected them to our cycloisomerization conditions (Scheme 45). For detailed synthetic schemes leading to **63-67**, see the Experimental section, **VIII.B.2**, pp 266-275 and **VIII.C.1**, pp 283-288.



Scheme 45. Au-Catalyzed cycloisomerization of 1,5-enynes **63**-**67**

Strikingly, simple modifications of the acetylenic substitution appeared to be crucial in affecting the outcome of the reaction. While **56** yielded a mixture of three products, **63** produced exclusively **68**, a bicyclo[3.1.0]hexene of type **61**. The reasons for such selectivity are still unclear but it is noteworthy that even in the NMR spectrum of the crude product no trace of other cycloisomerized compounds could be observed. Notably, compound **64**, with a

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phenyl group placed at the acetylenic position of the dienyne framework, led to a mixture of unidentified products. On the other hand, when the 1,6-enyne core was replaced by an alkyl chain, as in **65**, an acetylenic phenyl group was well tolerated and **65** produced mainly a "classical" cyclopronated product **69**, along with minor amount of **70** possessing the unprecedented architecture, as observed in **61**.

Alternatively, when a phenyl group was located at the propargylic position, geminal to the acetate, the allyl moiety remained unreacted and cyclization occurred on the phenyl group, leading to the formation of indene derivatives. Hence, **66** and **67** produced different types of indenes where the position of the acetate moiety as well as the position of the C=C in the five-membered ring varied, see **71**-**73**. The formation of these indenyl derivatives was considered extremely interesting and therefore further studied. Nevertheless, a clear mechanistic distinction can be made with the formation of cyclopropyl derivatives. Therefore, we will focus in this section on enyne cycloisomerization leading to cyclopropane-containing compounds and will present the results related to indene formation in section **III.B**.

3. A mechanistic rationale for the formation of 61

The aforementioned results, and particularly the formation of products **61** and **68**, exhibiting an unprecedented skeletal rearrangement, led us to explore some mechanistic aspects of this transformation. Focusing on **61**, we first assessed the possibility of a vinylcyclopropane rearrangement of **60** into **61**. A thermal rearrangement can be easily ruled out since the reaction occurs at room temperature. The reaction of **60** under cyclization conditions resulted in the recovery of the starting material at room temperature and in its degradation upon heating, excluding a hypothetical Au-catalyzed rearrangement.

In order to explain the formation of the three bicyclic cyclopropyl compounds from **56**, we propose a cationic pathway (Scheme 46). The route leading to **Au-VI** and **Au-VII** (that can be viewed as gold-methylidenes **Au-VI'** and **Au-VII'**) is similar to the one proposed for the $PtCl_2$-catalyzed cycloisomerization.[272] From **Au-VI**↔**Au-VI'**, cyclopropanation would provide **59**, as suggested in the case of platinum. From **Au-VII**, a 6-*endo* cyclization process followed by collapse of the carbon-gold bond would provide **60**. Alternatively, cationic rearrangement of intermediates **Au-VIII** or **Au-IX** leading to a bicyclo[3.1.0]hexane cation **Au-X**, that could be further stabilized via an oxonium, would produce the unprecedented compound **61**.

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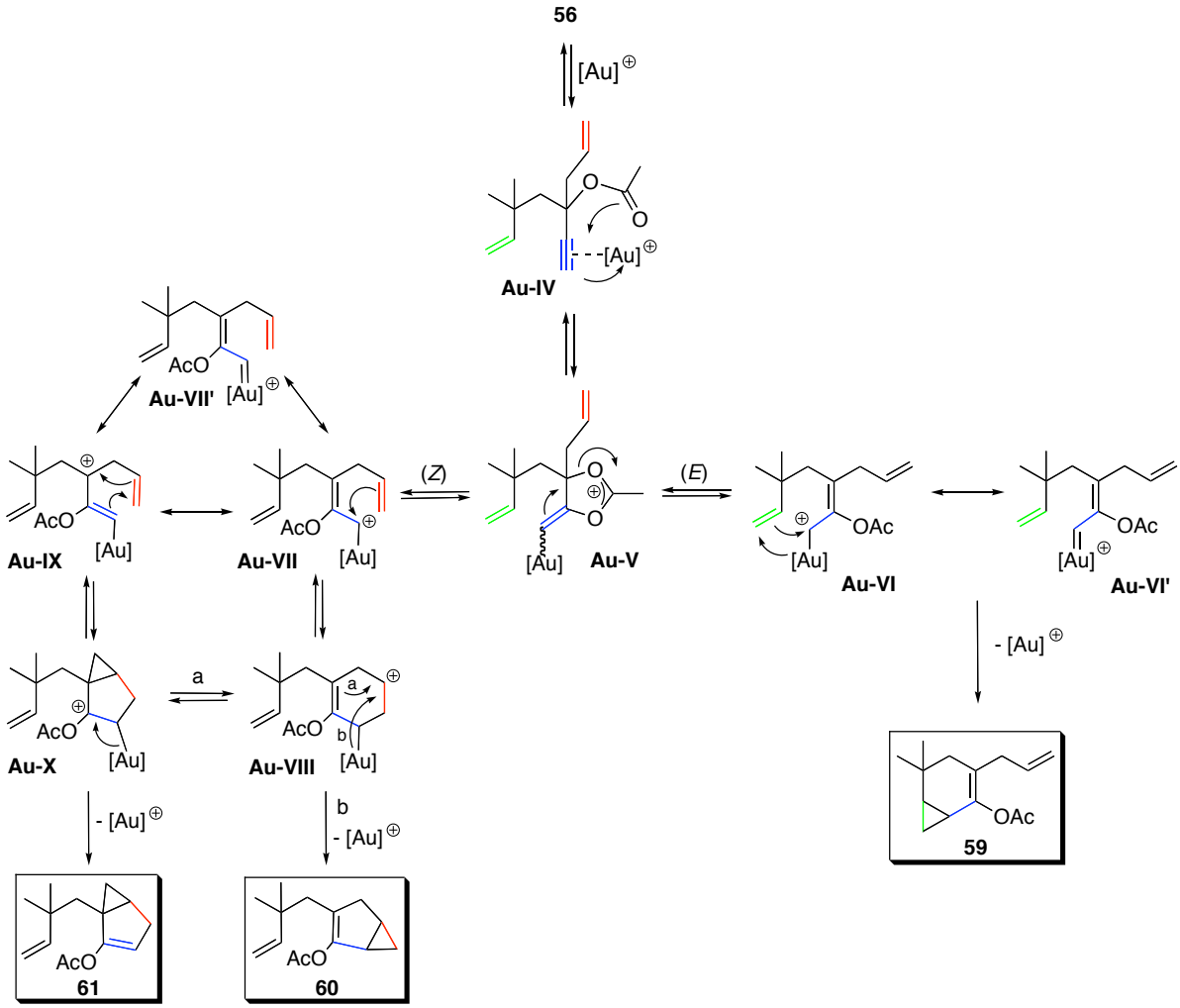

Scheme 46. Proposed mechanism for the cycloisomerization of **56**

C. Studies of the parameters influencing the formation of 61

1. Ligand on gold

We began the study of our model substrate **56** with the evaluation of the influence of the ligand on the formation of bicyclic product **61**, using simple electrophilic metal salts as well as the series of [(NHC)AuCl] complexes **Au1**-**Au12** previously synthesized in our laboratory[301,321] (Table 23). The use of simple "ligandless" gold(I) and gold(III) chloride salts conducted to the same selectivity,[322] yielding **59** and **60** in similar proportions and only small amounts of **61** (Entries 3 and 5).

[321] The [(IDD)AuCl] had not been reported previously, for details see the Experimental Part of this chapter, section **VIII.B.1**.

[322] Disproportionation of AuCl into Au^0 and $AuCl_3$ in DCM solution has been reported in the context of gold catalysis, see: (a) Lemière, G.; Gandon, V.; Agenet, N.; Goddard, J.-P.; de Kozak, A.; Aubert, C.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7596–7599. See also: (b) Vogler, A.; Kundely, H. *Coord.*

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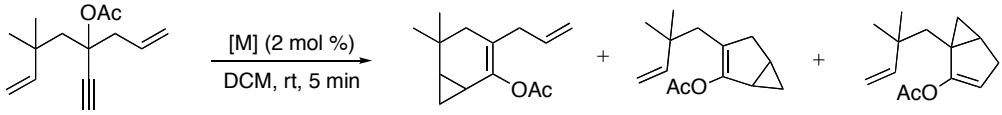
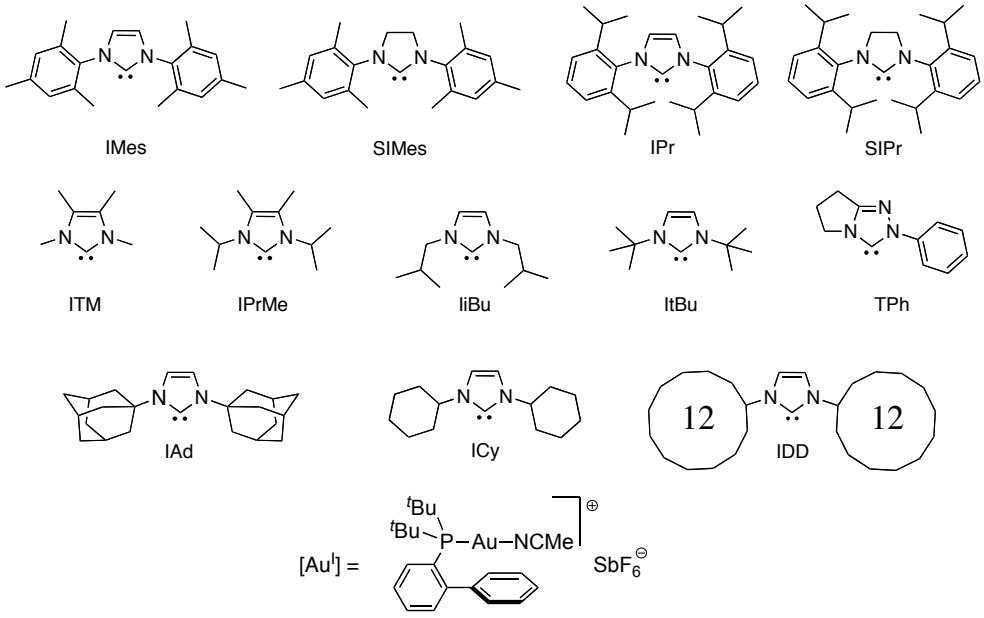
Table 23. Effect of ligands on the cycloisomerization of **56**



56 **59** **60** **61**

Ent	[M]	**59**:**60**:**61**[a]	Total yield[a]	Ent	[M]	**59**:**60**:**61**[a]	Total yield[a]
1[b]	$PtCl_2$	1/0.1/0	98%	12	[(SIPr)AuCl]/$AgBF_4$	1/0.3/0.9	90%
2[c]	$PtCl_2$/$AgBF_4$	1/0.1/0	33%	13	[(TPh)AuCl]/$AgBF_4$	1/0.5/0.4	94%
3	AuCl	1/0.7/0.2	86%	14[g]	[(ITM)AuCl]/$AgBF_4$	1/0.1/0.2	62%
4	AuCl/$AgBF_4$	1/0.5/0	84%	15	[(IiBu)AuCl]/$AgBF_4$	1/0.2/0.1	70%
5[d]	$AuCl_3$	1/0.8/0.2	88%	16[g]	[(IPrMe)AuCl]/$AgBF_4$	1/0.2/0.3	63%
6[e]	$AuCl_3$/$AgBF_4$	1/0.3/0	77%	17	[(ICy)AuCl]/$AgBF_4$	1/0.6/0.4	88%
7[f]	[(Me_2S)AuCl]	1/0.8/0.1	80%	18	[(ItBu)AuCl]/$AgBF_4$	1/0.1/0.6	73%
8[d]	[(Me_2S)AuCl]/$AgBF_4$	1/0.1/0	81%	19	[(IAd)AuCl]/$AgBF_4$	1/0.1/0.7	95%
9	[(IMes)AuCl]/$AgBF_4$	1/0.5/1.5	78%	20	[(IDD)AuCl]/$AgBF_4$	1/0.2/0.5	76%
10	[(SIMes)AuCl]/$AgBF_4$	1/0.4/1.7	72%	21[g]	[(PPh_3)AuCl]/$AgBF_4$	1/0.1/0.2	64%
11	[(IPr)AuCl]/$AgBF_4$	1/0.4/1.4	84%	22[h]	[Au^I]	1/0.6/0.1	54%

[a] Isolated yields, average of 2 runs, products ratio determined by ^1H NMR. [b] Reaction performed with $PtCl_2$ (5 mol %) in toluene at 80ºC for 2 h. [c] Reaction performed with $PtCl_2$ (5 mol %)/$AgBF_4$ (10 mol %) in toluene at 80ºC for 2 h. 26% of **56** were recovered and 8% of allenyl ester **62** along with significant amounts of oligomerized by-products were also formed. [d] Reaction stirred for 2 h. [e] Reaction performed with $AuCl_3$ (2 mol %)/$AgBF_4$ (6 mol %) for 1 h. [f] Reaction stirred for 2 h, 8% of allenyl ester **62** were also formed. [g] No starting material remaining, significant amounts of oligomerized by-products were formed. [h] Reaction stirred for 15 min. 42% of **56** was recovered.



Chem. Rev. **2001**, *219-221*, 489–507. (c) Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Chem.—Eur. J.* **2004**, *10*, 484–493.

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Interestingly, when these salts were employed in combination with a silver(I) salt, the formation of **61** was not observed and the proportion of **59** over **60** increased (Entries 4 and 6), approaching the selectivity displayed by $PtCl_2$ (Entry 1). Of note, the use of platinum(II) chloride in conjunction with 2 equivalents of $AgBF_4$ displayed a lesser activity than $PtCl_2$ alone.

The last "simple", and commercially available, gold salt tested was [(Me_2S)AuCl] (Entries 7 and 8). As expected, it could be used without silver salt (Entry 7) and, under these conditions, behaved as AuCl, supporting decoordination of Me_2S from the gold center prior to catalytic activity. On the other hand, the addition of $AgBF_4$ to [(Me_2S)AuCl] led to a selectivity comparable with those of AuCl/$AgBF_4$ and $AuCl_3$/$AgBF_4$ where the formation of **61** was not observed (Entry 8). This can be interpreted in two ways: either Me_2S as ligand has little influence on the course of the cycloisomerization or the catalytically active species is simply the gold cation, formed upon chloride abstraction and Me_2S decoordination.

Examining the influence of an ancillary ligand on the gold center and considering the formation of **61** as the main parameter, the total yields range from good to excellent with a slight decrease of activity for the less encumbered ones (Entries 14-16 and 21). More precisely, the ligands employed here can be divided into three classes. Those displaying low steric pressure furnished only minor amount of bicycle **61** (Entries 13-17 and 21, **59**:**61**, 1/<0.4) whereas the highly hindered ones led to slightly higher ratios **59**:**61** (≈ 1/0.6) (Entries 18-20). The third class of ligands can be regarded as intermediate, in terms of steric hindrance, between the first two ones.[323] It encompasses the widely used IPr and IMes ligands and their saturated analogues SIPr and SIMes. Only these ligands produced mixtures where **61** was the major compound (Entries 9-12). Considering the minor differences in the electronic properties of the NHCs employed here, we believe that the formation of the unexpected bicyclo[3.1.0]hexene **61** is mainly under steric control and responds favorably to a medium/high steric pressure.

2. Reaction temperature

First, it should be noted that prolonged reaction time, under strictly similar reaction conditions, led to comparable ratios of cyclopropyl carbocycles, excluding the possibility of chemical equilibrium between the different products. To further address the question of

[323] For reviews on the stereoelectronic parameters of NHCs, see: (a) Díez-González, S.; Nolan, S. P. *Coord. Chem. Rev*. **2007**, *251*, 874–883. (b) Strassner, T. *Top. Organomet. Chem*. **2004**, *13*, 1–20. See also the Introduction Chapter, section **III**.

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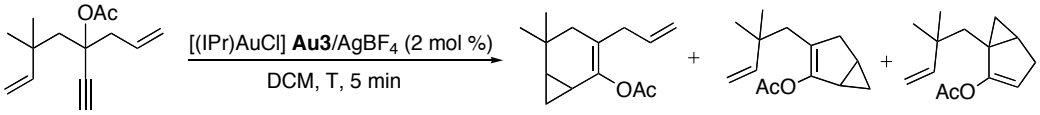
possible thermodynamic equilibriums, we carried out the cycloisomerization of **56** at different reaction temperatures; results are shown in Table 24. Surprisingly, increasing or decreasing the temperature induced the same result: the formation of **61** was not observed and **59** was produced in major quantity (Table 24, entries 1 and 4). Of note, a temperature of 70ºC was found deleterious for the reaction and led mainly to oligomerization of the dienyne (Entry 1).

Table 24. Influence of the temperature on the cycloisomerization of **56**



56 **59** **60** **61**

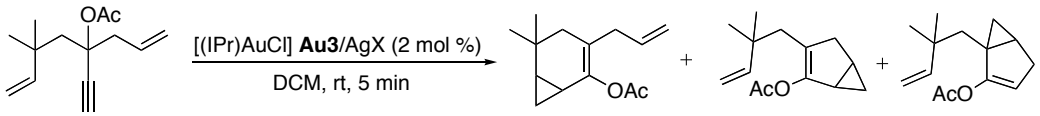
Entry	T (ºC)	**59**:**60**:**61**[a]	Total yield[a]
1[b]	70	1/0.3/0	20%
2	20	1/0.4/1.4	84%
3[c]	-10	1/0.3/0.9	81%
4[d]	-78	1/0.3/0	84%

[a] Isolated yields, average of 2 runs, products ratio determined by ^{1}H NMR. [b] No starting material remaining, significant amounts of oligomerized by-products were formed. [c] Reacted for 30 min. [d] Reacted for 15 h.

3. Silver salt additive

We then examined the effect of salt additives (Table 25) and found the **59**:**60**:**61** ratio significantly influenced by the counterion.

Table 25. Effect of silver salt additive on the cycloisomerization of **56**



56 **59** **60** **61**

Entry	AgX	**59**:**60**:**61**[a]	Total yield[a]
1	$AgBF_4$	1/0.4/1.4	84%
2	$AgPF_6$	1/0.6/1.2	90%
3	$AgSbF_6$	1/0.5/0.7	85%
4	AgOTf	1/0.2/0	76%
5[b]	AgOAc	**56** recovered	--

[a] Isolated yields, average of 2 runs, products ratio determined by ^{1}H NMR. [b] Reacted for 2 h.

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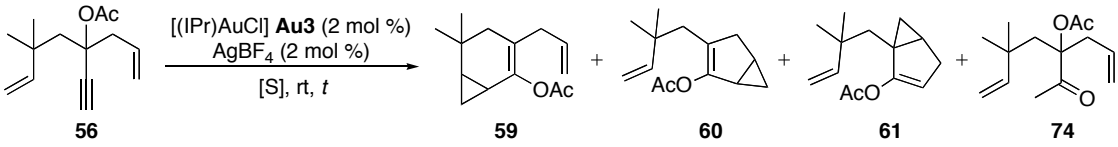
Formation of **61** was not observed using silver triflate while no reaction occurred with silver acetate (Entries 4 and 5), probably because in this case there is no generation of a cationic gold complex, the acetate anion lying in the coordination sphere of the gold atom.[275] A different trend was observed with fluorinated anions, which increased the ratio **59**:**61** from small (boron) to large (antimony) perfluoro anions. Thus, it appears that the formation of the bicyclo[4.1.0] derivative **59** is slightly favored in the presence of weakly bound counterions.

4. Solvent

Next, we studied the influence of the solvent. A set of classical organic solvents with different polarities was tested in the cycloisomerization of **56**; results are depicted in Table 26.

Table 26. Influence of the solvent on the cycloisomerization of **56**[a]



56 **59** **60** **61** **74**

Entry	[S]	**56**	**59**	**60**	**61**	**74**	Time
1	MeCN	--	37%	11%	29%	--	3 h
2	DCM	--	30%	12%	42%	--	5 min
3	THF	--	--	--	--	69%	2 h
4	4-Dioxane	75%	--	--	--	21%	15 h
5	Toluene	70%	--	--	--	24%	15 h
6	Pentane	85%	--	--	--	10%	15 h

[a] Isolated yields, average of 2 runs, products ratio determined by ^{1}H NMR.

The use of acetonitrile resulted in a longer reaction time (Entry 1), presumably due to coordination of the solvent to the cationic gold center,[324] lowering the turnover frequency of the catalyst but altering only slightly the ratio of bicycles **59**:**60**:**61**.

Moving towards less polar solvents induced a complete switch of the reactivity (Entries 3-6). Hence, in THF, the formation of methyl ketone **74**, resulting from the

[324] Acetonitrile adducts of NHC-containing cationic gold(I) complexes have been isolated, see section **III.B.1** of this chapter. For other acetonitrile gold(I) adducts, see: (a) Willner, H.; Schaebs, J.; Hwang, G.; Mistry, F.; Jones, R.; Trotter, J.; Aubke, F. *J. Am. Chem. Soc.* **1992**, *114*, 8972–8980. (b) Li, Q.-S.; Wang, C.-Q.; Zou, R.-Y.; Xu, F.-B.; Song, H.-B.; Wan, X. J.; Zhang, Z. Z. *Inorg. Chem.* **2006**, *45*, 1888–1890. (c) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5455–5459.

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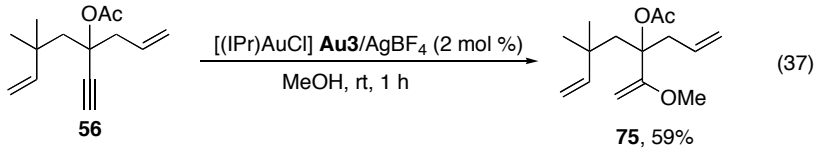
hydration of the alkyne moiety in **56**,[325] was observed in good yield (Entry 3) while only small amounts of **74** were formed in dioxane, toluene, and pentane (Entries 4-6). All these reactions were performed in technical grade solvents – mainly for practical reasons – and hydration reactions occurred thanks to water present in the solvent. Nevertheless, it should be noted that similar reactions carried out with anhydrous 4-dioxane and pentane produced comparable results, with no formation of carbocyclic products, though in longer reaction time (i.e. 24 h). We believe that, in these last cases, the hydration product was formed because of adventitious water added while controlling the advancement of the reaction.[326]

Subsequently, we attempted a trapping experiment using methanol as solvent. Under these conditions, we only observed the formation of enol ether **75**, resulting from methanol addition onto the alkyne moiety (Eq 37).[327]



(37)

D. Order of the acetate migration/cyclopropanation sequence

A key feature of the reactivity of propargylic acetates in the presence of soft π-Lewis acidic metals such as gold and platinum lies in the ability of the acetate moiety to act as an internal nucleophile, migrating in a 1,2- or 1,3-fashion onto the C≡C bond. In the context of enyne cycloisomerization, this migrating ability of the acetate has raised questions about the order of the migration/cyclopropanation sequence.[328,329] In a first approach, we proposed (a migration *then* cyclopropanation sequence, see **III.B.3**), which appeared more consistent with the formation of bicyclo[3.1.0]hexene **61**. Nevertheless, at that time we did not exclude

[325] For homogeneous Au-catalyzed hydration of alkynes, see: (a) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729–3731. (b) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4563–4565. (c) Casado, R.; Contel, M.; Laguna, M.; Romero, P.; Sanz, S. *J. Am. Chem. Soc.* **2003**, *125*, 11925–11935. (d) Roembke, P.; Schmidbaur, H.; Cronje, S.; Raubenheimer, H. *J. Mol. Cat. A* **2004**, *212*, 35–42. (e) Sanz, S.; Jones, L. A.; Mohr, F.; Laguna, M. *Organometallics* **2007**, *26*, 952–957.

[326] For a related observation in gold catalysis, see: Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442–1443.

[327] For Au^{I}-catalyzed addition of alcohols onto alkynes, see: Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415–1418.

[328] For theoretical calculations on this issue, see: (a) Soriano, E.; Ballesteros, P.; Marco-Contelles, J. *Organometallics* **2005**, *24*, 3182–3191. (b) Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2005**, *70*, 9345–9353. (c) Nieto Faza, O.; Silva López, C.; Álvarez, R.; de Lera, A. R. *J. Am. Chem. Soc.* **2006**, *128*, 2434–2437. (d) Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2007**, *72*, 1443–1448.

[329] In the case of an *intermolecular* cyclopropanation between a propargylic ester and an olefin, Toste showed that a sequence migration *then* cyclopropanation applied, see: Johansson, M.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002–18003.

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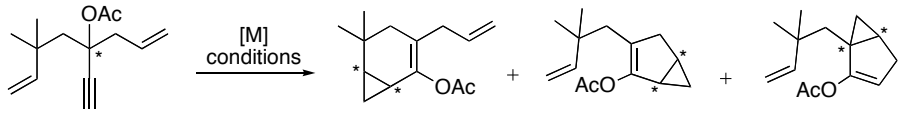
the possibility that a cyclopropanation *then* migration sequence could be at play for the formation of bicyclic compounds **59** and **60**. To gain insights on this crucial issue, we synthesized an enantioenriched dienyne **56** (For a detailed synthetic scheme, see the Experimental section, section **VIII.B.2**, pp 266) and subjected it to cycloisomerization conditions. In the case of a cyclopropanation *then* migration sequence, the chiral information should be translated into the product whereas in the case of the opposite sequence, the formation of intermediate **Au-II** (see Scheme 38) precludes chirality transfer.[330]

Enantioenriched **56**, in the presence of 5 mol % $PtCl_2$, yielded rearranged products **59** and **60** in comparable yields and ratios as previously observed but with distinct enantioselectivities (Table 27, entries 1 and 2). The cyclohexene derivative **59** was formed with 40% ee while the cyclopentene **60** was found racemic. Starting from a 66% ee enriched dienyne, this seems to indicate that both sequences are at play in the formation of **59** with a clear preference for the cyclopropanation *then* migration one.

On the contrary, the formation of **60** appears to result strictly from the migration *then* cyclopropanation sequence, leading to complete loss of chirality. Finally, the use of gold(III) chloride afforded **59** and **61** in very low ee's and **60** as a racemic mixture (Entry 3), indicating that with gold catalysts both sequences are likely to compete in the formation of the cyclopropanated products.

Table 27. Au- and Pt-Catalyzed cycloisomerization of enantioenriched **56**



56, 66% ee **59** **60** **61**

Entry	Conditions	**59**[a]	**60**[a]	**61**[a]
1	$PtCl_2$ (5 mol %), Tol, rt→80ºC, 2 h	88% (38% ee)	8% (rac)	--
2	$PtCl_2$ (5 mol %), Tol, rt, 2 h	83% (42% ee)	7% (rac)	--
3[b]	$AuCl_3$ (2 mol %), DCM, rt, 10 min	46% (8% ee)	36% (rac)	5% (4% ee)

[a] Isolated yields of **59**:**60**:**61** mixtures, ratios and ee's determined by chiral GC. [b] **56** (60% ee) was used.

At this point of our study, several mechanistic scenarios were still to be considered.

[330] This method has already been used by Fürstner and Fehr independently, see: (a) Fürstner, A.; Hannen, P. *Chem.–Eur. J.* **2006**, *12*, 3006–3019. (b) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2901–2904. For a theoretical approach, see: (c) Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2007**, *72*, 2651–2654.

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A plausible pathway that would involve cyclopropane ring-opening,[331] leading to isomerization between the different products, was discarded after we performed control reactions that showed no isomerization between **59**, **60**, and **61**. Finally, carbocyclization onto the oxonium intermediate before rupture of the C–O bond leading to regeneration of the ester function should also be mentioned as an alternative. This possibility, first proposed by Fehr,[330b] implies that the stereochemical information, still present in the oxocarbenium intermediate, is transferred in the cyclization step.

The additional information gathered so far on the cyclization of **56** and the formation of **59**, **60**, and **61** point clearly to competing pathways which balance can be shifted as a function of the ancillary ligand. In the presence of platinum(II) chloride, the formation of **59** is the result of two competing pathways, with an advantage given to the stereospecific one, while **60** is apparently formed through a migration *then* cyclopropanation sequence. When gold(III) is used, it seems that the latter pathway is favored for the three formed carbocycles **59**, **60**, and **61**. Nevertheless, at this point of our study a rationale for the formation of the unprecedented cyclopropyl derivative **61** remained elusive, notably because of little precedent in the literature.[332] We therefore decided to perform DFT calculations of a full catalytic cycle for the formation of **59**, **60**, and **61**, focusing notably on **61**.

E. DFT Calculations on the formation of 59, 60, and 61

1. General information

For the sake of clarity, we numbered the atoms in dienyne **56** (Figure 33) and we labeled structures from the DFT calculations with lowercase bold letters.

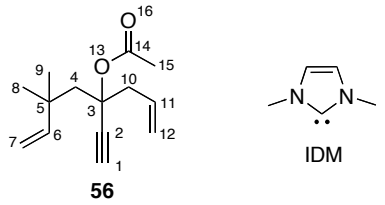

Figure 33. Atom numbering in **56** and structure of IDM

The only exceptions are the starting dienyne **56**, the allene **62**, and the bicyclic pro-

[331] (a) Hours, A. E.; Snyder, J. K. *Tetrahedron Lett.* **2006**, *47*, 675–678. (b) Hours, A. E.; Snyder, J. K. *Organometallics* **2008**, *27*, 410–417.
[332] This type of rearranged product has been isolated in one case but in very low amount (3%), see: Blaszykowski, C.; Harrak, Y.; Brancour, C.; Nakama, K.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Synthesis* **2007**, 2037–2049.

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ducts **59**, **60** and **61**. For these species we use labels such as **56Au**, **59Au** and so on, to indicate that these substrates are coordinated to Au.

Since N-heterocyclic carbene ligands are necessary in order to obtain satisfying amount of the unprecedented carbocycle **61**, we performed the calculations with IDM bound to the gold(I) center (IDM = 1,3-dimethylimidazol-2-ylidene, see Figure 33). For the reader's convenience, the different reaction pathways, which are interconnected, are discussed independently and compared when relevant. Accordingly, a figure depicting the mechanistic pathway and the potential energy profile for each main path provides the basis for the discussion in a first approach. Furthermore, in order to give a general – and closer to reality – picture of the mechanistic processes at play, which are interdependent, we have gathered in one single scheme, presented at the end of the discussion, every pathway considered here.

At this point, we wish to remark that the error associated with this kind of calculations can be easily as much as 10 kJ.mol^{-1}. Additionally, the conformational freedom associated with the flexible skeleton of the substrate implies that several structures very close in energy have to be considered. Although we tried to explore several conformers for each of the structures we considered, it cannot be excluded that in some cases a slightly better geometry could be located. This implies that all the calculations presented here have to be considered *cum granu salis*, and that they provide an overall scenario of chemical sense.

2. Formation of 59

The catalytic cycle starts with displacement of a BF_4^- anion from the [(IDM)Au]BF_4 species **a**, by the alkyne group of **56**, to furnish intermediate **56Au**.[333] In DCM, displacement of the BF_4^- counterion by the substrate is exergonic by 26 kJ.mol^{-1}. Structure **56Au** is then the branching point for three different reaction paths (Scheme 47, p 217).

The first consists of a nucleophilic attack of the C6–C7 double bond to the C1 atom; see Figure 34, blue path. This cyclopropanation step leads to intermediate **b**, which already presents the bicyclic skeleton of product **59**. The Au-carbene intermediate **b** is 60 kJ.mol^{-1} lower in energy than the starting alkyne coordinated intermediate **56Au**, and is reached through transition state **56Au-b**, with a rather low energy barrier of 32 kJ.mol^{-1} (Figure 34).

[333] For references on isolated and structurally characterized [(η^2-RC≡CR)Au^I] complexes, see: (a) Schulte, P.; Behrens, U. *Chem. Commun.* **1998**, 1633–1634. (b) Shapiro, N. D.; Toste, F. D. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 2779–2782.

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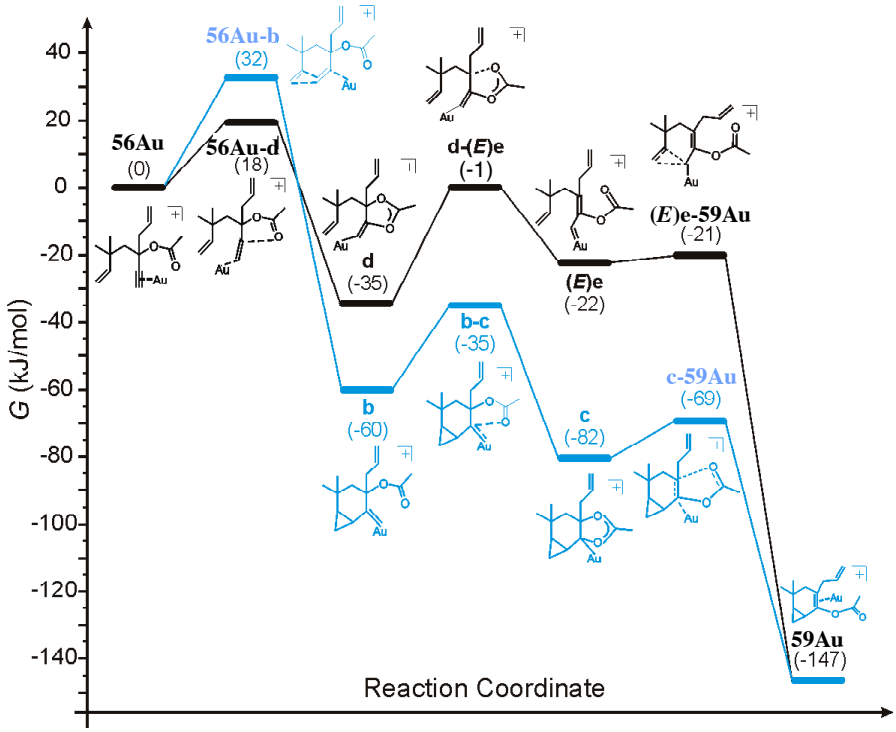

Figure 34. Energy profiles leading to **59**

Formation of **59** from **b** involves a 1,2-shift of the ester group from C3 to C2. After a first step leading to the formation of intermediate **c**, through transition state **b-c**, exhibiting a barrier of 25 kJ.mol^{-1}, the 1,2-shift is then completed via transition state **c-3Au**, with a barrier of 13 kJ.mol^{-1}, and finally affords the coordinated product **59Au**. Both the intermediate **c** and **59Au** are lower in energy than intermediate **56Au** (by 82 kJ.mol^{-1} and 147 kJ.mol^{-1}, respectively) and thus formation of **59Au** is a substantially downhill path from the starting alkyne coordinated species **56Au** to the product coordinated species **59Au**. Product release from **59Au** assisted by a coordinating BF_4^- counterion is endergonic by 6 kJ.mol^{-1}, leads to product **59** and closes the catalytic cycle by forming the starting [(IDM)Au]BF_4 species **a**.

On the other hand, product **59** can be reached from **56Au** through an alternative reaction pathway; see Scheme 34, black path. Indeed, as mentioned before, in addition to the cyclopropanation *then* migration sequence that we just examined, the migration *then* cyclopropanation sequence has to be considered. Hence, starting from the alkyne coordinated species **56Au**, a 1,2-shift of the ester group corresponding to attack of O16 to C2 leads to intermediate **d** through transition state **56Au-d**, with an energy barrier of 18 kJ.mol^{-1} (Figure 34). Intermediate **d**, which is 35 kJ.mol^{-1} lower in energy than **56Au**, is another branching point in this complex manifold of reactions. The branch that leads to **59**

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involves the breaking of the C3–O13 bond to furnish intermediate **(*E*)e**, with a barrier of 34 kJ.mol^{-1}, and a subsequent cyclopropanation step, corresponding to attack of the C6–C7 double bond to C1, through transition state **(*E*)e-59Au**. A last step with an almost negligible energy barrier of only 1 kJ.mol^{-1} leads to the product coordinated species **59Au**, from which **59** is released, closing the catalytic cycle. Intermediate **(*E*)e** is 22 kJ.mol^{-1} lower in energy than **56Au**.

In the framework of the Curtin-Hammett principle, the actual pathway that is followed to reach **59** is determined by the energy difference between the transition states of highest energy along the two alternative pathways, that is transition states **56Au-d** and **56Au-b**. According to our calculations, transition state **56Au-d** is lower in energy that **56Au-b** by 14 kJ.mol^{-1}, which suggests that the main reaction channel leading to **59** involves the 1,2-shift of the ester group first and then a cyclopropanation step, although the alternative path corresponding to the cyclopropanation *then* 1,2-shift sequence is competitive.

3. Formation of 60

We now focus on the formation of **60** (Figure 35), which can be reached through two alternative pathways (cyclopropanation *then* 1,2-shift or the reverse sequence) that are very similar to those just described to rationalize the formation of **59**.

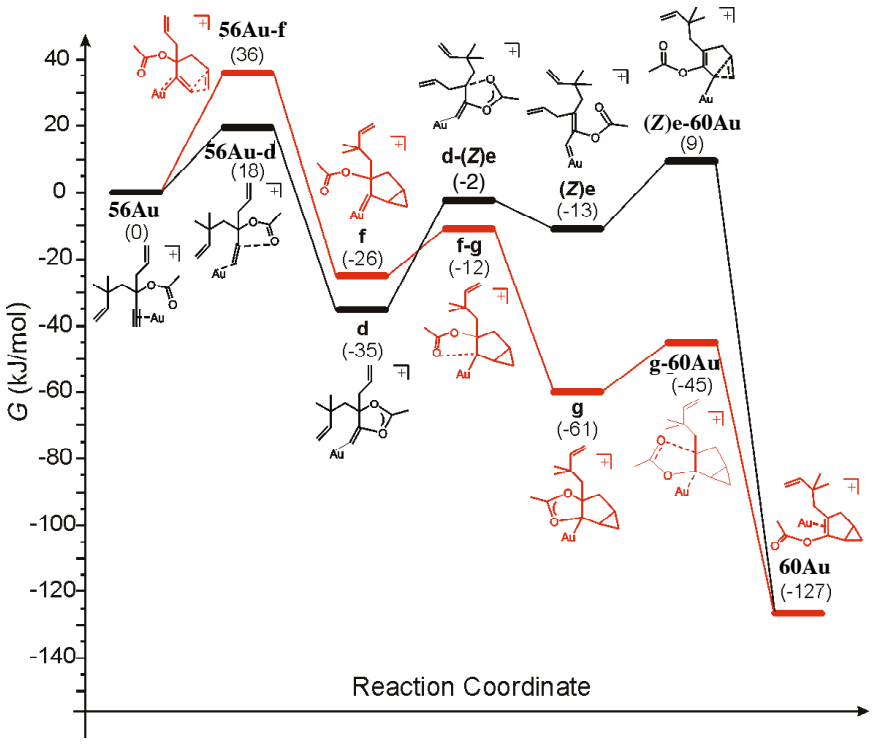

Figure 35. Energy profiles leading to **60**

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The first path involves again the nucleophilic attack of a C–C double bond to C1 but, in this case, it is the C11–C12 double bond that we have to consider (Figure 35, red path).

This cyclopropanation step leads to intermediate **f**, which already presents the bicyclic skeleton of product **60**. The Au-carbene intermediate **f** is 26 kJ.mol^{-1} lower in energy than the starting alkyne coordinated intermediate **60Au**, and is obtained *via* transition state **56Au-f**, with the rather low energy barrier of 36 kJ.mol^{-1}. Transition state **56Au-f** is slightly higher in energy than the similar transition state **56Au-b** because of the higher steric strain associated with formation of a more strained 5-membered ring in **56Au-f**, compared to formation of a more relaxed 6-membered ring in **56Au-b**. Formation of **60** from **f** involves then the 1,2-shift of the ester group from C3 to C2. The first step of this 1,2-shift is the formation of intermediate **g**, through transition state **f-g**, with a barrier of 14 kJ.mol^{-1}.

Final formation of the coordinated product **60Au** occurs through transition state **g-60Au** with an energy barrier of 16 kJ.mol^{-1}. Both intermediates **g** and **60Au** are lower in energy than intermediate **56Au** (by 61 and 127 kJ.mol^{-1}, respectively) and thus formation of **60Au**, similarly to that of **59Au**, is a substantially downhill path from the starting alkyne coordinated reactant **56Au** to the product coordinated structure **60Au** (Figure 35). Product release from **60Au** assisted by a coordinating BF_4^- counterion is endergonic by 13 kJ.mol^{-1}, leads to product **60** and closes the catalytic cycle by forming the starting [(IDM)Au$^+$]BF_4^- species **a**.

Alternatively, **60** can be reached from **56Au** through the alternative path that involves initially the 1,2-shift of the ester group; see Scheme 35, black path. As discussed above, the branching point is intermediate **d** (see Scheme 47, p 217). In fact, breaking of the C3–O13 bond can alternatively lead to intermediate (***Z***)**e**, with a barrier of 25 kJ.mol^{-1}, which, upon attack of the C11–C12 double bond to C1, leads to the product coordinated species **60Au** *via* transition state (***Z***)**e-60Au**, with an energy barrier of 22 kJ.mol^{-1}. Bicyclo[3.1.0]hexene **60** is then released from **60Au** by coordination of a BF_4^- anion and the catalytic cycle closed. Intermediate (***Z***)**e** is 13 kJ.mol^{-1} lower in energy than **56Au**, and it is less stable than the (***E***)**e** isomer by 9 kJ.mol^{-1}.

In conclusion, considering that transition state **56Au-d** is 18 kJ.mol^{-1} lower in energy than transition state **56Au-f**, we believe that formation of **60** proceeds to a great extent through a 1,2-shift followed by a cyclopropanation step.

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4. Formation of 61

While the possible mechanistic pathways explaining the formation of **59** and **60** from **56Au** were already proposed in the literature,[272,328,330] the formation of **61** from **56Au** had only little mechanistic explanation before this study.[306,334] We anticipated that **61** could be formed following, at least, three different reaction paths. In all cases the allene coordinated intermediate **62Au** is the key intermediate in order to rationalize the formation of **61** (see Scheme 47, p 217). The simplest pathway involves a 1,3-shift of the ester group from **56Au**, leading to intermediate **h** through transition state **56Au-h**, with an energy barrier of 41 kJ.mol^{-1} (see Figure 36). Intermediate **h**, which is 14 kJ.mol^{-1} lower in energy than **56Au**, then evolves, *via* transition state **h-62Au** and the almost negligible energy barrier of 3 kJ.mol^{-1}, to the allene coordinated species **62Au**, which is 36 kJ.mol^{-1} lower in energy than **56Au**.

We remark here that several geometries, each rather similar in energy, can be adopted by **62Au**. For the sake of simplicity, in all the reaction pathways presented we discuss the most stable isomer of **62Au**. The allene coordinated species **62Au** can evolve towards the product coordinated species **61Au** through simultaneous attack of the C11–C12 double bond to C1 and C3 to form the bicyclo[3.1.0]hexene skeleton of **61** in a single step, leading to intermediate **i** through transition state **62Au-i** and an energy barrier of 24 kJ.mol^{-1}. Finally, a 1,2-shift of the ester group of **i**, through intermediate **j** and transition states **i-j** and **j-61Au**, with energy barriers of 16 kJ.mol^{-1} and 19 kJ.mol^{-1} respectively, leads to the Au coordinated product **61Au**. Product release from **61Au** assisted by a coordinating BF_4^- counterion is endergonic by 14 kJ.mol^{-1}, leads to product **61** and closes the catalytic cycle by forming the starting [(IDM)Au]BF_4 species **a**.

Incidentally, it should be noted that the BF_4^- counterion can also displace allene **62** from **62Au**, yielding the starting [(IDM)Au]BF_4 species **a**, and releasing the allene **62** in the reaction media.

Formation of **61** can be also explained by two other pathways that branch from intermediates (***E***)**e** and (***Z***)**e**; intermediates that we already introduced to rationalize the formation of **59** and **60** respectively (see Figures 34 and 35; see Scheme 47, p 217 for a general overview). We will first discuss branching from intermediate (***E***)**e**. Instead of the cyclopropanation step corresponding to nucleophilic attack of the C6–C7 double bond to C1, (***E***)**e** can undergo a 1,2-shift of the ester group, leading initially to intermediate (***E***)**k**, *via*

[334] In a review on Au-catalyzed transformations, Echavarren proposed, for the transformation **56** → **61**, an alternative and interesting cyclopropanation/1,2-OAc shift/cationic rearrangement sequence, see ref. 276j.

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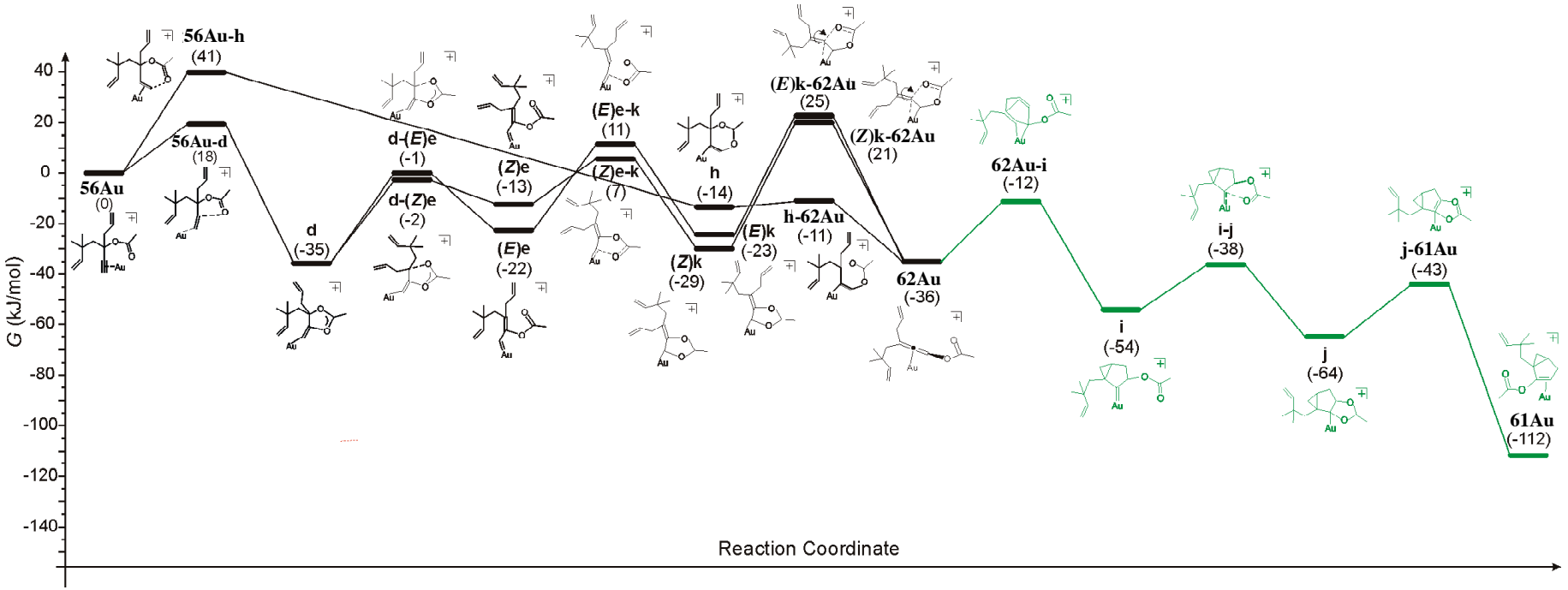

Figure 36. Energy profiles leading to **61**

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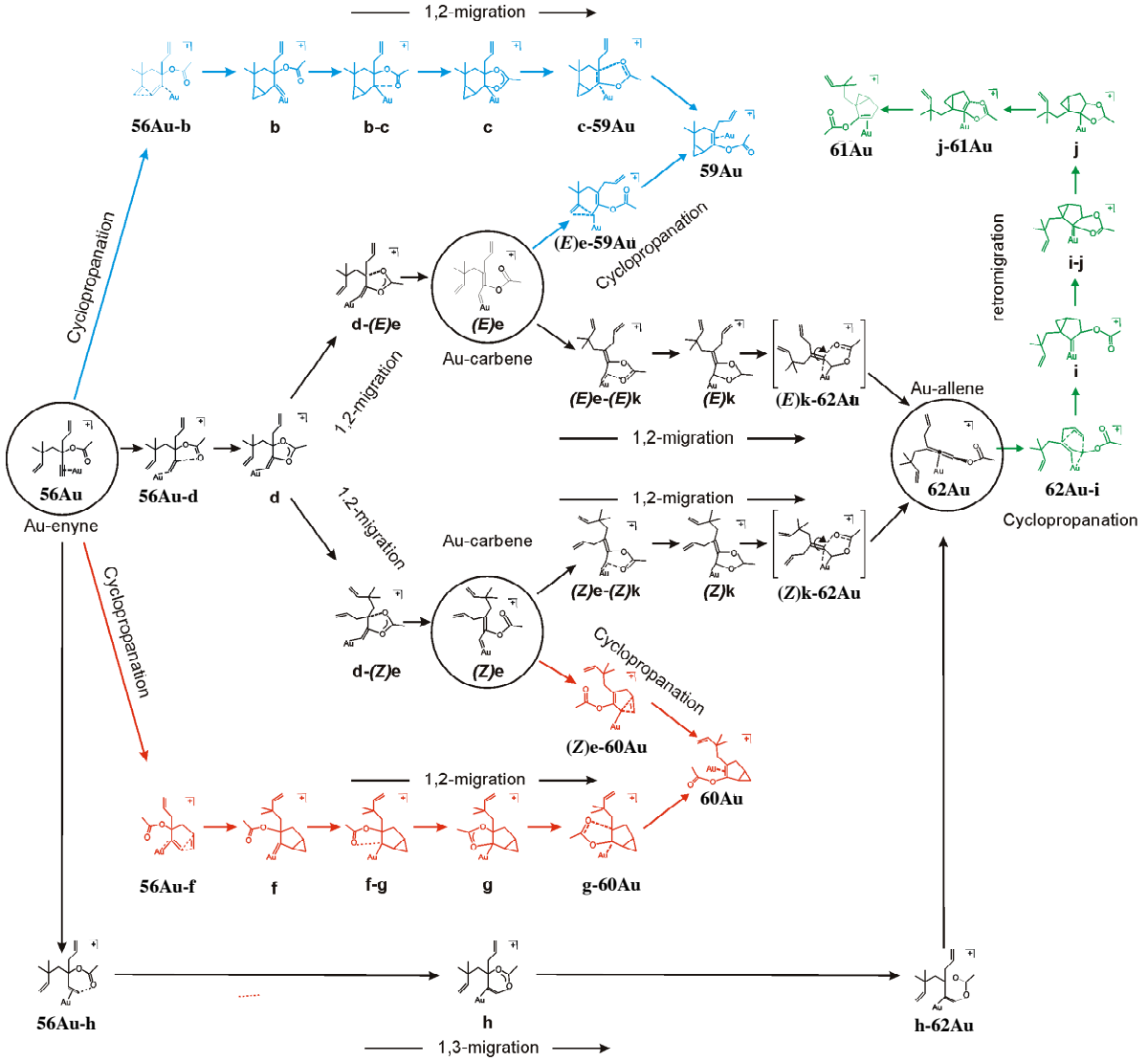
transition state **(*E*)e-(*E*)k** with an energy barrier of 33 kJ.mol^{-1}, and then to the Au-allene species **62Au** through transition state **(*E*)k-62Au** and an energy barrier of 48 kJ.mol^{-1}.

Once intermediate **62Au** has been reached, the reaction can evolve to **61** as described before (Figure 36). However, this branching is quite unlikely considering that the 1,2-shift transition state **(*E*)e-(*E*)k** has to compete with the cyclopropanation transition state **(*E*)e-59Au**, which is 32 kJ.mol^{-1} lower in energy (Figure 34). Considering the level of accuracy of this kind of calculations, we can state that once intermediate **(*E*)e** is reached, it cannot evolve to intermediate **62Au**.



Scheme 47. Possible mechanistic pathways based on calculations (Species in the golden-carousel are in black)

We now discuss branching from intermediate **(*Z*)e**. Instead of the cyclopropanation step corresponding to nucleophilic attack of the C11–C12 double bond to C1, **(*Z*)e**, similarly

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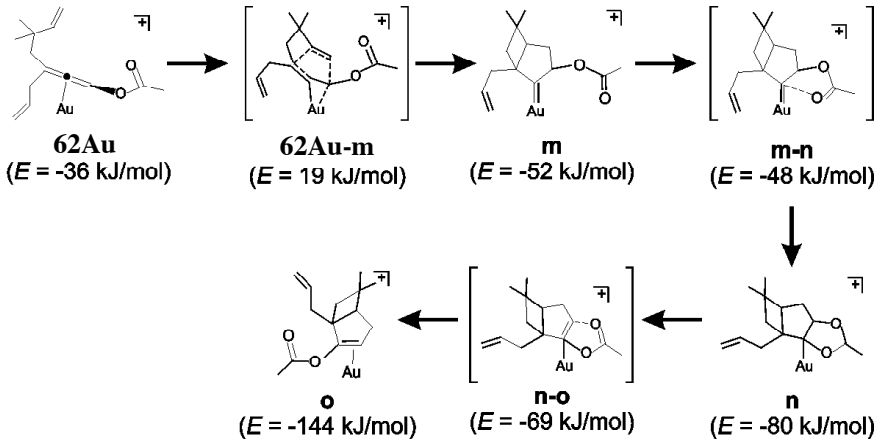
to **(*E*)e**, can undergo a 1,2-shift of the ester group leading initially to intermediate **(*Z*)k**, *via* transition state **(*Z*)e-(*Z*)k** with an energy barrier of 20 kJ.mol^{-1}, and then to the Au-allene species **62Au** through transition state **(*Z*)k-62Au** and an energy barrier of 50 kJ.mol^{-1}. Once intermediate **62Au** has been reached, the reaction can evolve to **61** as described before. In this case, we found that the 1,2-shift transition state **(*Z*)e-(*Z*)k** has to compete with the cyclopropanation transition state **(*Z*)e-60Au**, which is only 2 kJ.mol^{-1} higher in energy. This implies that branching from **(*Z*)e** along both reaction pathways is a very likely event.

5. Alternative cyclization of 62Au

We also explored if the C1 and C3 atoms of the **62Au** allene species can be attacked by the C6-C7 double bond of the substrate, see Scheme 48. In this case, the bicyclo[3.2.0]heptene skeleton of **o** is formed through transition state **62Au-m** and a barrier of 55 kJ.mol^{-1}. Transition state **62Au-m** is 31 kJ.mol^{-1} higher in energy than transition state **62Au-i**, which is in agreement with the experimental finding that no product with a bicyclo[3.2.0]heptene scaffold was observed. For the sake of completeness, we calculated the full catalytic cycle also in this case. Hence, intermediate **m** is 52 kJ.mol^{-1} lower in energy than **56Au**, and is connected to the product **o** through intermediate **n** at -80 kJ.mol^{-1}, and transition states **m-n** and **n-o**, at -48 kJ.mol^{-1} and -69 kJ.mol^{-1}, respectively. The product coordinated **o** is 144 kJ.mol^{-1} lower in energy than **56Au**.



Scheme 48. Alternative cyclization path from **62Au**

6. Alkene or alkyne activation?

Finally, we also explored the formation of **61** according to the pathway shown in Scheme 49. This pathway starts with displacement of the BF_4^- counterion from the [(IDM)Au]BF_4 species **a**, by the C11–C12 double bond of **56**, rather than from the C1–C2

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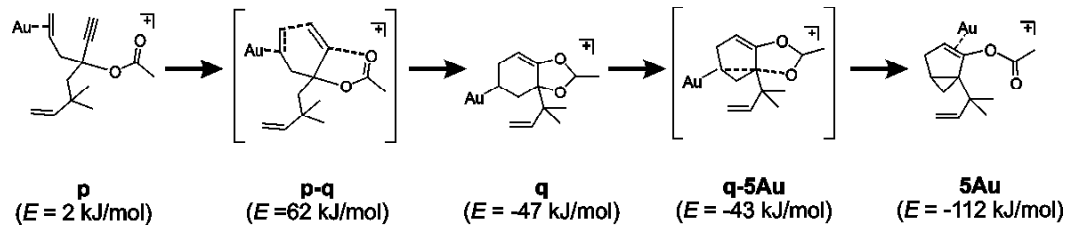
triple bond. Intermediate **m**, with the C11–C12 double bond coordinated to the Au atom,[335] is only 2 kJ.mol^{-1} higher in energy than **56Au**, which indicates that coordination of the alkyne or of the alkene group of the substrate is scarcely selective. Nucleophilic attack of the C1–C2 triple bond to the coordinated C11–C12 double bond proceeds through transition state **p-q**, which is 62 kJ.mol^{-1} higher in energy than **56Au**, which excludes this reaction path. For the sake of completeness, we calculated the full catalytic cycle. Hence, intermediate **q** is 41 kJ.mol^{-1} lower in energy than **p**, and is connected to **61Au** through transition state **q-61Au**, with an energy barrier of only 4 kJ.mol^{-1}.



Scheme 49. Alkene activation pathway to form **61**

7. A manifold of intricate pathways: a golden carousel for an enyne

The present calculations clearly indicate that this catalysis is characterized by a manifold of highly competitive reaction pathways. As a caution, we cannot exclude that there are other reaction pathways that we were not able to envisage. Nevertheless, calculations clearly demonstrate that the high reactivity of the starting structure **56Au** is at the origin of this variety. As we already indicated, the alkyne coordinated species can undergo both 1,2- and 1,3-shift of the ester group, leading respectively to the Au-carbene species **(*E*)e** and **(*Z*)e**, and to the Au-allene species **62Au**. All these species are connected in a catalytic cycle we labeled as golden-carousel. To better understand this point, the most relevant sections of the manifold of reaction pathways are shown in Scheme 50.

It appears clearly that the alkyne coordinated species **56Au** is the species of highest energy in the cycle, while the reservoir of active species are intermediate **d** (which is not a way off the cycle) and the allene species **62Au**. Intermediate **d** is easily formed from **56Au**. The Au-carbene species **(*E*)e** and **(*Z*)e** represent the way off to products **59** and **60**, respecti-

[335] For isolated Au^{I}-adducts of olefins, see: (a) Belli Dell'Amico, D.; Calderazzo, F.; Dantona, R.; Strähle, J.; Weiss, H. *Organometallics* **1987**, *6*, 1207–1210. (b) Dávila, R. M.; Staples, R. J.; Fackler, J. P., Jr. *Organometallics* **1994**, *13*, 418–420. (c) Cinellu, M. A.; Minghetti, G.; Cocco, F.; Stoccoro, S.; Zucca, A.; Manassero, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6892–6895. (d) Cinellu, M. A.; Minghetti, G.; Cocco, F.; Stoccoro, S.; Zucca, A.; Manassero, M.; Arca, M. *Dalton Trans.* **2006**, 5703–5716. (e) Dias, H. V. R.; Wu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7814–7816. (f) Dias, H. V. R.; Fianchini, M.; Cundari, T. R.; Campana, C. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 556–559. For a review, see: (g) Dias, H. V. R.; Wu, J. *Eur. J. Inorg. Chem.* **2008**, 509–522.

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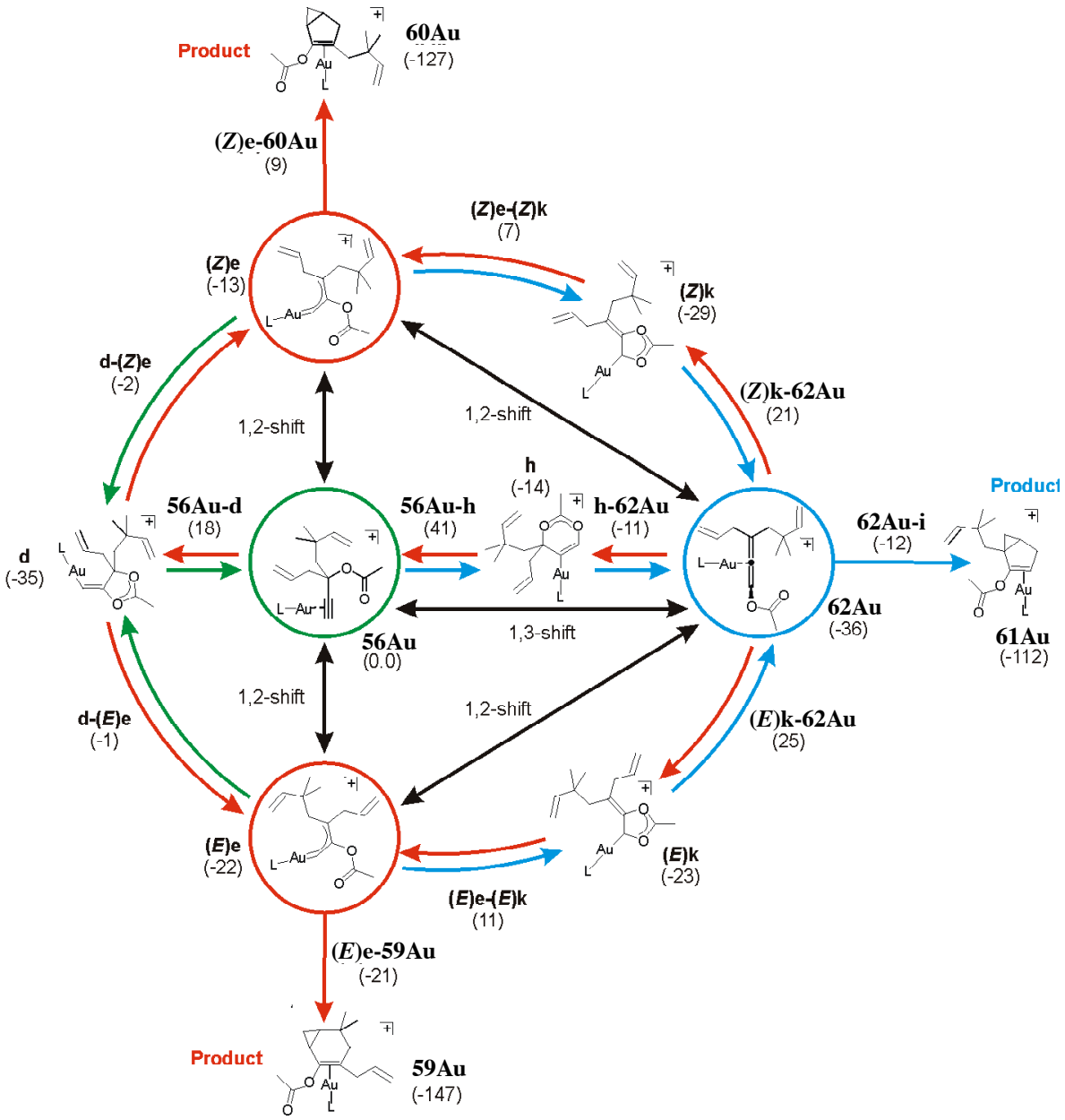

Scheme 50. A golden carousel for an enyne (energies in kJ.mol^{-1})

vely, while the Au-allene species **62Au** is the way off to product **61**. Evolution of **(*E*)e**, **(*Z*)e** and **62Au** depends on the relative energy of the three transition states (two of them correspond to clockwise and counter-clockwise movements in the golden-carousel, the third to a way off from the carousel) that can be reached from each of these intermediates.

Intermediate **(*E*)e** is an excellent way off the carousel, since the transition state that connects intermediate **(*E*)e** and product **59**, **(*E*)e-59Au**, is quite lower in energy (by 20 kJ.mol^{-1} and 30 kJ.mol^{-1}, respectively) than transition states **d-(*E*)e** and **(*E*)e-(*E*)k**, which are the transition states to be reached by **(*E*)e** in order to move in the carousel. This explains the easy formation of **59**.

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Differently, **(*Z*)e** is not a good way off the carousel, since the most likely event is a counter-clockwise move in the carousel, to yield the highly stable intermediate **d**. The two other transition states of highest energy accessible from intermediate **(*Z*)e**, **(*Z*)e-60Au** and **(*Z*)k-62Au**, correspond respectively to the way off the carousel leading to **60Au** and to a clockwise move towards the allene intermediate **62Au** (Scheme 50). They are 11 kJ.mol^{-1} and 23 kJ.mol^{-1} higher in energy than transition state **d-(*Z*)e**, which explains the scarce amount of products **60** and **61** formed with NHC ligands of low steric bulkiness such as ITM (see Table 23).

Finally, **62Au** is another excellent way off the carousel, since the transition state that connects intermediate **62Au** and product **61**, **62Au-i**, is quite lower in energy (by 33 kJ.mol^{-1} and 37 kJ.mol^{-1}, respectively) than transition states **62Au-(*Z*)k** and **62Au-(*E*)k**, which are the transition states to be reached by **62Au** in order to move in the carousel. Thus, the relatively scarce amount of **61** produced with **56Au** as entry point into the golden-carousel is explained by the relatively high-energy transition state **(*Z*)k-62Au**, which does not allow an easy formation of **62Au** from **(*Z*)e**. On the other hand, the direct 1,3-shift pathway from **56Au** to **62Au** is blocked by the relatively high-energy transition state **56Au-h**. To conclude, the golden carousel proposed here clearly explains the high amount of **61** that is formed as the allene **62Au** species is used as entry point.

F. Cyclization of allenenyl esters vs. enynyl esters

Overall, the theoretical results presented here have notably allowed us to rationalize the formation of the unprecedented bicyclo[3.1.0]hexene **61**. Hence, according to our calculations, the cyclization would occur after formation of the allenyl ester, between the allene and the ene part of the 1,4-allenene core.[336]

To verify this hypothesis, we prepared allene **62**, using a simple silver-catalyzed procedure,[319] and we subjected it to our cyclization conditions. In the presence of 2 mol % of [(IPr)AuCl] **Au3**/$AgBF_4$, the cyloisomerization of **62** led to the formation of **61** as the major product (Table 28, entry 1). The reaction was more selective in favor of **61** than the cyclization of **56** (i.e. **59**:**60**:**61**, 1/1.4/9.3 vs. 1/0.4/1.4), which strongly supports allenyl ester

[336] Au-Catalyzed cyclization of 1,4-allenenyl esters has been described previously on related systems but no migration of the ester was observed: (a) Buzas, A.; Gagosz, F. *J. Am. Chem. Soc*. **2006**, *128*, 12614–12615. For other reports on 1,4-allenenes cyclization in the presence of gold catalysts, see: (b) Huang, X.; Zhang, L. *J. Am. Chem. Soc*. **2007**, *129*, 6398–6399. (c) Huang, X.; Zhang, L. *Org. Lett*. **2007**, *9*, 4627–4630.

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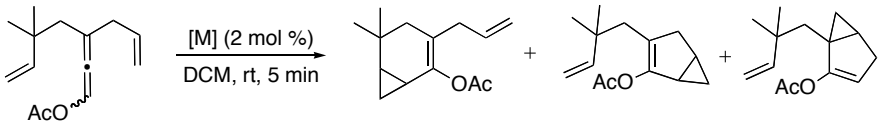
62 as intermediate in the transformation **56** → **61**. It should be noted that this is the first reaction producing **59** as the minor product.

Table 28. Cyclization of allenyl ester **62**



62 **59** **60** **61**

Entry	[M]	**59**:**60**:**61**[a]	Total yield[a]
1	[(IPr)AuCl] **Au3**/$AgBF_4$	1/1.4/9.3	93%
2[b]	[(Ph_3P)AuCl]/$AgBF_4$	1/0.5/0.7	51%
3[b]	AuCl	1/0.8/4.5	63%
4[b]	$AuCl_3$	1/1.4/1.9	50%

[a] Isolated yields, average of 2 runs, products ratio determined by ^{1}H NMR. [b] No starting material remaining, significant amounts of oligomerized by-products were formed.

The phosphine-containing catalyst notably produced significant amount of oligomerized products, as previously observed in the cyclization of dienyne **56**, and afforded a more contrasted ratio of cyclopropanated bicycles. Gold(I) and gold(III) chloride salts, despite the formation of oligomerized by-products, produced significantly higher amounts of **61** than in the reaction of dienyne **56**. This trend, which has been shown general for every catalyst, is in accordance with our proposal of allene **62** as intermediate in this cyclization.

Additionally, keeping in mind that products **59** and **60** are likely produced *via* direct cyclopropanation of enyne **56** and/or intermediate (***E***)**e** and (***Z***)**e** (see Scheme 50), both arising from "retro-migration" of the OAc in **62**, it appears that the competition between the acetate and the alkene as internal nucleophiles in **62** is strongly influenced by the ligand on gold. More precisely, and as predicted by the above theoretical studies, the allenyl acetate **62** seems to be less prone to isomerization back to (***E***)**e**/(***Z***)**e** and **56Au** when activated by the cationic [(NHC)Au] fragment when compared to the phosphine-gold catalyst.[337] Finally, the absence of rearranged product involving the 1,5-allenene framework seems to indicate a strong preference for the 1,4-allenene scaffold in the present catalytic system.[338,339]

[337] It has been predicted by DFT calculations that, in the Au-catalyzed isomerization [gold propargyl acetates **Au-I** ↔ gold carbenoid vinyl acetates **Au-II** ↔ gold allenyl acetates **Au-III**], a [(NHC)Au] species would favor the allene derivative while a [(PR_3)Au] species would isomerize more easily, see: Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 718–721.
[338] The preference of gold catalysts for the cyclization of 1,3-allenenes over 1,5-allenenes has already been reported, see: Lemière, G.; Gandon, V.; Cariou, K.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2007**, *9*, 2207–2209.

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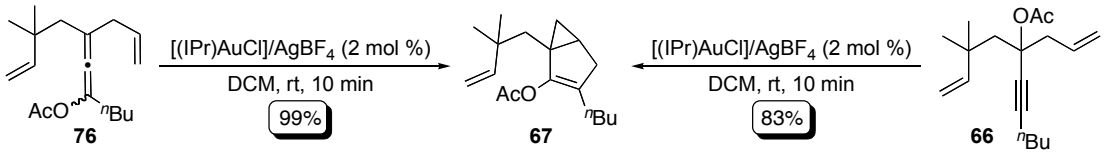
We also carried out the cycloisomerization of allenene **76**, which afforded quantitative yield of **67**, possessing the structure of the novel type of cyclopropyl compound (Eq 38). It should be noted that, in this case, the selectivity was already excellent starting from the corresponding propargylic actetate **66**, but that the yield of **67** was clearly improved. We remark as well that, while this total selectivity in favor of the new type of product was unexpected at the time of our first observations, it can now be rationalized. The formation of allene **76** from **66** is favored due to the alkyl substitution of the alkyne, therefore leading straightforwardly to cyclized product **67**.



(38)

G. Concluding remarks

While carrying out preliminary tests in homogeneous catalysis with [(NHC)AuCl] complexes developed in our laboratory, we discovered a novel type of enyne cycloisomerization. Thorough study of the reaction parameters allowed uncovering critical aspects involved in the formation of the unprecedented bicyclo[3.1.0]hexene **61**. Notably, the ancillary ligand present on the gold(I) center appeared to have the most influence on the outcome of the reaction, bulky N-heterocyclic carbenes such as IPr and IMes furnishing the best selectivity for the formation of **61**.

DFT Calculations, performed in collaboration with the research group of professor Luigi Cavallo, permitted to reveal that the apparent 1,2-shift of the OAc moiety was in fact a 1,3-shift, leading to allene **62**, followed by a "retro-1,2-shift" of the acetate. These theoretical findings, which also allowed for a better rationalization of the products ratio, were subsequently corroborated by experimental work. Indeed, it was found that when cyclization was performed from the allene, the selectivity was shifted toward the novel type of cyclopropyl derivative **61**.

[339] To the best of our knowledge, there is no report on Au-catalyzed reaction of 1,5-allenenes. For Au-catalyzed cyclization of 1,3-allenenes, see: (a) Lee, J. H.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 912–914 and ref. 338. For Au-catalyzed cyclization of 1,4-allenenes, see ref. 336. For Au-catalyzed cyclization of 1,6-allenenes, see: (b) Tarselli, M. A.; Chianese, A. R.; Lee, S. L.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 6670–6673. (c) Tarselli, M. A.; Gagné, M. R. *J. Org. Chem.* **2008**, *73*, 2439–2441.

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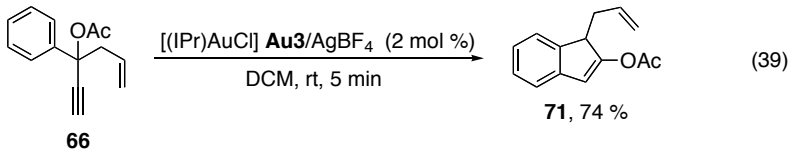
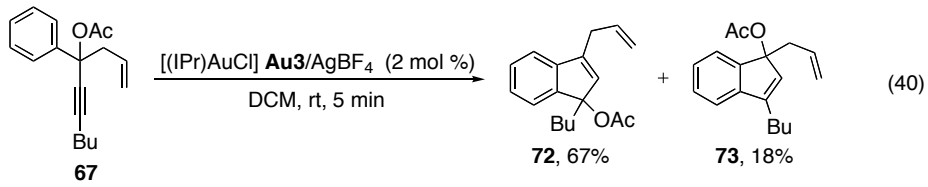
IV. Cyclization of arylpropargyl acetates[340]

A. Optimization of the catalytic system

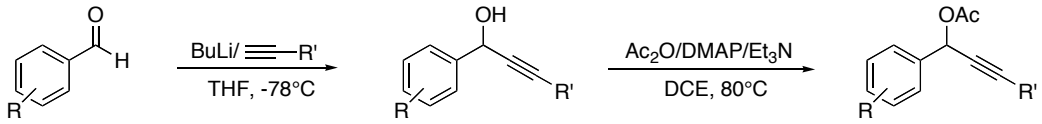
1. First observations

As described in section **III.B.2** of this chapter, we observed the formation of indene derivatives when arylpropargyl acetates were subjected to cyclization conditions for enyne cycloisomerization (see Eq 39 and 40 below). Strinkingly, no trace of bicyclo[3.1.0]hexene compounds was observed,[341] highlighting the chemoselectivity of the reaction.





Even though several interrogations, notably about the mechanistic aspects of this transformation, remained unanswered at the time, the wide accessibility of arylpropargyl acetates (a two-step high-yielding procedure from benzaldehyde-type precursors, see Scheme 51) and their straightforward cyclization under extremely mild conditions led us to investigate more deeply this reaction.



Scheme 51. Synthesis of arylpropargyl acetates

Carbocycles, and especially indenes, are compounds of great interest as synthetic targets and building blocks for pharmaceutical[342] and materials chemistry.[343] As the inter- or intramolecular formation of indenes usually requires high temperature and/or prolonged reaction time,[344] a mild and efficient assembly protocol is highly desirable.

---

[340] Marion, N.; Díez-González, S.; de Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647–3650.
[341] See section **III** of this Chapter.
[342] Korte, A.; Legros, J.; Bolm, C. *Synlett* **2004**, 2397–2399.
[343] (a) Barberá, J.; Rakitin, O. A.; Ros, M. B.; Torroba, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 296–299. (b) Yang, J.; Lakshmikantham, M. V.; Cava, M. P.; Lorcy, D.; Bethelot, J. R. *J. Org. Chem.* **2000**, *65*, 6739–6742.
[344] For recent selected reports on indene formation, see: (a) Xi, Z.; Guo, R.; Mito, S.; Yan, H.; Kanno, K.-i.; Nakajima, K.; Takahashi, T. *J. Org. Chem.* **2003**, *68*, 1252–1257. (b) Lautens, M.; Marquardt, T. *J. Org. Chem.*

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Surprisingly, using gold catalysts, the only related examples of intramolecular hydroarylation employ a heteroatom-containing tether, providing indoles, benzofurans or coumarins.[304,345,346] On the other hand, platinum and ruthenium have been shown to catalyze a similar transformation from arylpropargyl acetates. In these cases, the reaction is thought to proceed via a 1,2-OAc shift, generating a platina- or ruthena-carbene, which subsequently inserts an aryl C–H bond.[347]

2. Optimization of the reaction conditions

We first examined the reactivity of **77** with equimolar amounts of [(IPr)AuCl] **Au3** and $AgBF_4$. After 5 minutes at room temperature, **77** cleanly yielded indene **78** (Table 29, entry 1). Interestingly, even though the formation of indenes from benzylpropargyl acetates, such as **77**, has two precedents in the literature,[347] the architecture of **78** was unexpected (a thorough discussion on the mechanistic aspects of the reaction will be presented later). Reaction of **77** and $AgBF_4$ (Entry 3) resulted in the formation of allene **80** that showed little decomposition upon prolonged stirring and no formation of cyclized product. [(IPr)AuCl] alone was found inactive toward alkyne **77** (Entry 2).

To gauge the ligand influence in this transformation, we carried out reactions with various [(NHC)AuCl] complexes and silver tetrafluoroborate. Sterically demanding NHCs led to sluggish reactions (Table 29, entry 9) while less emcumbered ones, as well as PPh_3, lead to poor selectivity (Entries 8 and 10). Further optimization revealed that tetrafluoroborate or hexafluorophosphate were both suitable counterions (Entries 1 and 4) whereas hexafluoroantimonate produced a significant amount of oligomerization (Entry 5). It is noteworthy that ligandless AuCl alone or in conjunction with $AgBF_4$ did not lead to the desired product (Entries 11 and 12). Furthermore, $PtCl_2$, which has been reported recently to catalyze a closely related reaction,[347b] did not lead to **78** under our conditions (Entry 13).

2004, *69*, 4607–4614. (c) Chang, K.-J.; Rayabarapu, D. K.; Cheng, C.-H. *J. Org. Chem.* **2004**, *69*, 4781–4787. (d) Madhushaw, R. J.; Lo, C.-Y.; Hwang, C.-W.; Su, M.-D.; Shen, H.-C.; Pal, S.; Shaikh, I. R.; Liu, R.-S. *J. Am. Chem. Soc.* **2004**, *126*, 15560–15565. (e) Shi, M.; Xu, B.; Huang, J.-W. *Org. Lett.* **2004**, *6*, 1175–1178. (f) Nakamura, I.; Mizushima, Y.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9844–9847. (g) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2005**, *127*, 13498–13499. (h) Zhang, D.; Yum, E. K.; Liu, Z.; Larock, R. C. *Org. Lett.* **2005**, *7*, 4963–4966.

[345] (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992–1995. (b) Fürstner, A.; Mamane, V. *J. Org. Chem.* **2002**, *67*, 6264–6267. (c) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055–1058. (d) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581–584. (e) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669–3671.

[346] For a review on hydroarylation of alkynes, see: Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167–182.

[347] Ru-catalyzed: (a) Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505–8513. Pt-catalyzed: (b) Bhanu Prasad, B. A.; Yoshimoto, F. K.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468–12469.

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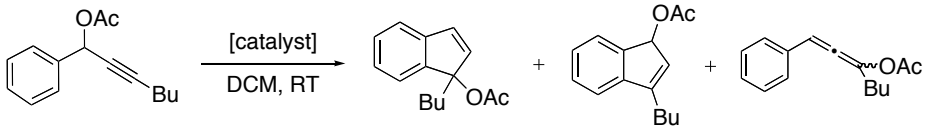
Table 29. Optimization of the formation of indene **78**[a]



77 **78** **79** **80**

entry	[catalyst] (2 mol %)	time	**78** (%)[b]	**79** (%)[b]	**80** (%)[b]
1	[(IPr)AuCl] **Au3**/$AgBF_4$	5 min	92	--	--
2	[(IPr)AuCl] **Au3**	overnight	no reaction		
3	$AgBF_4$	30 min	--	--	87
4	[(IPr)AuCl] **Au3**/$AgPF_6$	5 min	90	--	--
5	[(IPr)AuCl] **Au3**/$AgSbF_6$	5 min	73	--	--
6	[(SIPr)AuCl] **Au4**/$AgBF_4$	5 min	88	5	--
7	[(IMes)AuCl] **Au1**/$AgBF_4$	5 min	76	3	--
8	[(ITM)AuCl] **Au5**/$AgBF_4$	5 min	54	23	11
9	[(IAd)AuCl] **Au10**/$AgBF_4$	15 min	89	--	--
10	[(Ph_3P)AuCl]/$AgBF_4$	5 min	51	32	8
11	AuCl	30 min	unidentified mixture of products		
12	AuCl/$AgBF_4$	5 min	unidentified mixture of products		
13	$PtCl_2$	overnight	--	--	53

[a] Reaction conditions: alkyne **77** (0.5 mmol), [catalyst] (2 mol %), DCM (20 mL). [b] NMR yields with respect to 1,2-dichloroethane.

Finally, it should be added that, even though the reactions were set up without particular caution in air, the use of anhydrous dichloromethane was mandatory in order to avoid the formation of conjugated enone by-products.[348]

B. Scope of the reaction

The scope of the reaction was further investigated and results are presented in Scheme 52. The formation of indenes was found to be compatible with electron-poor or electron-rich arenes (**87**-**89**). Benzodioxole **84** reacted regioselectively to give **91** in excellent yield. *Ortho*-substituted indenes **92** and **94** were produced but they were accompanied by the formation of isomeric indenes **93** and **95** in minor amounts.

Interestingly, the naphthalene **86** produced regioselectively the phenalene **94**, upon cyclization on the distal phenyl ring.[349] Finally, we examined the influence of the substitution at the acetylenic position.

[348] This aspect of the reactivity of propargylic acetates will be developed later, see section **IV** of this chapter.

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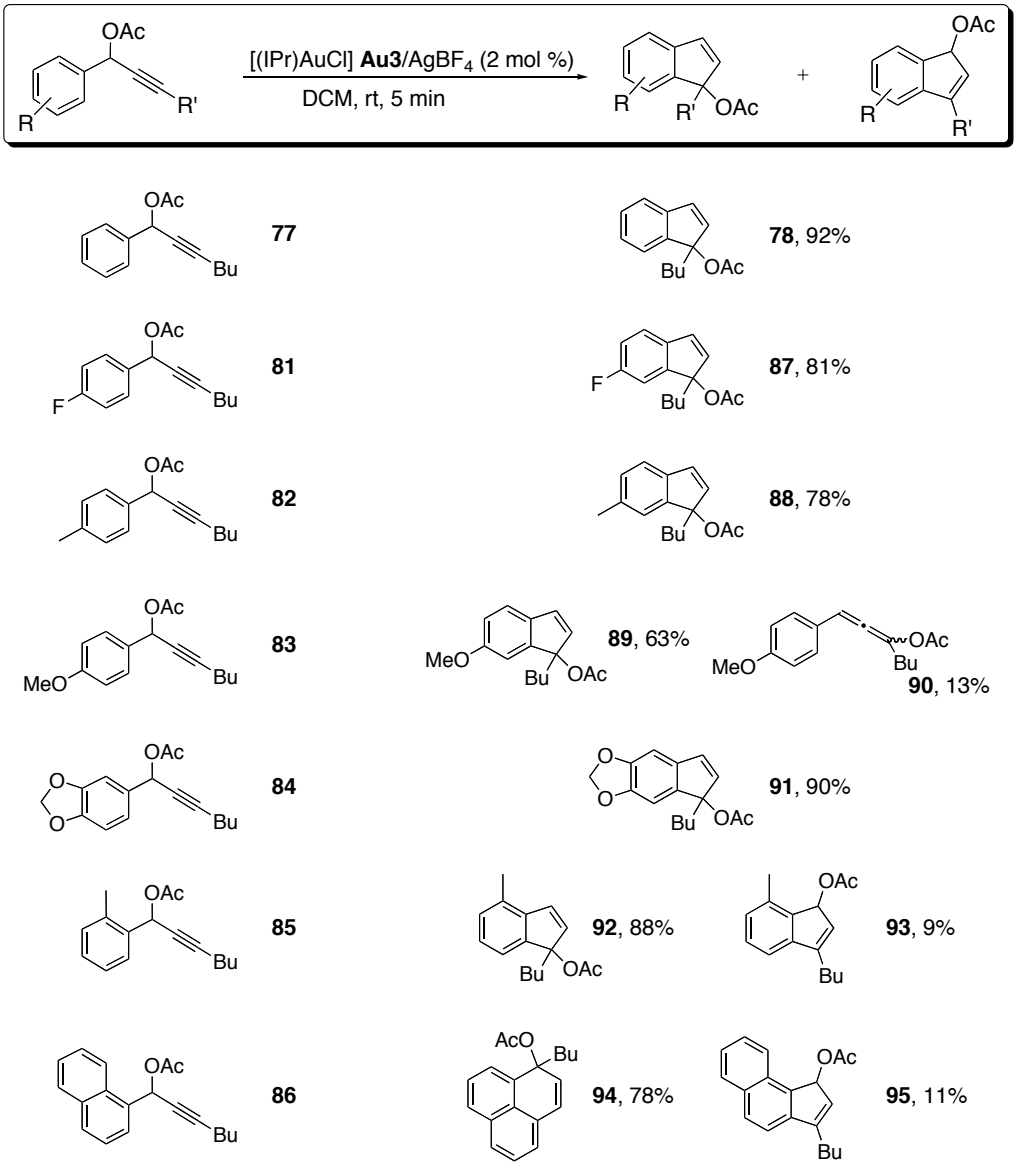

Scheme 52. Au-Catalyzed of indene derivatives

Introduction of a phenyl group resulted in oligomerization of the reaction mixture. Additionally, substrates possessing a trimethylsilyl group at the acetylenic position did not react under the present reaction conditions. Substrates presenting a terminal alkyne led, as for phenylacetylene derivatives, mainly to oligomerization.

As an exception, the formation of **97**, resulting primarily from a 1,2-migration of the propargylic acetate in **96** was observed (Eq 41). In the latter case, the reactivity of the benzylpropargyl acetate is similar to what Uemura and Sarpong reported with ruthenium and platinum, respectively.[347] Therefore, it appears that the behavior of Au^+, and subsequently

[349] Characteristic signals for the expected indene could be observed in the ^{1}H NMR spectrum of the reaction crude, accounting for ≈ 5%, but this product could not be cleanly isolated.

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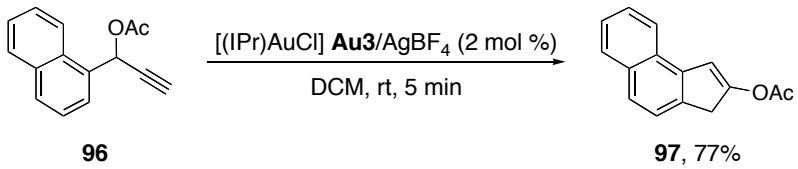
the outcome of the reaction, is highly dependent of the substitution pattern at the acetylenic position.[350]

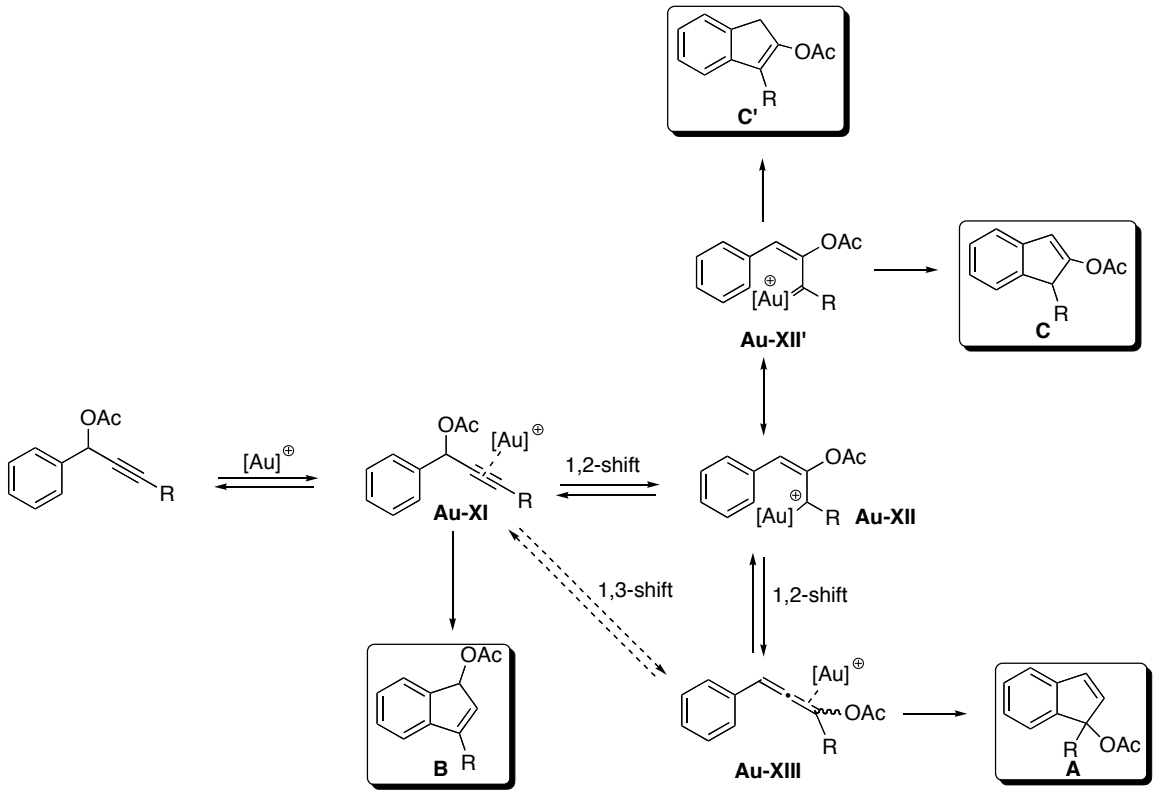


96 **97**, 77% (41)

C. Mechanistic studies

1. Mechanistic proposal

The apparent 1,3-migration of the acetate moiety in the main indene products and the observation of allene **90** led us to propose the mechanism depicted in Scheme 53.



Scheme 53. Mechanistic proposal for the formation of indene derivatives **A**, **B**, and **C**

π-Complexation of the *in situ* generated cationic gold complex to the C≡C bond and subsequent direct nucleophilic attack by the electron-rich phenyl ring would lead to products

[350] For a study on this topic in the context of Pt^{II} catalysis, see: Hardin, A. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 4547–4550.

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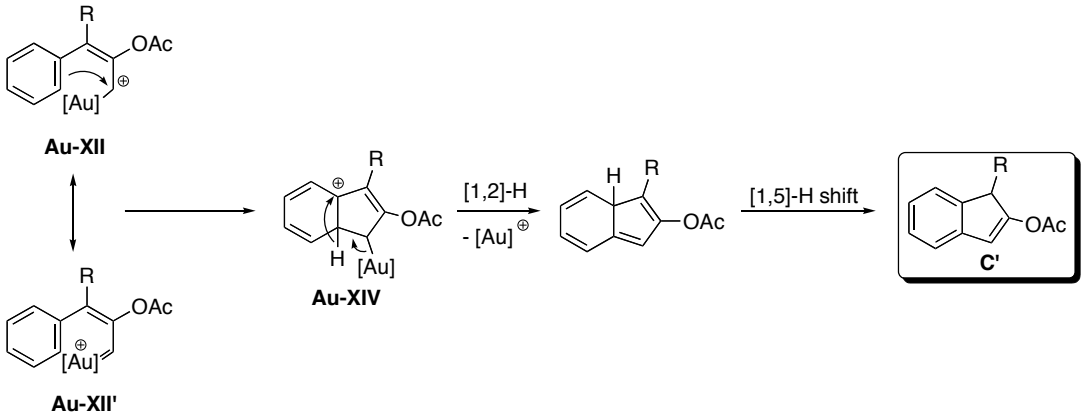
of type **B**, which have been observed in minor amounts.[351,352] On the other hand, electrophilic activation of the alkyne could trigger a 1,2-migration of the acetate to produce intermediate **Au-XII↔Au-XII'**, possessing a carbenoid character, which, upon C–H insertion would furnish indenes of type **C**. Finally, allene **Au-XIII**, produced after two successive 1,2-OAc migrations or a single 1,3-migration, could be further activated by [Au^+] for hydroarylation,[353,354] leading to products of type **A**.

A rationale for the formation of derivatives **C'**, which are C=C isomers of type **C** indenes that we observed only once with the formation of **71**, is less straightforward. Isomerization of indenes **C** into **C'** seems unlikely since in the case we observed, the indenyl compound **C** is thermodinamically more stable than its counterpart **C'**. Recently, Ohe and Wang independently reported the formation of indene of type **C'** from related precursors.[355] Following Ohe's hypothesis for the formation of **C'** type indenes, we present in Scheme 54 a plausible mechanism for the formation of **71**.



Scheme 54. Plausible mechanism for the formation of indenes **C'**

[351] For selected examples of intramolecular electrophilic activation of an alkyne toward aromatic substitution, see: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc*. **1996**, *118*, 6305–6306. (b) Nevado, C.; Echavarren A. M. *Chem.–Eur. J*. **2005**, *11*, 3155–3164. See also ref. 345.

[352] For an extensive study of the Au-catalyzed intermolecular hydroarylation reaction, see: Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem*. **2003**, 3485–3496.

[353] Intramolecular hydroarylation of arylallenes leading to indenes can be catalyzed by strongly acidic media, by metals (Al, Rh, Co) or photochemically and usually requires high temperature and/or prolonged reaction time for moderate chemical yield. For reviews, see: (a) Taylor, D. R. *Chem. Rev*. **1967**, *67*, 317–359. (b) *Allenes in Organic Synthesis*; Schuster, H. F., Coppola, G. M., Eds.; John Wiley & Sons: New York, 1984. (c) *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004.

[354] For recent reports on Au-catalyzed intramolecular allene hydroarylation, see: (a) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett*. **2007**, *9*, 4821–4824. (b) Dudnik, A. S.; Schwier, T.; Gevorgyan, V. *Org. Lett*. **2008**, *10*, 1465–1468. See also ref. 339c.

[355] (a) Peng. L; Zhang, X.; Zhang, S.; Wang, J. *J. Org. Chem*. **2007**, *72*, 1192–1197. (b) Nakanishi, Y.; Miki, K.; Ohe, K. *Tetrahedron* **2007**, *63*, 12138–12148.

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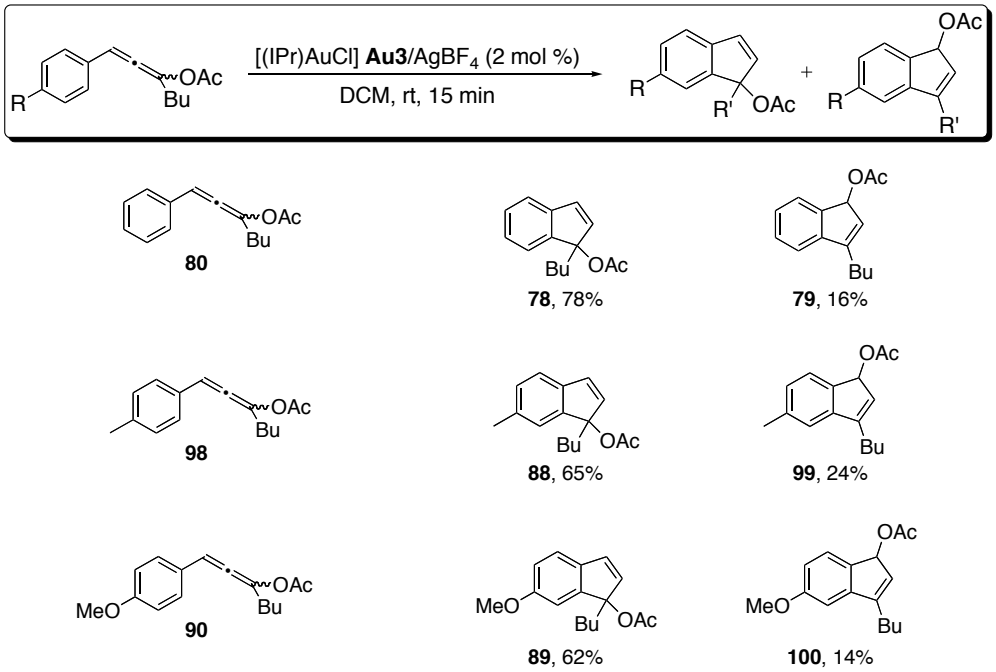
Hence, Friedel-Crafts cyclization would lead to **Au-XIV**, which, instead of undergoing aromatization and proto-deauration to yield **C**-type indenes, could undergo a [1,2]-H shift/demetallation/[1,5]-H shift sequence to furnish **C'**-type indenes.

2. Cyclization of arylallenes

To gain insight into the mechanism we proposed and a possible involvement of [3,3] rearranged allenes, we synthesized compounds **80**, **98**, and **90** by reacting $AgSbF_6$ with propargylic acetates **77**, **82**, and **83**, respectively. The newly formed allenyl esters were then subjected to standard cyclization conditions and we observed the formation of the corresponding indenes **78**, **88**, and **89** after 15 minutes of reaction (Scheme 55).



Scheme 55. Au-Catalyzed cyclization of arylallenes

Unexpectedly, we observed slightly longer reaction times than with the propargylic acetates. This could be a consequence of a higher alkynophilicity than allenophilicity of Au^+, that is not observed starting from alkynes due to the mandatory proximity of the gold center to the newly formed allene moiety.[356] Finally, the minor formation of **79**, **99**, and **100**, products of direct hydroarylation of the alkyne, emphasizes the reversibility of the Au^I-catalyzed [3,3] rearrangement and the advantage of using the alkynes in this reaction to obtain a higher selectivity.

[356] An alternate explanation would imply that the reaction might not go through a discrete allene intermediate; hence a concerted mechanism would be worth considerating.

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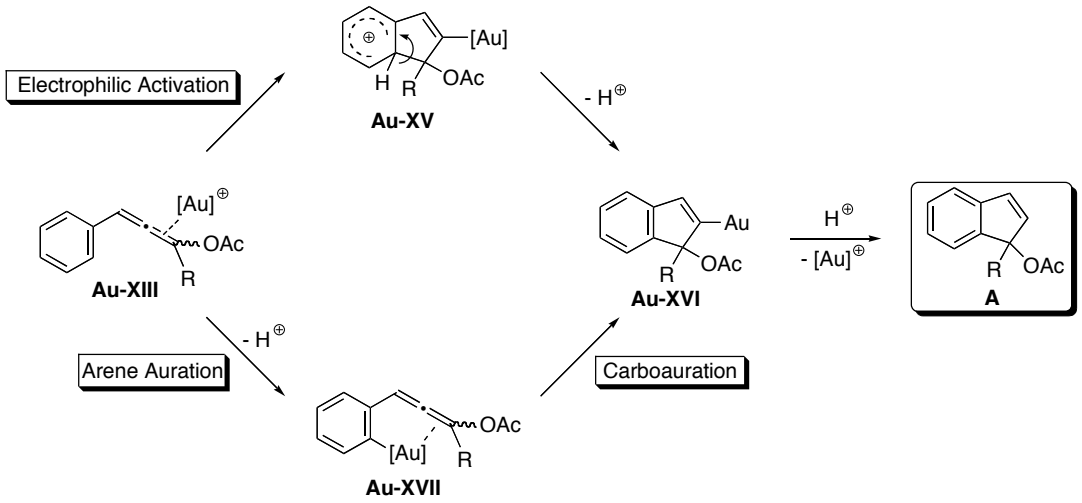
The above experiments support [3,3] rearranged allenes as reaction intermediates in the formation of indenes from arylpropargyl acetates. Two hypotheses can be made about their cyclization mode (Scheme 56).



Scheme 56. Cyclization modes for the hydroarylation of allenes

As depicted in Scheme 56, cyclization occuring through C–H activation and arene auration (bottom path) cannot at this time be ruled out. Nevertheless, based on the existing literature,[357] we favor a Friedel-Crafts type mechanism (top path).

D. Concluding remarks

In this section, it has been shown that [(NHC)AuCl] pre-catalysts can efficiently activate both alkyne and allene moieties in a tandem reaction. Hence, from readily accessible arylpropargyl acetates, diversely substituted indene derivatives were obtained in good to excellent yields. As an added advantage, the conditions used are extremely mild and the reactions can be performed without particular precautions on a bench-top.

Preliminary mechanistic studies have shown that [3,3] rearranged allenyl acetates are likely intermediates in this transformation. Furthermore, the observation of the formation of different isomers, with respect to the oxy-function and the indenyl C=C bond, calls for future investigation.

[357] Arene auration is not known with gold(I) compounds. For gold(III) arene auration in homogeneous catalysis, see: (a) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596–13597. (b) Li, Z.; Capretto, D. A.; Rahaman, R. O.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 12058–12059.

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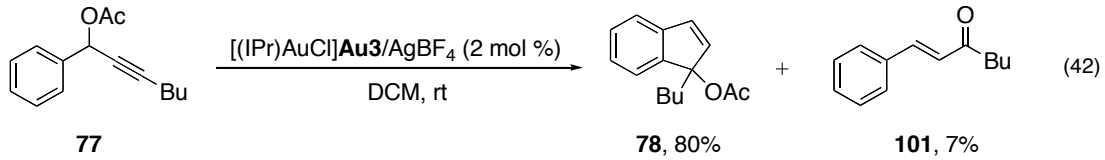
V. Formation of conjugated enones from propargylic acetates[358]

A. Investigation of a by-product

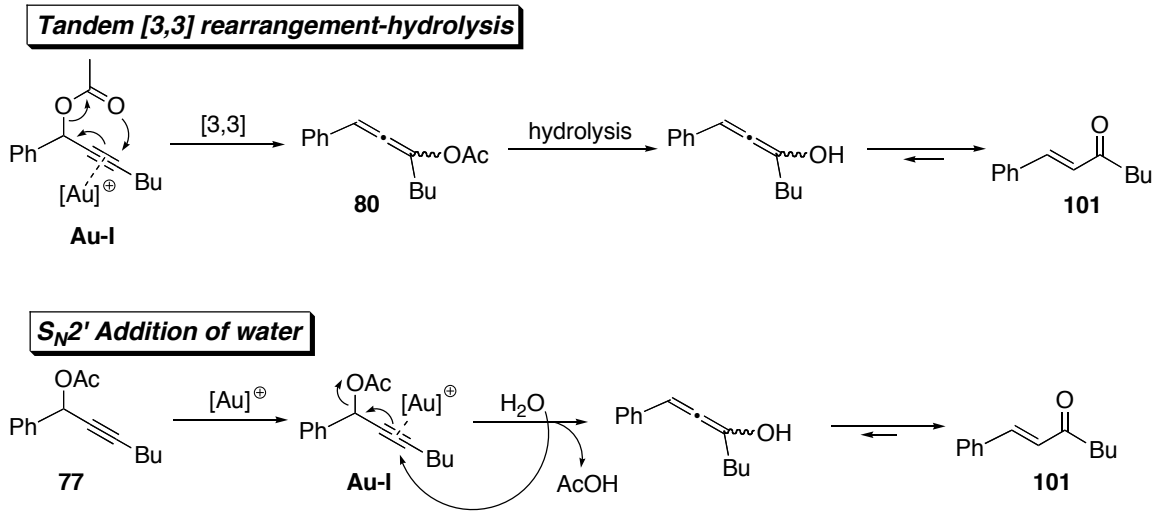
1. Structure determination of a by-product

In the course of the studies on the formation of indene derivatives presented in section **IV**, we observed, in the ^{1}H NMR spectrum of the crude reaction mixture, the formation of an unidentified by-product in a very minor amount (ca. 5%). More disturbing, these observations were proved irreproducible. We then carried out a scale-up cyclization of alkyne **77** (10 mmol) to isolate and fully characterize this by-product. After purification, the ^{1}H NMR spectrum of the by-product presented two characteristic doublets at δ = 7.55 ppm and δ = 6.75 ppm (J = 16.2 Hz) accounting for both vinylidene protons of a disubstituted olefin placed in a *E* arrangement. Additionally, a signal accounting for a carbonylic carbon (δ = 200.9 ppm) was observed in the ^{13}C NMR spectrum and permitted an unequivocal characterization of α,β-unsaturated ketone **101** (Eq 42).



2. Hypotheses on the formation of enones from propargylic acetates

To rationalize the formation of conjugated enone **101**, we envisaged the two mechanisms depicted in Scheme 57.



Scheme 57. Mechanisms envisioned for the formation of **101**

[358] Marion, N.; Carlqvist, P.; Gealageas, R.; de Frémont, P.; Maseras, F.; Nolan, S. P. *Chem.–Eur. J.* **2007**, *13*, 6437–6451.

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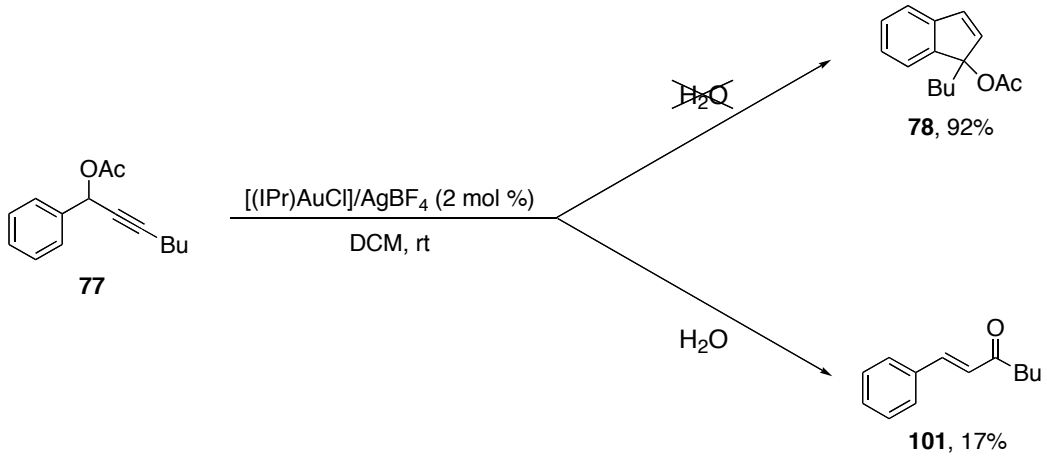
The first hypothesis, depicted at the top of Scheme 57, relies on the Au-catalyzed formation of allene **80**, which was shown to be a plausible intermediate en route to indene **78**.[359] The allenyl acetate would then be further hydrolized under the reaction conditions, leading to enone **101**. Alternatively, the C≡C bond would be activated by a cationic gold species for nucleophilic attack of water onto **Au-I**. Rather than a classical hydration product,[325] the presence of a leaving group at the propargylic position would allow for the formation of an allenol, which would further tautomerize to the conjugated enone **101**. At this point of our studies, it was unclear whether the departure of the AcO^- fragment would be assisted by the gold species, nevertheless the overall process could be considered as a S_N2' reaction. More importantly, regardless of the adopted mechanism, the presence of water appeared mandatory to produce the enone compound. We then thought that anhydrous conditions should inhibit the formation of **101** and yield only indene **78**. Conversely, addition of water should promote the formation of the enone.

3. The key role of water

To validate the aforementioned hypothesis, we carried out two experiments under identical conditions, with anhydrous dichloromethane (DCM) and with DCM saturated with water, respectively. The presence of water changed dramatically the outcome of the reaction affording selectively the enone or the indene (Scheme 58).



Scheme 58. Critical role of water in the reaction of phenylpropargyl acetate **77**

The use of anhydrous DCM rendered the formation of **78** almost quantitative and simply adding water to the reaction mixture produced **77** cleanly as the (*E*)-olefin, albeit in poor yield (the remaining mass balance was the starting propargylic acetate). Having been

[359] See section **IV.C.2** of this Chapter.

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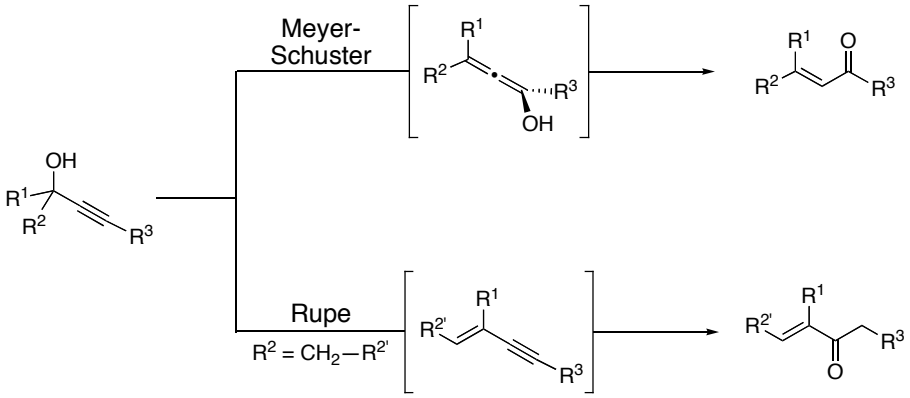
able to suppress the pathway to indene formation, we started a thorough investigation of this methodology leading to conjugated enones.

Indeed, conjugated enones arguably represent one of the most useful building blocks in organic synthesis,[360] two of their main uses are as reactants in 1,4-addition and Diels-Alder reactions.[361,362] α,β-Unsaturated ketones and aldehydes are usually obtained by aldol- or Knoevenagel-type condensations,[363] and by Horner-Wadsworth-Emmons reaction.[364,365] These methods generally require a strong basic media and therefore functional group compatibility and selectivity issues can be problematic.

Other methods to afford enones include the use of widely available propargylic alcohols.[366] The Meyer-Schuster rearrangement[367] of propargylic alcohols, involving a formal 1,3-shift of the hydroxyl moiety, and the Rupe rearrangement,[368] proceeding *via* a 1,3-enyne, produce α,β-unsaturated carbonyl compounds that are isomers (Scheme 59).



Scheme 59. Meyer-Schuster and Rupe rearrangements of propargylic alcohols

[360] (a) Patai, S.; Rappoport, Z. *The Chemistry of Enones*; Wiley: Chichester, 1989. (b) Foster, C. E.; Mackie, P. R. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier Ltd: Oxford, UK, 2005, Vol. 3, p. 215.
[361] For recent reviews on 1,4-addition reactions, see: (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196. (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3236. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844. (d) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354–366.
[362] For recent reviews on Diels-Alder reactions, see: (a) Takao, K.-i.; Munakata, R.; Tadano, K.-i. *Chem. Rev.* **2005**, *105*, 4779–4807. (b) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580–591.
[363] For reviews: (a) Jones, G. *Org. React.* **1967**, *15*, 204–599. (b) Smith, M. B.; March, J. *Advanced Chemistry: Reactions, Mechanisms, and Structure,* 5th ed.; John Wiley & Sons: New York, NY, 2001, pp. 1218–1231.
[364] (a) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73–253. (b) Stec, W. J. *Acc. Chem. Res.* **1983**, *16*, 411–417.
[365] For an extensive list of preparative methods for enones, see: Smith, M. B.; March, J. *Advanced Chemistry: Reactions, Mechanisms, and Structure,* 5th ed.; John Wiley & Sons: New York, NY, 2001, pp. 1691.
[366] Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429–438.
[367] (a) Meyer, K. H.; Schuster, K. *Chem. Ber.* **1922**, *55*, 819–823. (b) Clapperton, E. T.; MacGregor, W. S. *J. Am. Chem. Soc.* **1950**, *72*, 2501–2502. (c) Hennion, G. F.; Fleck, B. R. *J. Am. Chem. Soc.* **1955**, *77*, 3253–3258. (d) Edens, M.; Boerner, D.; Chase, C. R.; Nass, D.; Schiavelli, M. D. *J. Org. Chem.* **1977**, *42*, 3403–3408. (e) Andres, J.; Cardenas, R.; Silla, E.; Tapia, O. *J. Am. Chem. Soc.* **1988**, *110*, 666–674. (f) Yoshimatsu, M.; Naito, M.; Kawahigashi, M.; Shimizu, H.; Kataoka, T. *J. Org. Chem.* **1995**, *60*, 4798–4802.
[368] (a) Rupe, H.; Kambli, E. *Helv. Chim. Acta* **1926**, *9*, 672. (b) Hennion, G. F.; Davis, R. B.; Maloney, D. E. *J. Am. Chem. Soc.* **1949**, *71*, 2813–2814. (c) Smissman, E. E.; Johnsen, R. H.; Carlson, A. W.; Aycock, B. F. *J. Am. Chem. Soc.* **1956**, *78*, 3395–3400.

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Despite some reports on the utilization of the Meyer-Schuster reaction under mild conditions,[369,370] these isomerization reactions have not been widely used nor developed. Several reports using transition metals in order to activate the C≡C bond for Meyer-Schuster rearrangement have appeared, but with only limited success in terms of scope and reaction conditions.[371]

Having in mind all of the above, we decided to attempt optimizing the present catalytic system and to investigate thoroughly the formation of conjugated enones from propargylic acetates using gold(I) catalysts.

B. Optimization studies

1. Solvent optimization

After control experiments with only [(IPr)AuCl] **Au3**, and no metal catalyst that both led to recovery of the starting propargylic acetate **77**, $AgBF_4$ alone was found, as expected, to produce the [3,3] rearranged allene **80**.[319] We then attempted to obtain complete conversion of the precursors into enone products. Room temperature reaction, even with prolonged time, led only to partial conversion (Table 30, entry 2). On the other hand, increasing the temperature permitted total conversion of **77** but yielded minor amounts of allene **80** as by-product along with substantial amount of oligomerization (Entry 3).

We then screened a large number of solvents (Table 30, entries 4-12). 1,2-Dichloroethane and 1,4-dioxane did not prove better than DCM and showed unsatisfying selectivity (Entries 4 and 12), while using acetone resulted in the formation of a complex mixture of products (Entry 7). THF provided by far the best results, allowing for the conversion of **77** into **101** almost quantitatively (Entry 8).

Since, in this reaction, water seemed to act as a reagent, it was appealing to concomi-

[369] For examples of Meyer-Schuster reactions observed under mild conditions, see: (a) Narasaka, K.; Kusama, H.; Hayashi, Y. *Tetrahedron* **1992**, *48*, 2059–2068. (b) Lorber, C. Y.; Osborn, J. A. *Tetrahedron Lett*. **1996**, *37*, 853–856. (c) Crich, D.; Natarajan, S.; Crich, J. Z. *Tetrahedron* **1997**, *53*, 7139–7158. (d) Sun, C.; Lin, X.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 3159–3166.

[370] Recently, two reports on the observation of the Meyer-Schuster rearrangement as a competing reaction appeared: (a) Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc*. **2003**, *125*, 15760–15761. (b) Trost, B. M.; Chung, C. K. *J. Am. Chem. Soc*. **2006**, *128*, 10358–10359.

[371] For Ag-promoted Meyer-Schuster rearrangement, see: (a) Shigemasa, Y.; Oikawa, H.; Ohrai, S.-i.; Sashiwa, H.; Saimoto, H. *Bull. Chem. Soc. Jpn*. **1992**, *65*, 2594–2598. For Au, see: (b) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc*. **2005**, *127*, 14180–14181. (c) Engel, D. A.; Dudley, G. B. *Org. Lett*. **2006**, *8*, 4027–4029. (d) Lopez, S. S.; Engel, D. A.; Dudley, G. B. *Synlett* **2007**, 949–953. For Re, see: (d) Narasaka, K.; Kusama, H.; Hayashi, Y. *Chem. Lett*. **1991**, 1413–1416. For Sc, see: (e) Engel, D. A.; Lopez, S. S.; Dudley, G. B. *Tetrahedron* **2008**, *64*, DOI: 10.1016/j.tet.2008.02.030.

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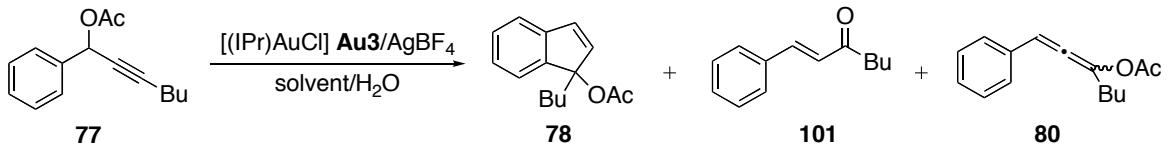
tantly use it as solvent, notably for environmental reasons.[372] Unfortunately, as with DMF, pentane, Et_2O and, to a lesser extent, toluene, precursor **77** was recovered unreacted after 24 h (Entries 5-6 and 9-11) under these conditions.

Table 30. Solvent optimization in the formation of **101**[a]



77 **78** **101** **80**

Entry	Solvent	*T* (ºC)	*t*	**78** (%)[b]	**101** (%)[b]	**80** (%)[b]
1	DCM	25	5 min	--	17	--
2	DCM	25	24 h	--	58	--
3[c]	DCM	45	24 h	--	72	12
4[c]	DCE	80	2 h	8	64	4
5	DMF	90	24 h	--	3	--
6	Pentane	40	24 h	No reaction		
7	Acetone	50	4 h	Unidentified mixture of products		
8	THF	60	4 h	--	90	--
9	Toluene	90	24 h	--	--	10
10	H_2O	90	24 h	No reaction		
11	Et_2O	40	24 h	No reaction		
12[c]	1,4-Dioxane	90	4 h	--	56	--

[a] Reaction conditions: alkyne **77** (0.5 mmol), [(IPr)AuCl] **Au3**/$AgBF_4$ (2 mol %), solvent (5 mL), H_2O (0.5 mL). [b] ^1H NMR conversions. [c] Substantial amount of oligomerization.

We attribute these last observations to the insolubility of the gold species in these solvents. On the other hand, THF seems to possess the right combination of miscibility with water and solubility of the [(NHC)AuCl] complex to allow for full conversion.

2. Ligand and silver additive optimization

Next, we carried out the optimization of the ligand on the gold center (Table 31). The steric hindrance of the ligand appeared to be crucial for the selectivity of the reaction. The more sterically encumbering the ligand, the more selective the formation of α,β-unsaturated

[372] For reviews on water as reaction media, see: (a) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741–760. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, NY, 1997. (c) *Organic Synthesis in Water*, Grieco, P. A., Ed.; Blackie Academic & Professional: London, UK, 1998. (d) Katritzky, A. R.; Nichols, D. A.; Siskin, M.; Murugan, R.; Balasubramanian, M. *Chem. Rev.* **2001**, *101*, 837–892. (e) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095–3166. (f) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68–82. (g) Chen, L.; Li, C.-J. *Adv. Synth. Catal.* **2006**, *348*, 1459–1484.

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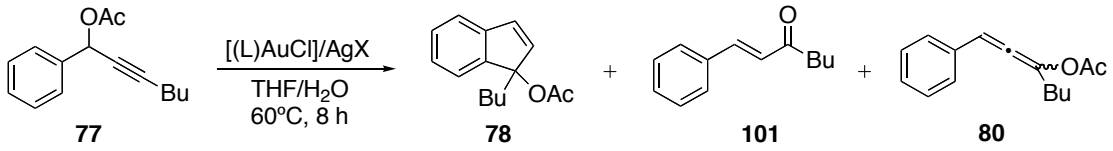
ketone **101** (Entries 1-5) proved to be. Hence, the extremely bulky ItBu and IAd, when compared to IPr and IMes, cleanly yielded enone **101** (Entries 3 and 4) whereas the use of the unemcumbered ITM resulted in the formation of substantial amount of oligomerization products (Entry 5). Finally, a short screening of silver salts showed a similar behavior for $AgBF_4$, $AgPF_6$, and $AgSbF_6$ (Entries 3, 6, and 7).

Table 31. Ligands and silver salts optimization in the formation of **101**[a]



77 **78** **101** **80**

Entry	L	AgX	**78** (%)[b]	**101** (%)[b]	**80** (%)[b]
1	IPr (**Au3**)	$AgBF_4$	--	90	--
2	IMes (**Au1**)	$AgBF_4$	--	87	6
3	ItBu (**Au8**)	$AgBF_4$	--	98	--
4	IAd (**Au10**)	$AgBF_4$	--	98	--
5[c]	ITM (**Au5**)	$AgBF_4$	6	63	4
6	ItBu (**Au8**)	$AgPF_6$	--	95	--
7	ItBu (**Au8**)	$AgSbF_6$	--	96	--

[a] Reaction conditions: alkyne **77** (0.5 mmol), [(L)AuCl]/AgX (2 mol %), THF (5 mL), H_2O (0.5 mL). [b] ^1H NMR conversions. [c] Substantial amount of oligomerization.

C. Scope of the reaction

1. Formation of cinnamyl ketones and aldehydes

We first examined the effect of substitution on the phenyl ring (Table 32). Overall, the reaction was not affected by aromatic substitution and cinnamyl ketones possessing neutral, electron-withdrawing, and electron-donating groups were produced in excellent yields (Entries 1-5).

In the case of electron-rich arenes, the formation of addition products, either onto the alkene or the ketone moiety, as described by Hashmi and Dyker was not observed.[373] This is problably due to the oxidation state of the gold atom (Au^I), since this type of reactivity has only been described with Au^{III} species. Additionally, this highlights the chemoselectivity of

[373] (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285–2288. (b) Dyker, G.; Muth, E.; Hashmi, A. S. K.; Ding, L. *Adv. Synth. Catal.* **2003**, *345*, 1247–1252. (c) Hashmi, A. S. K.; Grundl, L. *Tetrahedron* **2005**, *61*, 6231–6236. (d) Hashmi, A. S. K.; Schwarz, L.; Rubenbauer, P.; Blanco, M. C. *Adv. Synth. Catal.* **2006**, *348*, 705–708.

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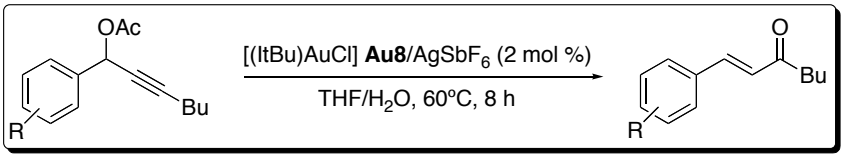
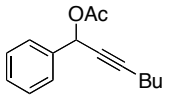
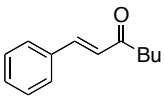
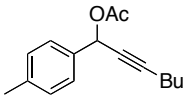
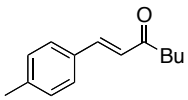
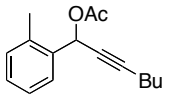
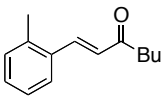
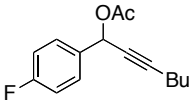
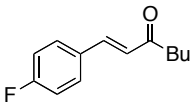
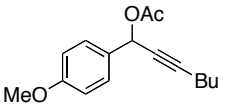
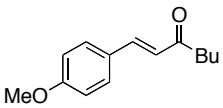
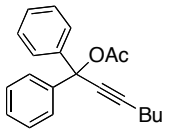
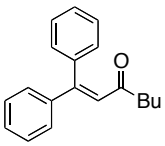
the present catalytic system and its robustness towards disproportionation under the reaction conditions.

Table 32. Gold-catalyzed formation of cinnamyl ketones[a]



Entry	Propargyl acetate		Enone[b]	
1		**77**		**101**, 98%
2		**82**		**103**, 97%
3		**85**		**104**, 98%
4		**81**		**105**, 91%
5		**83**		**106**, 89%
6		**102**		**107**, 88%

[a] Reaction conditions: alkyne (1 mmol), [(ItBu)AuCl] **Au8**/$AgSbF_6$ (2 mol %), THF (10 mL), H_2O (1 mL). [b] Isolated yields, average of 2 runs.

Of note, while conjugated enone **101** could be produced in 4 hours, the formation of **103**-**106** required extended reaction times. Tertiary acetate reacted similarly, yielding trisubstituted olefin in good yield (Entry 6). It is noteworthy that this procedure is extremely simple to launch and does not require any precautions since the gold complex is air- and moisture-stable.

Because of the high potential of enals as electrophiles in organic synthesis, we decided to subject terminal alkynes to our catalytic system. As shown in Table 33, the

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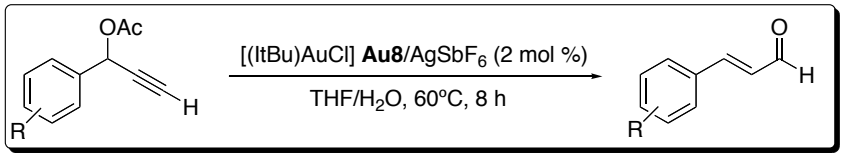
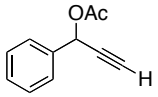
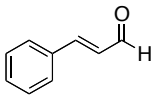
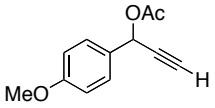
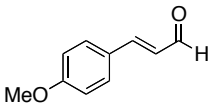
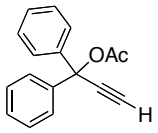
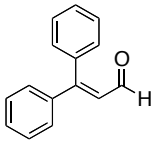
reaction is tolerant to aryl substitution (Entries 1-2). Furthermore, a tertiary acetate has been converted into a trisubstituted enal (Entry 3).

Table 33. Gold-catalyzed formation of cinnamaldehydes[a]



Entry	Propargyl acetate	Enal[b]
1	 **108**	 **111**, 98%
2	 **109**	 **112**, 97%
3	 **110**	 **113**, 88%

[a] Reaction conditions: alkyne (1 mmol), [(ItBu)AuCl] **Au8**/$AgSbF_6$ (2 mol %), THF (10 mL), H_2O (1 mL). [b] Isolated yields, average of 2 runs.

2. Effect of the acetylenic substitution

We turned our attention to the influence of acetylenic substitution; results are presented in Table 34. As presented above, cinnamaldehyde **111** was produced in excellent yield (Entry 2). Similarly, *trans*-chalcone **117** was obtained, showing the compatibility of the reaction with phenylacetylenes (Entry 3).

We examined the possibility of obtaining acylsilanes by subjecting precursor **115** to Au-catalysis. The TMS-containing alkyne did not react even at high catalyst loading (10 mol %), at elevated temperature and/or prolonged reaction time (Entry 4). Lack of reactivity of silylated alkynes, notably towards cycloisomerization, has already been reported.[374] Interestingly, the presence of a *tert*-butyl group at the acetylenic position in **116** resulted in a similar lack of reactivity (Entry 5). We therefore believe that, in this reaction, more than an

[374] (a) Cariou, K.; Mainetti, E.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2004**, *60*, 9745–9755. (b) Harrison, T. J.; Dake, G. R. *Org. Lett.* **2004**, *6*, 5023–5026. (c) Marco-Contelles, J.; Arroyo, N.; Anjum, S.; Mainetti, E.; Marion, N.; Cariou, K.; Lemière, G.; Mouriès, V.; Fensterbank, L.; Malacria, M. *Eur. J. Org. Chem.* **2006**, 4618–4633.

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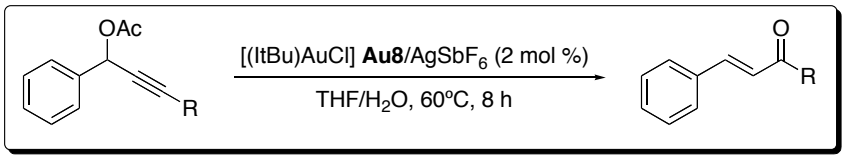
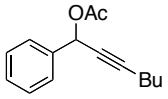
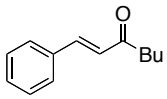
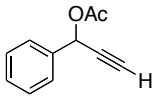
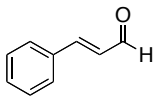
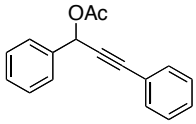
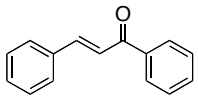
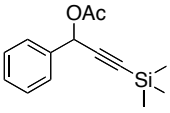
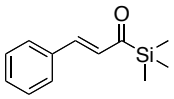
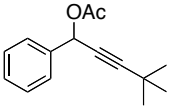
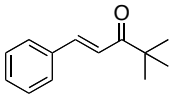
eventual electronic effect of the trimethylsilyl group, it is its bulky character that inhibits the reactivity.

Table 34. Effect of acetylenic substitution on the reaction[a]



Entry	Propargyl acetate		Enone/Enal[b]	
1		**77**		**101**, 98%
2		**108**		**111**, 90%
3		**114**		**117**, 92%
4		**115**		NR[c]
5		**116**		NR[c]

[a] Reaction conditions: alkyne (1 mmol), [(ItBu)AuCl] **Au8**/$AgSbF_6$ (2 mol %), THF (10 mL), H_2O (1 mL). [b] Isolated yields, average of 2 runs. [c] NR = No Reaction, conditions: [(ItBu)AuCl] **Au8**/$AgSbF_6$ (10 mol %), 24 h.

3. Formation of unactivated enones and enals

All substrates examined to this point possessed an aryl moiety at the propargylic position, therefore yielding enones or enals featuring a fully conjugated π-system from the carbonyl to the aryl. We envisaged that this full conjugation could be a major driving force for the formation of enones.

To address this possibility and to further expand the scope of the reaction, we tested alkyl and benzyl acetates (Table 35). When subjected to Au-catalysis, benzylpropargyl acetate **118** afforded butylketone **124** in good yield (Entry 1), expanding the scope of this enone synthesis to non-fully conjugated systems. Even without the driving force of a full conjugation, the reaction scope proved remarkably broad. α,β-Unsaturated aldehydes can be produced (Entry 2) in excellent yield, as can phenylketones (Entry 3) or divinylketones (Entry 5).

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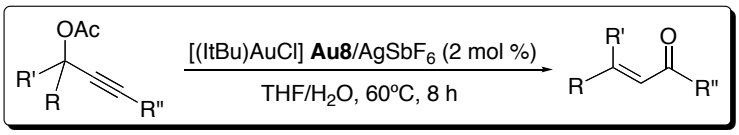
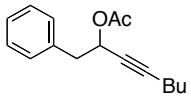
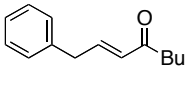
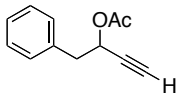
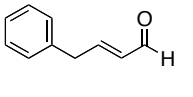
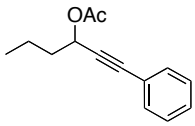
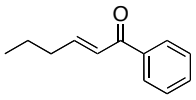
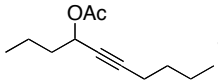
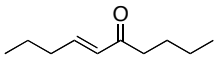
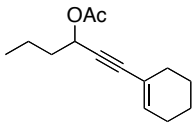
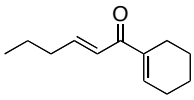
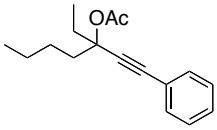
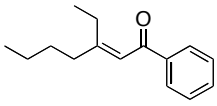
Table 35. Gold-catalyzed formation of unactivated enones and enals[a]



Entry	Propargyl acetate		Enone/Enal[b]	
1		**118**		**124**, 87%
2		**119**		**125**, 94%
3		**120**		**126**, 82% (*E*:*Z*, 12:1)
4		**121**		**127**, 94%
5		**122**		**128**, 89%
6		**123**		**129**, 90% (*E*:*Z*, 1.2:1)

[a] Reaction conditions: alkyne (1 mmol), [(ItBu)AuCl] **Au8**/$AgSbF_6$ (2 mol %), THF (10 mL), H_2O (1 mL). [b] Isolated yields, average of 2 runs.

Totally unactivated propargyl acetate **121** afforded alkyl-alkyl enone **127** in excellent yield (Entry 4), highlighting the efficiency of this synthetic method. Additionally, trisubstituted enone **129** was produced in good overall yield but, as expected, with poor *E*:*Z* selectivity since ethyl and butyl groups bear only slight structural differences.

4. Microwave-assisted reactions

Gold-catalyzed transformations usually exhibit extremely short reaction time (e.g. minute time frame) even for reactions performed at room temperature. A possible drawback of the catalytic system presented herein could be the lengthy reaction time (i.e. 8 h) required for the synthesis of enones or enals. As we wished this protocol to be as user friendly as possible to synthetic chemists, we investigated the use of microwave heating in order to shorten the reaction times. Microwave-assisted organic and organometallic syntheses have

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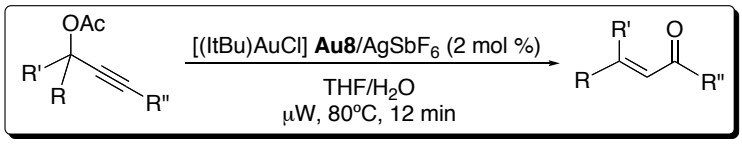
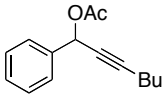
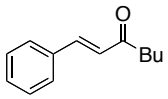
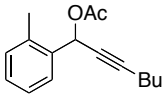
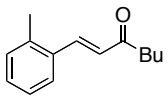
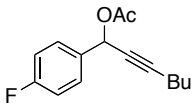
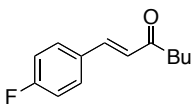
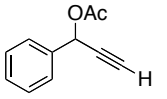
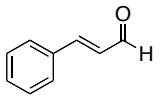
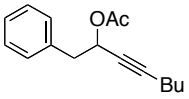
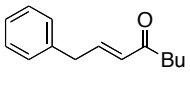
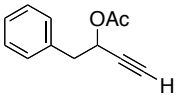
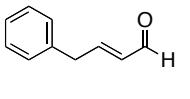
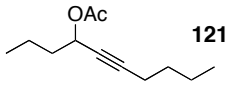
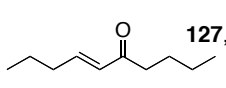
recently witnessed a true explosion, notably because of its ability to shorten considerably reaction times.[375]

After a short optimization,[376] enone **101** could be produced in high yield under microwave heating, after only 12 minutes at 80ºC in THF (Table 36, entry 1).

Table 36. Microwave-assisted Au-catalyzed formation of enones and enals[a]



Entry	Propargyl acetate		Enone/Enal[b]
1		**77**	 **101**, 98%[c]
2		**85**	 **104**, 99%[c]
3		**81**	 **105**, 90%
4		**108**	 **111**, 98%[c]
5		**118**	 **124**, 93%
6		**119**	 **125**, 93%[c]
7		**121**	 **127**, 95%[c]

[a] Reaction conditions: alkyne (1 mmol), [(ItBu)AuCl] **Au8**/$AgSbF_6$ (2 mol %), THF (10 mL), H_2O (1 mL). [b] Isolated yields, average of 2 runs. [c] No purifcation by column chromatography needed.

[375] For reviews on microwave-assisted reactions, see: (a) Varma, R. S. *Green Chem.* **1999**, *1*, 43–55. (b) *Microwaves in Organic Synthesis*, Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2002. (c) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284. (d) de la Hoz, A.; Díaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164–178.

[376] We focused our optimization on reaction times and temperatures only. Neither solvents nor additives were screened.

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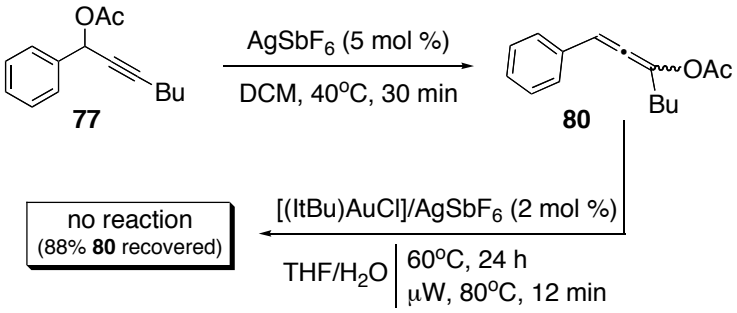
We screened more substrates and were able to obtain α,β-unsaturated ketones and aldehydes, including strongly unactivated alkyl-alkyl substrates (Entry 7), in excellent yields and in remarkably shortened reaction times (Table 36). Of note, most of the conjugated carbonyl compounds produced by microwave heating did not require further purification by column chromatography and were found >95% pure by ^{1}H NMR. It should be noted that, under these conditions, the NHC-containing gold catalytic system proved remarkably robust.[377]

D. Mechanistic studies

1. Allenyl acetates as intermediates?

Keeping in mind the striking effect of water in the outcome of the reaction, as depicted in Scheme 54, we investigated the possible mechanisms for this transformation. The first pathway we envisaged involves a [3,3] sigmatropic rearrangement of the propargylic acetate into allene **80** (see Scheme 57) that would further undergo hydrolysis of the ester group, yielding an allenol, tautomer of enone **101**.[378] To address this possibility, we synthesized and isolated allene **80**, by Ag-catalyzed [3,3] sigmatropic rearrangement of propargylic acetate **77**,[319] and subjected it to the catalytic conditions for enone formation. Strikingly, even after prolonged reaction time, both under conventional and microwave-assisted heating, the formation of enone **101** was not observed (Scheme 60), ruling out a possible hydrolysis pathway under these reaction conditions.



Scheme 60. Formation of allene **80** and its subjection to gold catalysis

[377] For rare examples of microwave-assisted gold-catalyzed reaction, see: (a) Liu, X.-Y.; Li, C.-H.; Che, C.-M. *Org. Lett.* **2006**, *8*, 2707–2710. (b) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269–279. See also ref. 295.

[378] The Hg^{II}-catalyzed formation of enones from propargylic acetates has been reported; the authors proposed the formation of a six-membered oxonium species resulting from the attack of the acetate onto the C≡C bond as intermediate, see: Imagawa, H.; Asai, Y.; Takano, H.; Hamagaki, H.; Nishizawa, M. *Org. Lett.* **2006**, *8*, 447–450.

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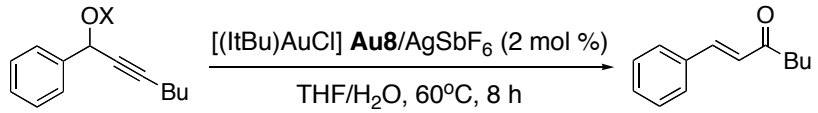
Additional information supporting the non-involvement of allenes as intermediates in the enone formation was provided by experiments shown in Scheme 61. In an attempt to evaluate the influence of the hypothetical leaving group at the propargylic position and to gather supplementary information related to the reaction mechanism, we synthesized analogues of acetate **77** and tested them for the production of enone **101**.



X = H, **130**..... **101**, 25%
Me, **131**.....**101**, 62%
Ac, **77**.....**101**, 98%

Scheme 61. Effect of *O*-substitution on the formation of **101**

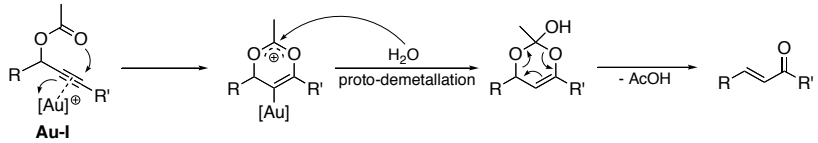
Alcohol **130** reacted under our catalytic conditions but was converted to **101** only in poor yield (25%). This Meyer-Schuster-like reaction has been observed previously in the context of gold catalysis.[371b-d] Interestingly, precursor **131**, the methylether analogue of **77**, afforded enone **101** in moderate yield.[379] We believe that this last result strongly supports the non-participation of allene **80** as a possible intermediate considering the inability of methoxy groups for [3,3] rearrangement.[380]

2. An S_N2'-like mechanism?

The "intuitive" mechanism we could propose for the transformation of propargylic acetates into enones is depicted in Scheme 62.

Considering a S_N2'-like mechanism, three approaches were considered: 1) a concerted mechanism with assistance of cationic gold, in accordance with most proposals on gold homogeneous catalysis, to render the alkyne more prone to nucleophilic attack (middle pathway in black); 2) a stepwise mechanism involving the addition of water and the formation of a vinylgold species **Au-XVIII**, followed by expulsion of acetic acid (top path in red); and 3) another stepwise mechanism proceeding through release of AcO^- followed by

[379] This type of reactivity has already been described with Au^{III} and Hg^{II} catalysts, although in moderate yields and with a limited scope, see: Fukuda, Y.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013–2015.
[380] Additionally, the formation of **101** from **131** seems to exclude a mechanism where the oxonium intermediate of the 1,3-shift would be trapped by water, forming an ortho-ester-like intermediate that would rearrange to the enone (see scheme below); unless two distinct mechanisms are in action for propargylic ethers and esters.



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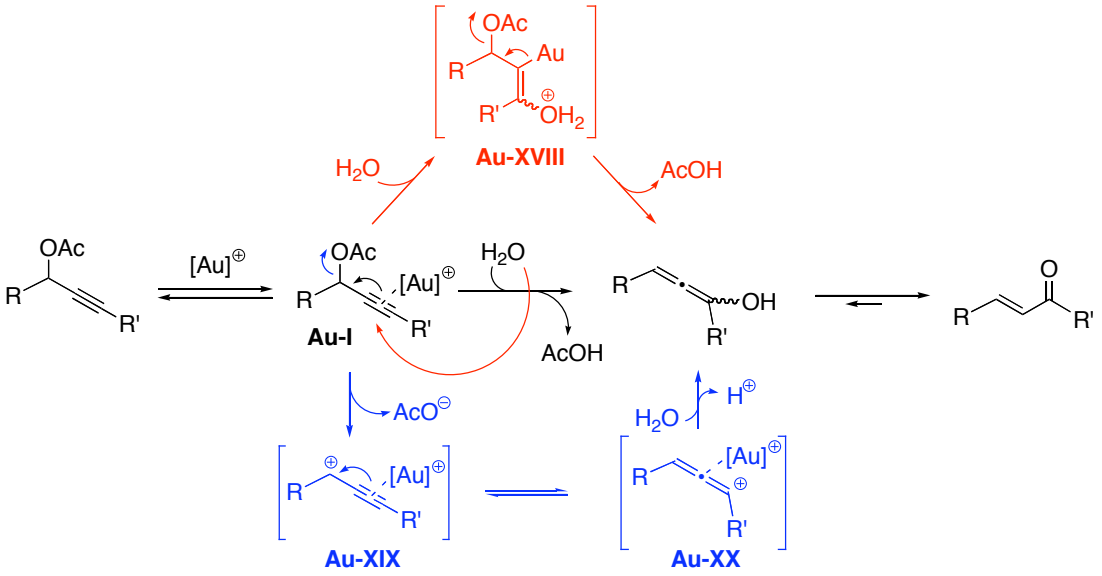
addition of water (bottom path in blue). We evaluated the possibility of these S_N2' mechanisms with the help of theoretical chemistry in the frame of a collaboration with Professor Feliu Maseras. DFT, Becke3LYP calculations were carried out on a model system where the leaving group was formate, the propargylic and alkyne substituents were methyls, and the NHC was represented by IDM (*N*,*N*'-dimethylimidazol-2-ylidene). All energetic data discussed are enthalpies calculated at 298.15 K and 1 atm ($\Delta H_{G,\,298.15\,K}$).



Scheme 62. "Intuitive" mechanism for the formation of enones

Unexpectedly, these calculations failed to support the mechanisms proposed in Scheme 62. Following the black path, the nucleophilic addition of water onto a complex where a cationic gold species is bound to the alkyne, we were not able to locate a transition state leading to the allenol. Our optimization trials inevitably reverted to the reactants. When optimizing the vinylgold intermediate **Au-XVIII** proposed in the red path, it was found to be unstable, reverting to **Au-I** and water. We consider these results conclusive, because neither of the paths related to the allenol or to species **Au-XVIII** involves charge separation, which, therefore, makes them very unlikely to be affected by solvation effects. Finally, intermediate **Au-XIX**, leading to complete charge separation, with an acetate as the leaving group is difficult to treat with gas phase calculations and would require solvation effects to be considered. However, it was found to have an energy more than 200 kcal.mol^{-1} above **Au-I**. We strongly believe that such a large energy gap prohibits the formation of **Au-XIX**, therefore rendering the blue pathway highly unlikely, even in the condensed phase.

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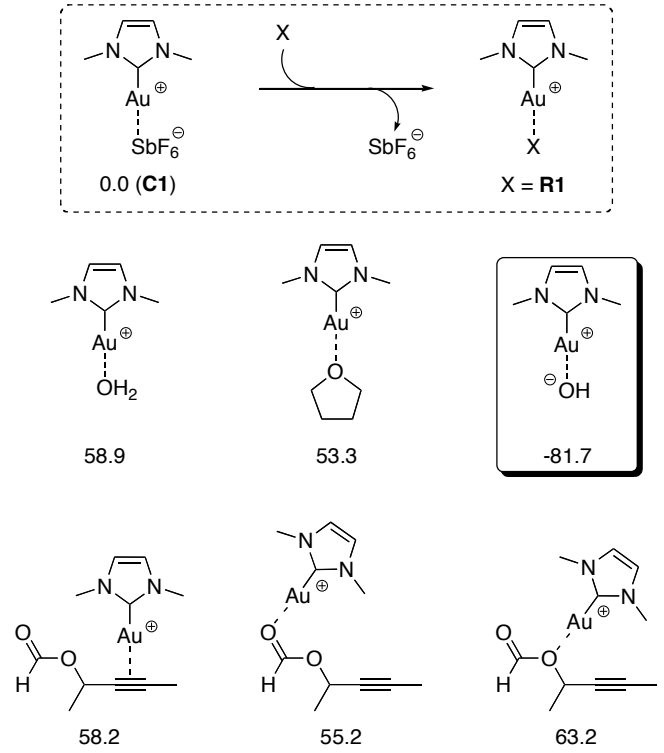
3. What catalytically active species?

Interaction with the cationic gold center

The mechanistic proposals depicted in Scheme 62 are based on the assumption that the role of the gold catalyst is to activate the alkyne. This is exemplified by the initial formation of species **Au-I**, a π-coordinated alkyne–gold complex evoked many times as starting point of gold catalytic cycle. The unexpected failure of our initial calculations to support this mechanism prompted us to examine the possibility of the cationic gold species activating a water molecule or another coordinating species in solution. From an experimental point of view, the former possibility is not unlikely, since experiments reported above showed that in the absence of water a different chemical transformation takes place (i.e. indene formation).

The energies of different gold species that can be formed in the reaction mixture from the cationic [(NHC)Au]SbF_6 complex are shown in Scheme 63.



Scheme 63. Relative binding energy of ligands to gold species present in the reaction mixture (energies in kcal.mol^{-1})

Since cationic complexes of the type [(NHC)Au]X, where X is a non-coordinating ligand, are known to exist experimentally and have been characterized,[320] the energies given are relative to [(NHC)Au]SbF_6 (**C1**). Two groups of ligands were analyzed, neutral (**77'** [the

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model–alkyne we used], H_2O, THF) and anionic (SbF_6^-, OH^-). It should be noted that comparison between the different groups is hampered by the lack of solvation effects but the analysis of the trends within each group is informative. Regarding the neutral species, of the three possible complexes between **77'** and a cationic NHC–gold species, the most stable one shows the gold coordinated to the carbonyl oxygen and not to the triple bond as expected. Moreover, the calculations indicate that the THF–gold complex is more stable than the corresponding complexes with the propargylic formate.

The very stable complex formed by the association of a hydroxy anion and the cationic gold center caught our attention.[381,382] The [(NHC)AuOH] species **C2** could be the active form of the catalyst in solution. We decided to analyze the possible formation of this complex from the initial species **C1**. Direct reaction of **C1** with water can indeed produce **C2**, but the reaction is endothermic by 48.9 kcal.mol^{-1} because the additional product is $HSbF_6$, a high-energy compound with a strong acidity. However, in the presence of water, $HSbF_6$ would be strongly solvated. We found in fact that its association with four water molecules leads to a reasonable network of hydrogen bonds, with abstraction of the proton from the antimonate and a species better described as $SbF_6^-\cdots H_7O_3^+$. Formation of [(NHC)AuOH] **C2** and $SbF_6^-\cdots H_7O_3^+$ from [(NHC)Au]SbF_6 and four water molecules is exothermic by 21.1 kcal.mol^{-1}, thus favorable. **C2** is therefore likely present under our reaction conditions. On the other hand, the protonated water cluster is unlikely to play any role in the subsequent reaction, because it is not acidic enough to transfer its proton to the weak basic centers in the media. In contrast, the hydroxyl complex **C2** is a viable candidate as catalyst.

A Brønsted acid-catalyzed reaction?

At this point of our study, the possibility of a Brønsted acid-catalyzed reaction could not be overruled and accordingly two control reactions were performed. Alkyne **77**, when heated at 60ºC for 16 h in THF and water in the presence of up to 20 mol % of HPF_6, was mainly recovered (80%) along with degradation products (15%) and traces amount of **101** (<5%). When HBF_4 was employed in the same conditions, only small amount of degradation (5%) was observed with unreacted alkyne **77**. It seems then reasonable to exclude the possibility of the catalytic activity of strong Brønsted acids in this transformation.

[381] Even though scarce, gold(I) hydroxo complexes are known, see: Kissner, R.; Welti, G.; Geier, G. *J. Chem. Soc., Dalton Trans.* **1997**, 1773–1777.
[382] For a review on gold complexes containing anionic oxygen ligands, see: Agostina, M.; Minghetti, G. *Gold Bull.* **2002**, *35*, 11–20.

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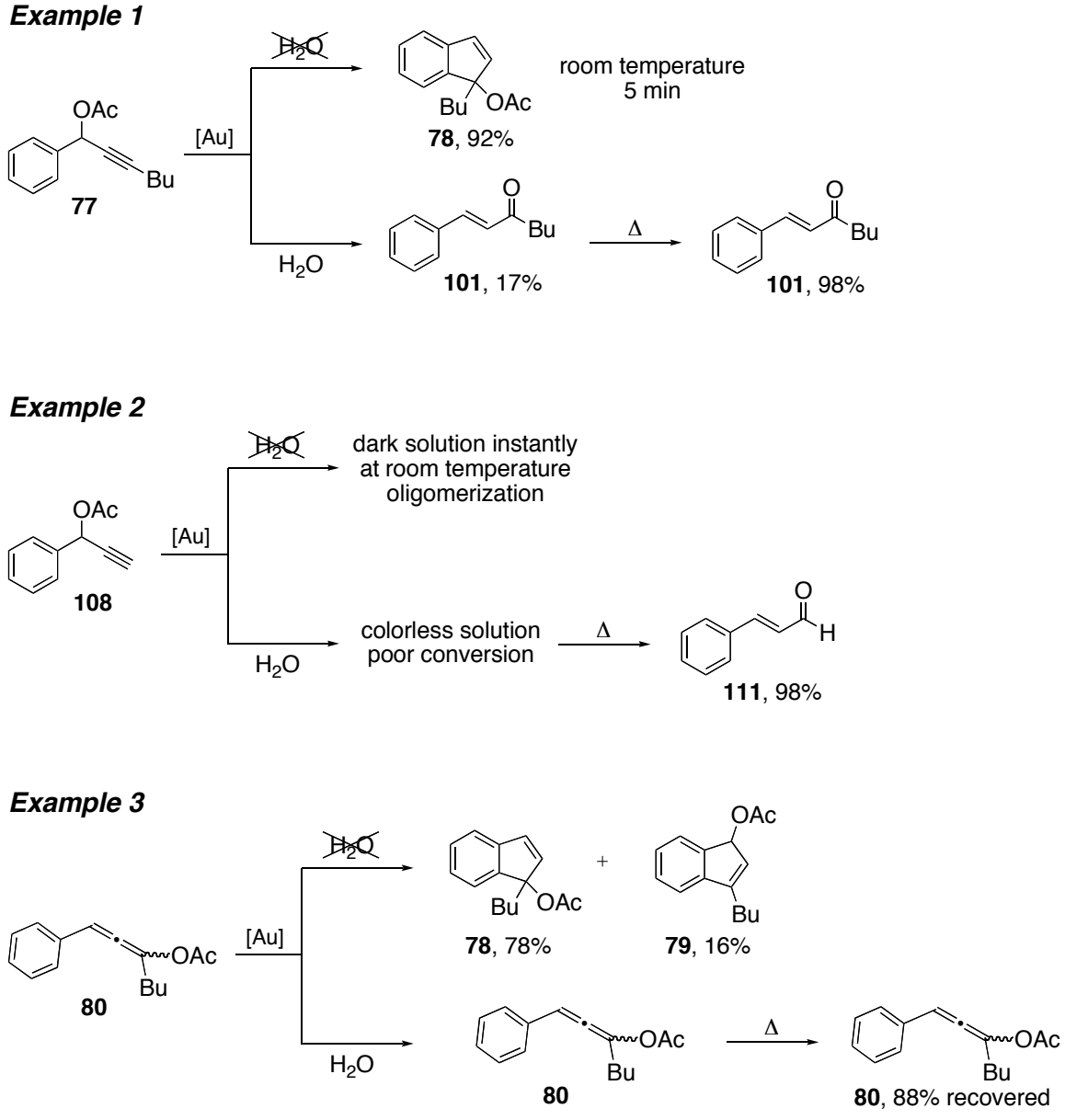
Enones vs. indenes: two distinct catalytic species

Additionally, the fact that from the exact same propargylic acetate, two extremely different compounds are produced simply upon the presence or the absence of water could account for two distinct catalytic species. It should also be noted that not only the nature of the products but the reaction conditions are dramatically altered for the transformation to proceed. Thus, extended reaction time and heating are required for the formation of enones while indenes were produced at room temperature in minutes as shown in Scheme 64.



Scheme 64. Influence of water on the reactivity

From these observations, the presence of water slows down the reaction significantly and leads to a new type of product. This means that water does not only allow for the

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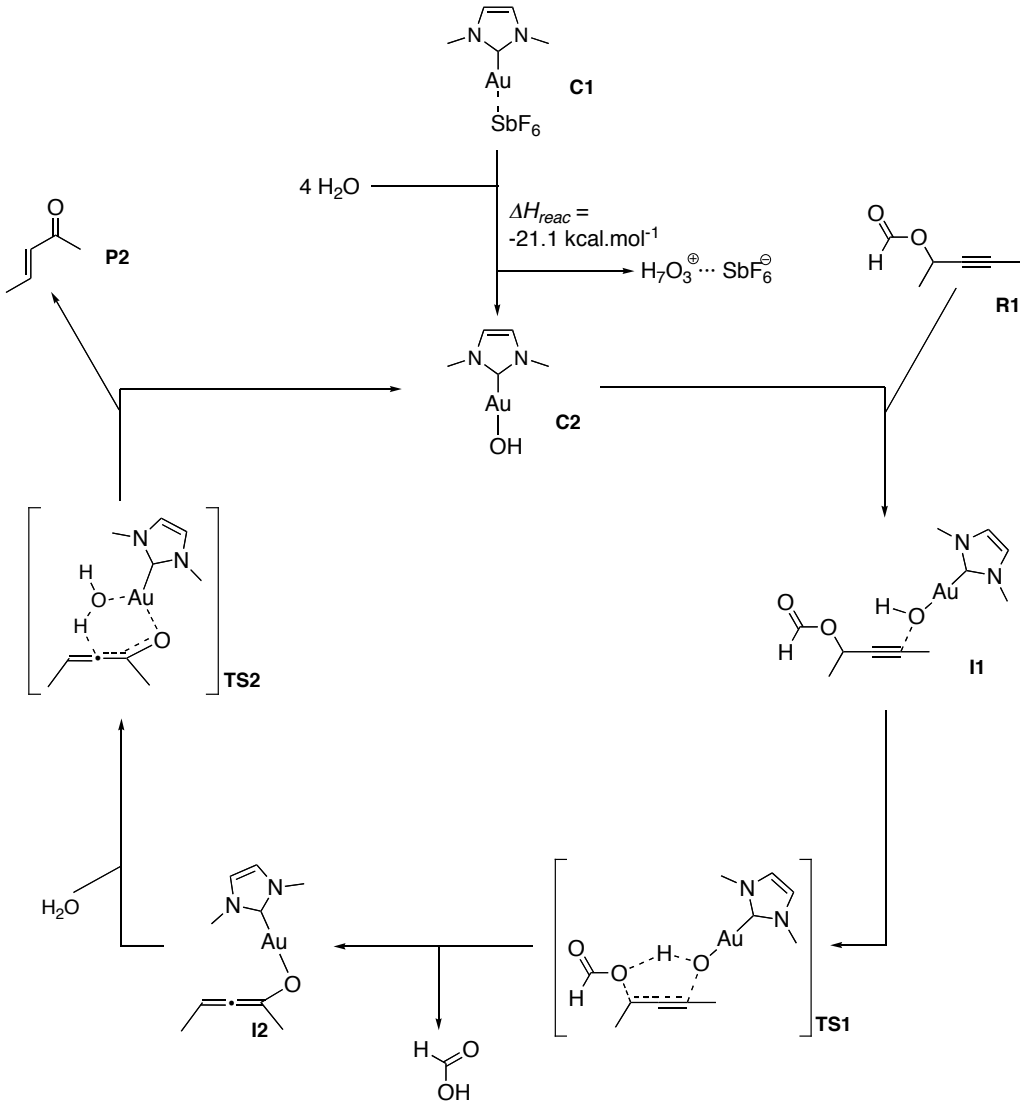
formation of enones but inhibits the pathway leading to indenes. We therefore believe that these observations, together with the results of our computational studies, strongly support two distinct catalytic species for the formation of indenes and enones, a cationic [(NHC)Au]X species and [(NHC)AuOH] respectively.

4. A new catalytic cycle by DFT calculations

The Au-catalyzed reaction

Following the general S_N2' scheme presented earlier (Scheme 57 on p 232, bottom path), but considering complex **C2** as the active species, we propose the catalytic cycle presented in Scheme 65.



Scheme 65. Proposed reaction mechanism for the Au-catalyzed formation of α,β-unsaturated carbonyl compounds based on calculations

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In contrast to our first suggestion, where the gold center was thought to activate the carbon-carbon triple bond of **77**, the gold instead activates water by forming the hydroxide complex **C2** and releasing a solvated cluster of $HSbF_6$.

In order to verify the suggested mechanism, all the stationary points in the catalytic cycle have been calculated and are presented in the potential energy profile (Figure 37). The optimized geometries of some key structures (**I1**, **TS1**, and **I2**) are shown in Figure 38. Unless stated otherwise, all energies discussed are relative to the free reactant **R1** and the gold-complex **C2**.

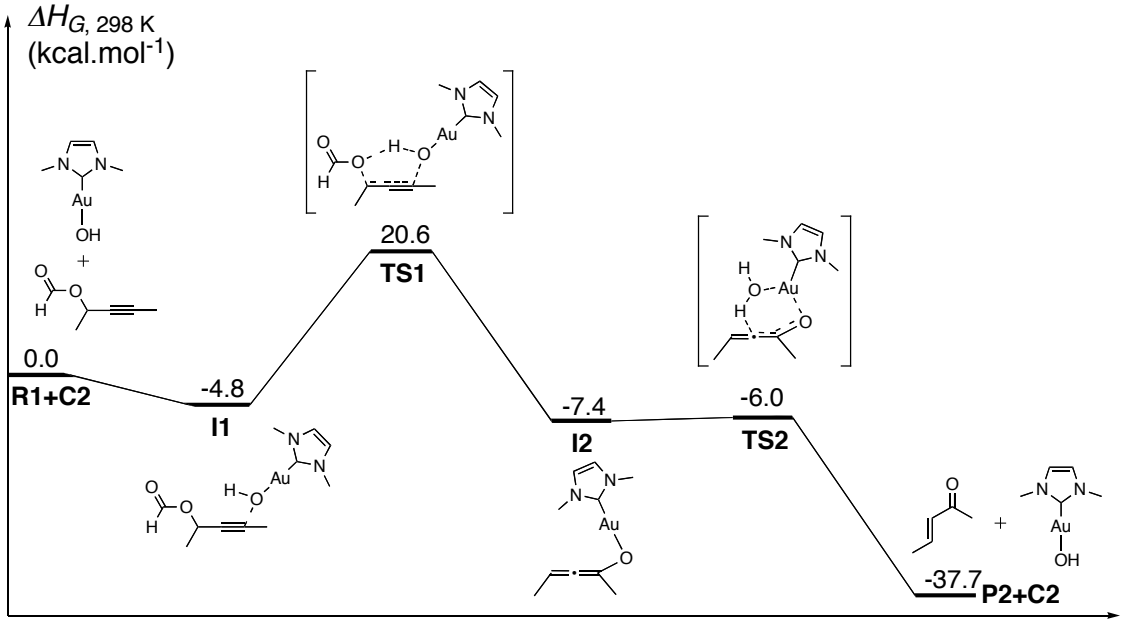

Figure 37. Computed potential energy profile for the gold-catalyzed formation of enones

In the first step of the reaction a complex (**I1**) between **C2** and **R1** is formed, with an energy of –4.8 kcal.mol^{-1}. This complex rearranges to transition state **TS1**, where the proton of the hydroxyl group of **C2** is transferred to the inner oxygen of **R1**. Concertedly, the oxygen of **C2** binds to the most electron deficient carbon of the triple bond in **R1**, "delivering" the oxygen to the alkyne.[383] Formic acid is formed and acts as a leaving group. A possible alternative transition state (TS) would be the transfer of the proton to the carbonyl oxygen. However, this TS was found to have a higher energy than **TS1**. The transition step has an energy of 20.6 kcal.mol^{-1}, and the formation of gold allenolate **I2** is exothermic by 7.4 kcal.mol^{-1}. To complete the catalytic cycle, water is added to **I2** through a cyclic six-membered ring TS (**TS2**), leading to the formation of the enone and regenerating

[383] A somewhat similar "delivery" of oxygen bound to a cationic gold(I) species to an alkyne moiety has already been proposed, see ref. 327.

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catalyst **C2**. The barrier for this step is only 1.4 kcal.mol^{-1} relative to **I2** and the overall process is exothermic by nearly 40 kcal.mol^{-1} relatively to the free reactants. The computed barrier for the rate-determining step of the Au-catalyzed reaction, from **I1** to **TS1**, is 25.4 kcal.mol^{-1}.

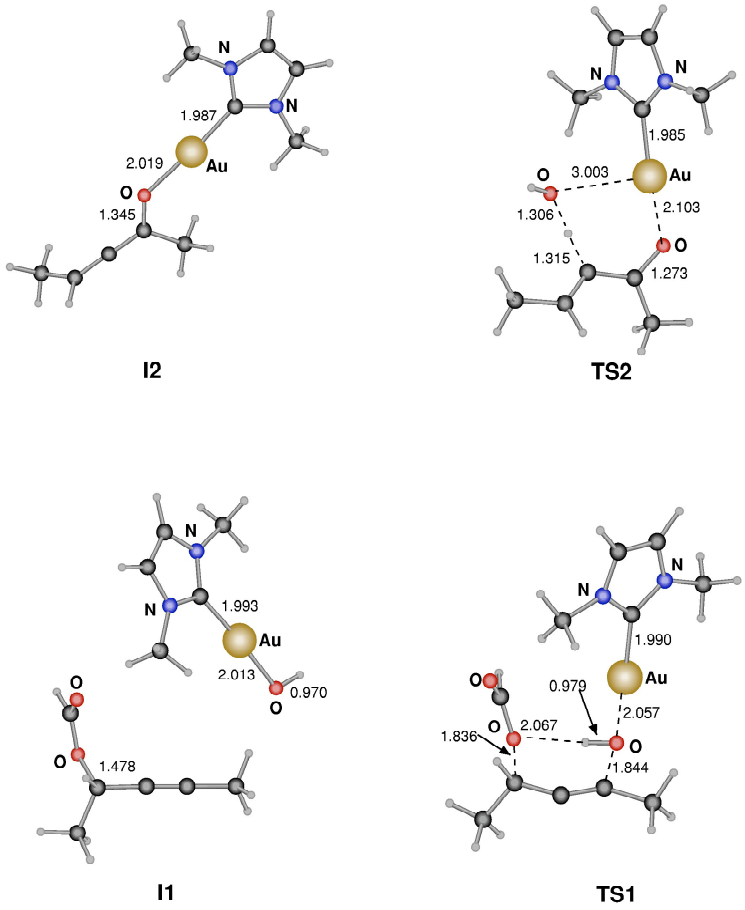

Figure 38. Geometries of stationary points in the gold-catalyzed reaction

The uncatalyzed reaction

For comparison of the energetics and to learn more about the catalytic function of the gold complex the corresponding uncatalyzed reaction was investigated, i.e. the addition of water to **R1**.

The reaction mechanism for the uncatalyzed reaction is presented in Scheme 66 and its energy profile in Figure 39. In the first step, a reaction complex is formed with water bound to the reactant, forming complex **I3**, exothermic by 9.6 kcal.mol^{-1}. Allenol **P1** is formed *via* transition state **TS3**, where a proton from H_2O is transferred to the carbonyl oxygen of **R1**, forming formic acid that departs concomitantly to the formation of the C–O bond. This is in sharp contrast to the gold catalyzed reaction where the proton from **C2** is transferred to the inner oxygen of **R1** and not to the carbonyl oxygen. An alternative

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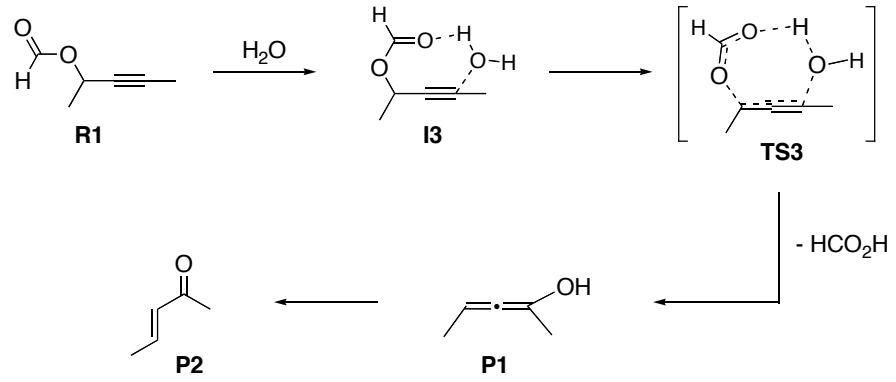
transition state for the uncatalyzed reaction, corresponding to **TS1** was optimized. However, this six-membered structure was found to have a higher energy than **TS3** (3.4 kcal.mol^{-1} above **TS3**).



Scheme 66. Plausible mechanism for the uncatalyzed formation of enones

TS3 has an energy of 26.6 kcal.mol^{-1} relative to **R1** + H_2O. The computed barrier for the rate-limiting step of the uncatalyzed reaction, from **I3** to **TS3**, is 36.2 kcal.mol^{-1}. This barrier is 10.8 kcal.mol^{-1} higher than for the Au-catalyzed reaction. The catalytic effect is thus properly reproduced.

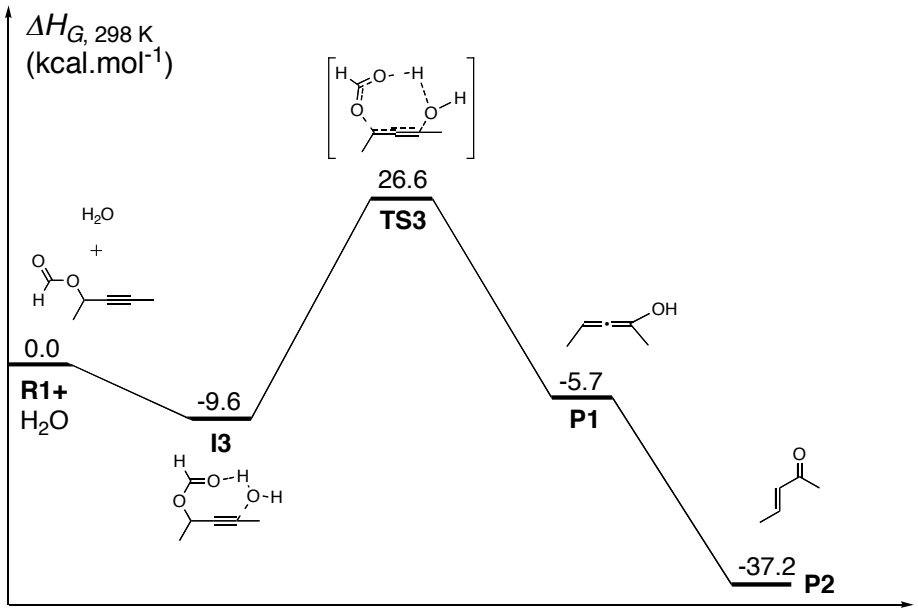


Figure 39. Computed potential energy profile for the uncatalyzed formation of enones

Finally, we noticed that in the key rate-determining step from **I1** to **TS1**, the sum of Mulliken charges in the [(NHC)Au] fragment changes from +0.432 to +0.542 atomic units, a change of 0.090. On the other hand, in the uncatalyzed reaction, the change of the Mulliken charge of the proton occupying the equivalent position is only of 0.045 atomic units (from

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+0.470 to +0.515) in the equivalent step going from **I3** to **TS3**. Therefore, the advantage of replacing a proton by a gold species lies probably in the better ability of the latter to ease stabilize the positive charge that develops at this position throughout the reaction cycle.

E. Concluding remarks

In summary, we have described in this section a novel type of Au^{I}-catalyzed transformation enabling the formation of α,β-unsaturated carbonyl compounds from easily accessible propargylic acetates. The use of [(NHC)AuCl] complexes in conjunction with a silver salt has allowed for the efficient and stereoselective formation of a wide array of conjugated (*E*)-enones and (*E*)-enals in high yields.

The striking observation of the crucial role of water on the outcome of the reaction has been investigated by means of computational methods. These studies led to the proposal of an unprecedented type of reactivity in the field of Au-catalysis and strongly support [(NHC)AuOH] as the active catalyst. Based on calculations of a full catalytic cycle, this gold species is proposed to deliver its hydroxyl moiety to the alkyne, forming a gold-allenolate intermediate that would be hydrolyzed by water to produce the enone and regenerate [(NHC)AuOH].

Furthermore, while additional types of rearrangement of the acetate moiety have been proposed,[384] the propensity of an acetate to behave as a leaving group has never been observed in the context of Au-catalysis prior to this study. Additional research to experimentally verify this unprecedented reactivity of gold(I) complexes are being devised.

VI. Rearrangement of allylic acetates[385]

While propargylic acetates are being extensively studied, including by our laboratories (see sections **III**, **IV**, and **V** of this chapter), for their valuable reactivity in the presence of gold catalysts,[316a] almost no attention has been paid to their allylic

[384] (a) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 8414–8415. (b) Wang, S.; Zhang, L. *Org. Lett.* **2006**, *8*, 4585–4587.
[385] Marion, N.; Gealageas, R.; Nolan, S. P. *Org. Lett.* **2007**, *9*, 2653–2656 [Additions & Corrections: *Org. Lett.* **2008**, *10*, 1037].

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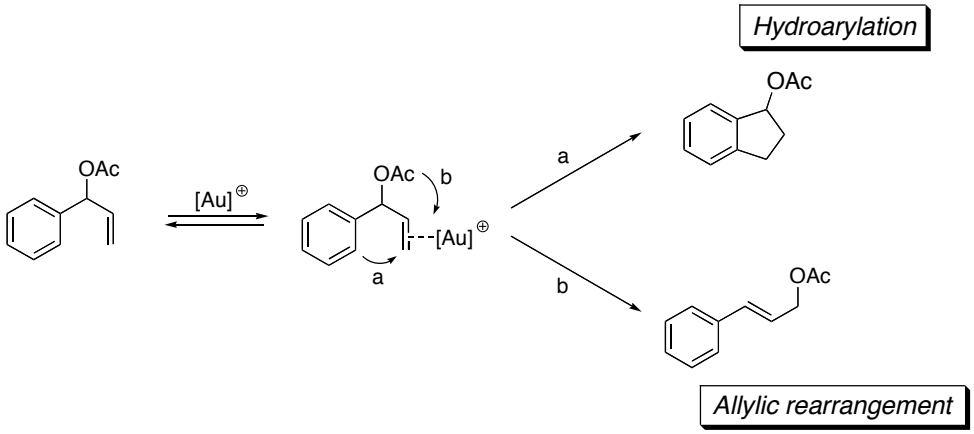
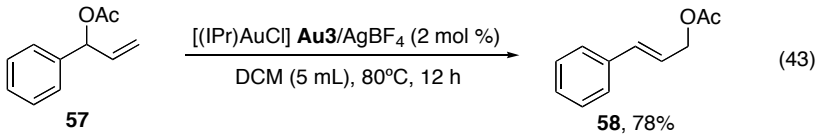
counterparts.[386] Similarly to propargylic esters,[387] we envisaged that the acetate moiety might undergo a 1,3-shift upon complexation of Au^+ fragment onto the alkene, resulting ultimately in the formation of an isomerized allylic acetate. Alternatively, activation of the alkene could lead to a Friedel-Crafts-type reactivity, producing upon hydroarylation indane derivatives (Scheme 67).



Scheme 67. Envisaged transformations for arylallyl acetates upon gold activation

A. Preliminary results

Capitalizing on catalytic systems we previously developed in the context of homogeneous gold catalysis, we attempted the isomerization of allylic acetate **57** with [(IPr)AuCl] **Au3**/$AgBF_4$ in DCM (Eq 45).



(43)

We observed the formation of the rearranged product **58** with complete selectivity for the *E*-isomer. Hence, it was established that cationic NHC–gold(I) catalyst **Au3**/$AgBF_4$ promotes the allylic rearrangement over the hydroarylation reaction.

It should be noted here that the allylic rearrangement provides an efficient and atom-economical access to primary oxo-derivatives. It has been described with various transition

[386] During the completion of this work, a study on the isomerization of allenyl esters, a peculiar class of allylic acetates, catalyzed by Au^I complexes appeared, see: Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 985–988.

[387] For selected examples of Au-mediated 1,3-shift of propargylic esters, see: (a) Fürstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546–2547. (b) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805. (c) Buzas, A.; Istrate, F.; Gagosz, F. *Org. Lett.* **2006**, *8*, 1957–1959. (d) Oh, C. H.; Kim, A.; Park, W.; Park, D. I.; Kim, N. *Synlett* **2006**, 2781–2784.

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metals,[388] most studies focusing on Pd^{II},[389] but remains unprecedented in the presence of gold catalysts.[386]

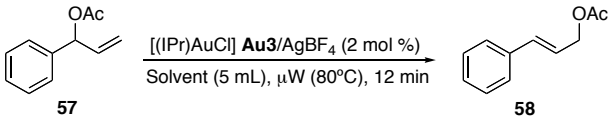
B. Optimization studies

As seen above, we observed the formation of **58** with complete selectivity for the *E*-isomer but results, both under thermal and microwave-assisted heating, were not reproducible. Nevertheless, encouraged by this preliminary finding, we engaged in a thorough optimization of the reaction conditions.

1. Solvent optimization

Several solvents were tested under both conventional and microwave-assisted heating, with equal results (Table 37, entries 1-5).

Table 37. Solvent optimization for the Au-catalyzed allylic rearrangement



57 58

entry	solvent	58[a]
1[b,c]	DCM	60 - 90%
2[c]	DCE	99%
3[c]	Toluene	16%
4[b,c]	THF	< 5% - 14%
5[c]	H_2O	< 5%
6	1,4-Dioxane	< 5%
7	DMAc	< 5%
8[b]	Et_2O	< 5%
9	Hexane	< 5%
10[d]	DME	7%

[a] ^{1}H NMR conversions, average of at least 2 runs. [b] Results were not reproducible. [c] Similar results were obtained under the following reaction conditions: conventional heating, reflux for 12 h. [d] Substantial amount of oligomerization.

[388] (a) Hg: Overman, L. E.; Campbell, C. B.; Knoll, F. M. *J. Am. Chem. Soc.* **1978**, *100*, 4822–4834. (b) Co: Mukhopadhyay, M.; Reddy, M. M.; Maikap, G. C.; Iqbal, J. *J. Org. Chem.* **1995**, *60*, 2670–2676. (c) Eu: Shull, B. K.; Sakai, T.; Koreeda, M. *J. Am. Chem. Soc.* **1996**, *118*, 11690–11691. (d) Yb: Krishna, P. R.; Kannan, V.; Sharma, G. V. M. *Synth. Commun.* **2004**, *34*, 55–64.
[389] (a) Henry, P. M. *J. Chem. Soc. D* **1971**, 328–329. (b) Henry, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 5200–5206. (c) Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, *4*, 321–324.

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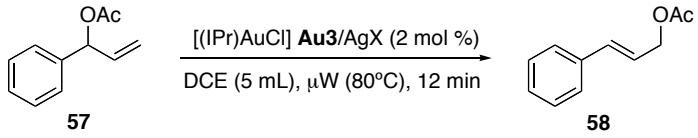
Room temperature reactions led only to partial conversions. The reaction performed best in polychlorinated solvents, DCE being the most efficient (Entry 2). We then decided to continue these studies using microwave conditions,[390] notably because of the great gain in time.

2. Silver additive optimization

To ensure that we were in presence of a gold-catalyzed reaction, three control experiments were carried out. Acetate **57** was fully recovered when neither Au nor Ag were added to the reaction and [(IPr)AuCl] alone showed very little catalytic activity. On the other hand, $AgBF_4$ was found to catalyze the isomerization but in low yield and with no reproducibility. In order to avoid any "contaminating" silver(I) catalysis, we decided to employ an excess of gold(I) complex (3 mol % of Au and 2 mol % of Ag) to ensure a Au-catalyzed reaction. Then, the influence of the counteranion was evaluated (Table 38).

Table 38. Silver additive otimization in the formation of **58**



57 58

entry	AgX	58[a]
1	$AgBF_4$	99%
2	$AgPF_6$	86%
3[b]	$AgSbF_6$	63%
4	AgOTf	98%
5	$AgNO_3$	< 5%
6	Ag(TFA)	< 5%
7	AgOTs	< 5%

[a] ^{1}H NMR conversions, average of at least 2 runs. [b] Substantial amount of oligomerization.

While BF_4^-, PF_6^-, and TfO^- showed similar behavior, SbF_6^- led to a significant amount of oligomerization.

[390] The amount of solvent, the reaction time and the temperature have been optimized using a scientific microwave reactor Biotage Initiator 2.0.

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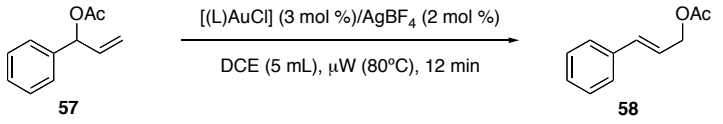
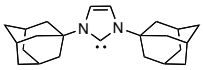
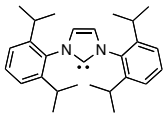
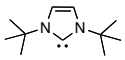
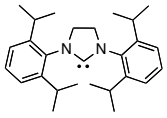
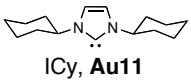
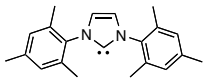
3. Ligand optimization

Next, we screened a number of NHCs with varying stereoelectronic properties (Table 39).[391] Interestingly, a strong steric effect was observed: only the most encumbering NHCs produced the isomerized acetate **58** in quantitative yields (Table 39, entries 2-6). The less sterically demanding ligands led to sluggish reactions and lower yields (Entries 7-9).

Table 39. Ligand optimization in the formation of **58**



57 58

entry	L	58[a]	entry	L	58[a]
1[b]	none	< 5%	5	 IAd, **Au10**	97%
2	 IPr, **Au3**	99%	6	 ItBu, **Au8**	98%
3	 SIPr, **Au4**	98%	7[b]	 ICy, **Au11**	61%
4	 IMes, **Au1**	95%	8[b]	 ITM, **Au5**	56%
			9[b]		53%

[a] ^{1}H NMR conversions. [b] Substantial amount of oligomerization.

Since ItBu and IAd, which performed extremely well, are the most σ-donating ligands of the series, an explanation relying on electronic properties was appealing. But it can be easily ruled out in view of the behavior of IMes and ICy that possess similar electronics and performed oppositely. A purely steric influence of the ligand on gold appears as the most plausible hypothesis; ItBu, IAd, IPr, SIPr, and IMes being the five most encumbered ligands of the series we tested. The greatest steric hindrance of the latter ligands could be seen as a protection of the gold center, preventing clusterization or precipitation of gold(0), which could inhibit the catalytic activity.[392,393]

[391] For a discussion on the stereoelectronic properties of NHCs, see the Introduction Chapter, section **III**.
[392] For key reports on Au···Au interactions, see: (a) Schmidbaur, H.; Graf, W.; Müller, G. *Angew. Chem., Int. Ed.* **1988**, *27*, 417–419. (b) Schmidbaur, H.; Scherbaum, F.; Huber, B.; Müller, G. *Angew. Chem., Int. Ed.*

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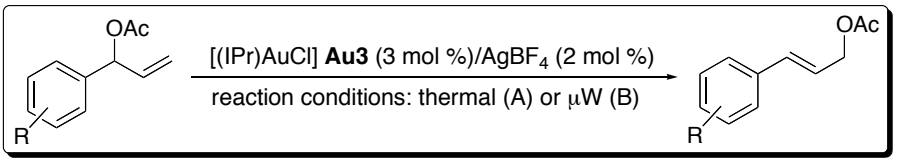
C. Scope of the reaction

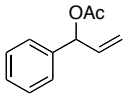
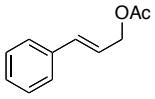
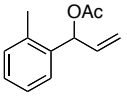
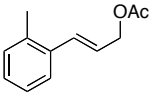
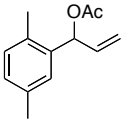
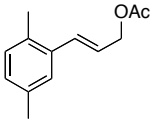
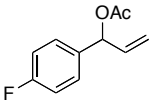
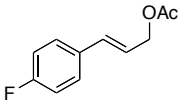
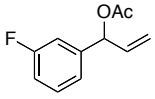
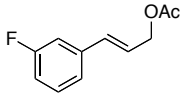
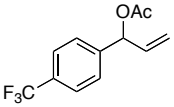
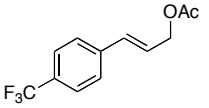
With a fully optimized catalytic system in hand, the scope of the reaction was examined (Tables 40-42). It is important to note that this procedure is extremely simple to carry out and does not require anhydrous reagents nor anaerobic conditions.

1. Formation of phenyl-substituted styrene derivatives

Various substitution patterns on the phenyl ring did not alter the yield nor the stereochemistry of the isomerized products **137**-**141** (Table 40, entries 2-6).

Table 40. Au-Catalyzed rearrangement of various arylallyl acetates



Entry	Substrate		Product	Yields[b] (Method)
1		**57**		**58**, 95% (A) 97% (B)
2		**132**		**137**, 92% (A) 90% (B)
3		**133**		**138**, 87% (B)
4		**134**		**139**, 95% (A) 95% (B)
5		**135**		**140**, 75% (A) 81% (B)
6		**136**		**141**, 94% (A) (*E*:*Z*, 93:7)[c]

[a] Reaction conditions. General: alkene (1 mmol), [(IPr)AuCl] **Au3** (3 mol %), $AgBF_4$ (2 mol %), DCE (20 mL). Method A: oil bath, reflux, 12 h. Method B: μW, 80ºC, 12 min. [b] Isolated yields, average of two runs. [c] Ratio determined by ^1H NMR.

1988, *27*, 419–421. (c) Scherbaum, F.; Huber, B.; Müller, G.; Schmidbaur, H. *Angew. Chem., Int. Ed.* **1988**, *27*, 1542–1544. (d) Scherbaum, F.; Grohmann, A.; Huber, B.; Krüger, C.; Schmidbaur, H. *Angew. Chem., Int. Ed.* **1988**, *27*, 1544–1546.

[393] For reports on aurophilic interactions in NHC–Au^I complexes, see: (a) Wang, H. M. J.; Chen, C. Y. L.; Lin, I. J. B. *Organometallics* **1999**, *18*, 1216–1223. (b) Baker, M. V.; Barnard, P. J.; Berners-Price, S. J.; Brayshaw, S. K.; Hickey, J. L.; Skelton, B. W.; White, A. H. *J. Organomet. Chem.* **2005**, *690*, 5625–5635. (c) Ray, L.; Shaikh, M. M.; Ghosh, P. *Inorg. Chem.* **2008**, *47*, 230–240.

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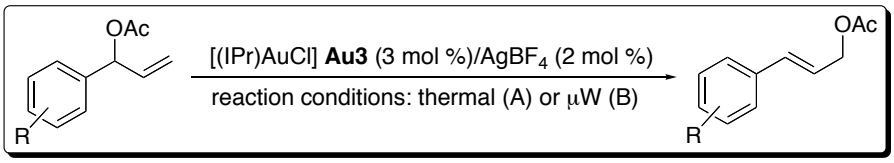
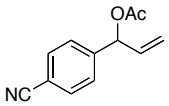
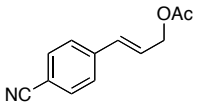
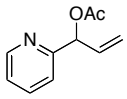
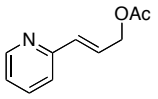
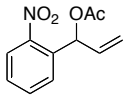
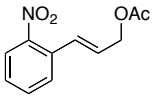
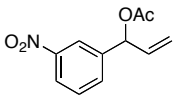
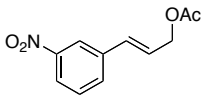
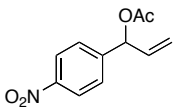
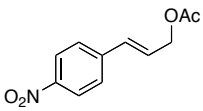
The tolerance of the present catalytic system to various substitutions on the phenyl ring is not surprising since the aryl moiety remains unchanged from the substrates to the products. On the other hand, it can be viewed as an indirect proof of the absence of disproportionation of the Au^{I} catalyst into Au^{0} and Au^{III}. Indeed, Au^{III} catalysts, unlike Au^{I}, are known to activate C^{Ar}–H bonds,[357] an event that could occur with the substrates and the products of the rearrangement. Additionally, NHC–Au^{III} catalysts have been shown recently to promote the polymerization of styrene derivatives[292] such as the products formed here.

It was then surprising to observe the quantitative recovery of **142** bearing a cyano group in *para* position (Table 41, entry 1). Despite repeated attempts using both methods A and B, we never detected the formation of the rearranged acetate.

Table 41. Au-catalyzed allylic rearrangement of substrates possessing a coordinating group



Entry	Substrate		Product	Yields[b] (Method)
1		**142**		NR (A) NR (B)
2		**143**		NR (A) NR (B)
3		**144**		NR (A) NR (B)
4[d]		**145**		**147**, 53% (B) (*E*:*Z*, 70/30)[c]
5		**146**		**148**, 96% (A) (*E*:*Z*, 92/8)[c] 98% (B) (*E*:*Z*, 95/5)[c]

[a] Reaction conditions. General: alkene (1 mmol), [(IPr)AuCl] **Au3** (3 mol %), $AgBF_4$ (2 mol %), DCE (20 mL). Method A: oil bath, reflux, 12 h. Method B: μW, 80ºC, 12 min. [b] Isolated yields, average of two runs. [c] Ratio determined by ^1H NMR. [d] Substantial amounts of oligomerization. NR = no reaction.

This could be due to coordination of the nitrile moiety of **142** to the gold center, since linear two-coordinated cationic gold(I) complexes containing NHC ligands and

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acetonitrile have been reported as fairly stable compounds.[324] Hence, an hypothetical [(IPr)Au(**142**)]BF_4 might be inert under the present reaction conditions. Decoordination of the nitrile upon work-up would release **142** unaffected. A similar feature was observed when a 2-pyridynyl group was attached to the allyl moiety (Entry 2). Again, complexation of the substrate to the gold center is the most likely explanation, since in this case, in addition to a linear coordination of the nitrogen,[394] formation of a 5-membered *N*,*O*-chelate is possible.

Examination of the results from entries 3-5 seems to corroborate this hypothesis.[395] When the nitro group is placed in *ortho* position, no conversion is observed and the starting material is recovered (**144**). Then, the conversion increases as a function of the distance between the nitro and the acetate (from *ortho* to *para*), resulting in quantitative formation of **148** where the nitro group is located in *para* position.

2. Reactivity of substituted olefins

The formation of trisubstituted olefins, often challenging synthetically, was found efficient (Table 42, entries 1-4 and 6). Tertiary acetates **149** and **150** were converted into **155** and **156** in good yields. Di- and trisubstituted alkenes participated as well in the isomerization reaction affording **159** and **160** in good yields and selectivity (Entries 3 and 4).

It should be noted that in the cases of the formation of tri-substituted olefins **156**-**158**, the *E*:*Z* selectivity observed is relatively good in view of the close steric requirement of the alkene substituents.

Further expanding the scope of the reaction, a benzoate group at the allylic position isomerized similarly as an acetate (Entry 5) and an alkyl substituted allylic acetate produced in high yield the rearranged trisubstituted olefin (Entry 6).

Finally, it is worth noting that several reactions were carried out using both conventional (i.e. oil bath) and microwave heating and produced very similar, if not identical, results even in terms of selectivity (Table 40, entries 1, 2, 4, 5; table 41, entries 1-3, 5; table 42, entry 6).

[394] Pyridine-adducts of gold(I) compounds are known. For selected references, see: (a) Adam, H. N.; Hiller, W.; Strahle, J. *Z. Anorg. Allg. Chem.* **1982**, *485*, 81–91. (b) Conzelmann, W.; Hiller, W.; Strahle, J.; Sheldrick, G. M. *Z. Anorg. Allg. Chem.* **1984**, *512*, 169–176. (c) Bayler, A.; Schmidbaur, H. *J. Am. Chem. Soc.* **1996**, *118*, 5324–5325. (d) Pyykkö, P.; Schneider, W.; Bauer, A.; Bayler, A.; Schmidbaur, H. *Chem. Commun.* **1997**, 1111–1112. (e) Yip, J. H. K.; Feng, R.; Vittal, J. J. *Inorg. Chem.* **1999**, *38*, 3586–3589. (f) Catalano, V. J.; Etogo, A. O. *Inorg. Chem.* **2007**, *46*, 5608–5615. (g) Lin, J. C. Y.; Tang, S. S.; Sekhar Vasam, C.; You, W. C.; Ho, T. W.; Huang, C. H.; Sun, B. J.; Huang, C. Y.; Lee, C. S.; Hwang, W. S.; Chang, A. H. H.; Lin, I. J. B. *Inorg. Chem.* **2008**, *47*, 2543–2551.

[395] Attempts to isolate one of the hypothetical complexes mentioned in the text were, to this point, unsuccessful.

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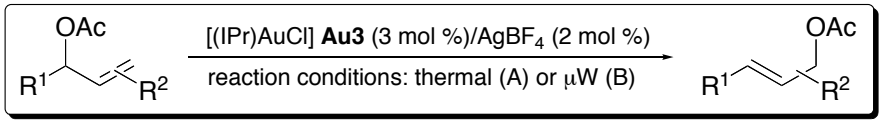
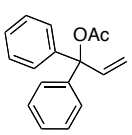
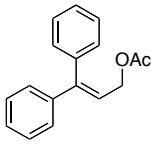
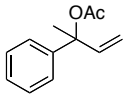
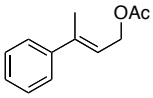
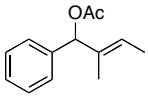
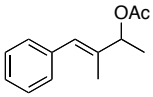
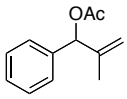
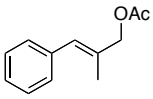
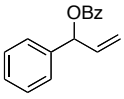
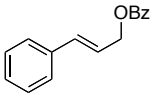
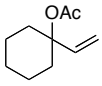
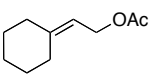
Table 42. Extended scope of the Au-catalyzed allylic rearrangement

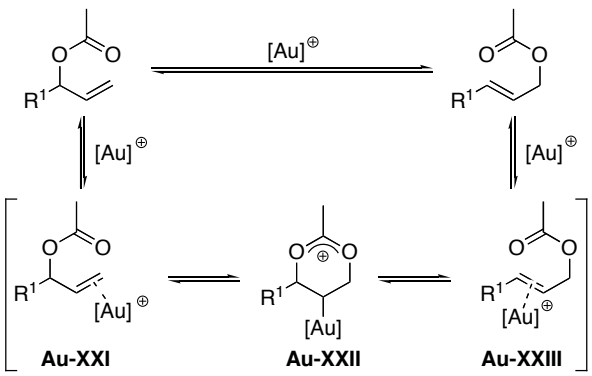


Entry	Substrate		Product	Yields[b] (Method)
1		**149**		**155**, 88% (B)
2		**150**		**156**, 78% (B) (*E*:*Z*, 75/25)[c]
3		**151**		**157**, 76% (B) (*E*:*Z*, 85/15)[c]
4		**152**		**158**, 93% (B) (*E*:*Z*, 85/15)[c]
5		**153**		**159**, 90% (B)
6		**154**		**160**, 97% (A) 98% (B)

[a] Reaction conditions. General: alkene (1 mmol), [(IPr)AuCl] **Au3** (3 mol %), $AgBF_4$ (2 mol %), DCE (20 mL). Method A: oil bath, reflux, 12 h. Method B: μW, 80ºC, 12 min. [b] Isolated yields, average of two runs. [c] Ratio determined by ^1H NMR.

D. Mechanistic proposal

In terms of mechanism, as depicted in Scheme 68, we propose that π-coordination of the alkene moiety onto the cationic gold center triggers an intramolecular nucleophilic attack of the carbonyl, leading to a 6-membered stabilized 1,3-acetoxonium.



Scheme 68. Plausible mechanism for the Au-catalyzed allylic rearrangement

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Completion of the 1,3-shift of the acetate would produce the isomerized olefin and regenerate the Au^+ fragment. By this proposal, which is in line with previous studies carried out with mercury[388a] and palladium,[389] we consider this reaction as a cyclization-induced rearrangement as defined by Overman.[396]

E. Concluding remarks

In summary, in this section we have developed an efficient [(NHC)Au^I]-catalyzed rearrangement of allylic acetates under conventional or microwave-assisted heating that proved versatile. It was notably shown that an extremely bulky ligand bound to the gold center was crucial to obtain full conversions to the isomerized product.

VII. Conclusion

Overall, this work led to the evaluation of the catalytic performance of [(NHC)AuCl] complexes in various organic transformations. The versatility of these pre-catalysts has allowed for the activation of alkynes, allenes, and alkenes. It has notably been shown that N-heterocyclic carbenes are viable supporting ligands in Au-based catalysis and that, more than mimics, they should be considered complementary to phosphine ligands.

First envisaged as a simple preliminary test for the catalytic activity of NHC–Au^I complexes prepared in our laboratory, the cycloisomerization reaction of dienyne **61** turned out to be a treasure trove of unexpected discoveries. At the offset of this project, the formation of a new type of cycloisomerized product generated more questions on mechanistic issues than was answered. Nevertheless, thorough examination of the different reaction parameters coupled with theoretical studies on the formation of bicyclo[3.1.0]hexane **61** allowed for a mechanistic rationale that has been supported by further experimental work.

[396] (a) Overman, L. E.; Campbell, C. B. *J. Org. Chem.* **1976**, *41*, 3338–3340. (b) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579–587. (c) Overman, L. E.; Owen, C. O.; Pavan, M. M. *Org. Lett.* **2003**, *5*, 1809–1812. (d) Watson, M. P.; Overman, L. E.; Bergman, R. G. *J. Am. Chem. Soc.* **2007**, *129*, 5031–5044.

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While studying the reactivity of 1,5-enynes in the presence of [(NHC)AuCl] catalysts, we observed the formation of indene derivatives in substrates possessing an aryl group at the propargylic position. Interestingly, the cyclization of the enyne moiety was not observed and indicated that the process leading to indenes is chemoselective. Extension of the reaction scope permitted the synthesis of several indenyl derivatives and revealed that the migration type of the acetate group (1,2- or 1,3-shift) occurred as a function of the nature of the acetylenic substituent. Finally, allenyl acetaes, resulting from [3,3] rearrangement of the arylpropargyl acetates, were shown to be likely intermediates in this transformation.

Capitalizing on the observation of a synthetically interesting by-product in the formation of indenes described above, we have uncovered and optimized a novel type of Au^{I}-catalyzed transformation enabling the formation of α,β-unsaturated carbonyl compounds from easily accessible propargylic acetates. The use of [(NHC)AuCl] complexes in conjunction with a silver salt has allowed for the efficient and stereoselective formation of a wide array of conjugated (*E*)-enones and (*E*)-enals in high yields. The striking observation of the crucial role of water on the outcome of the reaction has been investigated by means of computational methods. These studies led to the proposal of an unprecedented type of reactivity in the field of Au-catalysis and strongly support [(NHC)AuOH] as the active catalyst. Based on calculations of a full catalytic cycle, this gold species was proposed to deliver the hydroxyl moiety to the alkyne.

Taking advantage of the results previously obtained with propargylic acetates, we investigated their olefinic counterparts, namely the allylic acetates. This has allowed us to develop an efficient [(NHC)Au^{I}]-catalyzed rearrangement of allylic acetates under conventional or microwave-assisted heating that proved versatile. It was notably shown that a bulky ligand bound to the gold center was crucial to obtain full conversions to the isomerized product.

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VIII. Experimental section

A. General information

- All reagents were used as purchased.
- Dry tetrahydrofuran (THF) was distilled over Ph_2CO/Na or was purified by passing through a purification column from Innovative Technology Inc. (SPS-400-6).
- Dry dichloromethane (DCM) was purified by passing through a purification column from Innovative Technology Inc. (SPS-400-6).
- Silver salts were stored in a dessicator wrapped in aluminum foil.
- The microwave-assisted reactions were carried out using a Biotage Initiator 2.0.
- [(NHC)AuCl] complexes **Au1**-**Au11**[301] and **Au13**[320] were synthesized according to literature procedures.
- Thin-layer chromatography (TLC) analysis of reaction mixtures was performed on EMD Chemicals silica gel 60 F_{254} plates and visualized by UV.
- Flash chromatography was performed on silica gel 60 (230-400 mesh, Silicycle).
- ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian-300, Varian-400 or Bruker-300 MHz spectrometer at ambient temperature in $CDCl_3$ containing tetramethylsilane. Chemical shifts were referenced to the peak of tetramethylsilane (0.0 ppm). Assignments of some ^{1}H and ^{13}C NMR signals rely on COSY and/or HMBC experiments.
- Infrared spectra were recorded on a Bruker TENSOR 27 equipped with an ATR Diamond.
- Chiral GC analyses were performed using isothermal conditions (110°C) on a chiral colomn CP-Chirasil-DEX CB (25 m).
- Elemental analyses were performed at Robertson Microlit Laboratories, Inc., Madison, NJ, USA.
- Crystallographic data for **61'** and **Au12** can be downloaded free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax (+44) 1223-336-033.

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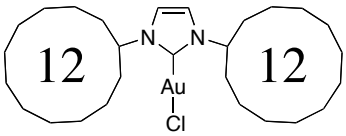
B. Enyne cycloisomerization

1. Synthesis of [(IDD)AuCl] (Au12)

In a round-bottom flask, [(IDD)AgCl][397] (200 mg, 0.37 mmol, 1.0 equiv) and dimethylsulfide gold(I) chloride (130 mg, 0.44 mmol, 1.0 equiv) were dissolved in minimal amount of DCM and the solution was stirred overnight at room temperature. Charcoal was added and the reaction mixture stirred for 3 extra hours. After filtration over Celite, a clear greenish solution was obtained. The volume of DCM was reduced and the desired complex was precipitated and washed with pentane to yield 180 mg (77% yield) of the title complex as a white powder characterized.



Au12

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94 (s, 2H, CH^{Im}), 4.91 (pent, *J* = 6.6 Hz, 2H, $CH^{Cyclododecyl}$), 2.06-1.96 (m, 4H), 1.69-1.60 (m, 8H), 1.56-1.5 (m, 2H), 1.46-1.28 (m, 30H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.8 (C, C–Au), 117.6 (CH, CH^{Im}), 58.0 (CH, $CH^{Cyclododecyl}$), 31.2 (CH_2), 23.7 (CH_2), 23.5 (CH_2), 23.4 (CH_2), 23.2 (CH_2), 21.6 (CH_2). **Calcd. HRMS** for $C_{29}H_{52}AuN_3$ (M-Cl+MeCN): 639.3827. Found: 639.3835. **CCDC-679915** contains the supplementary crystallographic data for this complex.

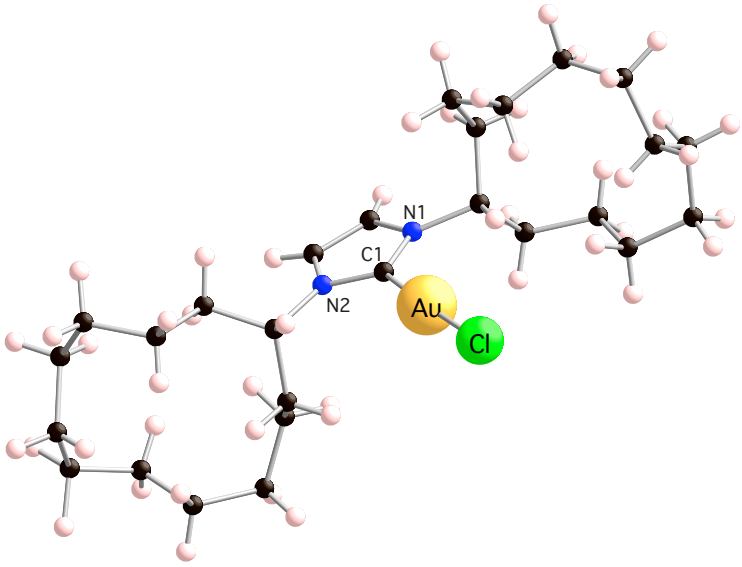


Figure 37. Ball-and-stick representation of [(IDD)AuCl] **Au12**

[397] For details on the synthesis of [(IDD)AgCl], see: de Frémont, P.; Scott, N. M.; Stevens, E. D.; Ramnial, T.; Lightbody, O. C.; Macdonald, C. L. B.; Clyburne, J. A. C.; Abernethy, C. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 6301–6309.

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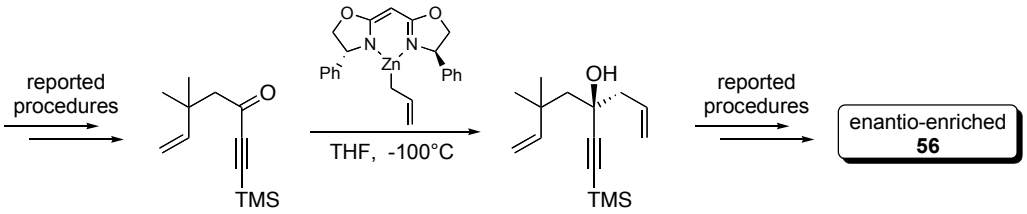
2. Synthesis and characterization of enynes 56, 56', and 63-65

Enal **56-a** and dienyne **56** were synthesized according to literature procedures.[398] Spectroscopic data were in good accordance with previous reports.

*Preparation of enantio-enriched dienyne **56***

As depicted below, the synthetic route to enantio-enriched **56** follows the procedures used for its racemate[398] with the exception of the allylation step where the chirality is introduced following a literature procedure.[399]



To a solution of bis-oxazoline (322 mg, 1.05 mmol, 1.05 equiv) and 2,2'-bipyridine (0.2 mg) in THF (1.8 mL) was added a 2.2 M solution of BuLi in hexanes at 0°C still the solution turns red. After completion of addition, the reaction mixture became a red-brown suspension. The reaction was warmed to room temperature and stirred for 15 min. A 1.5 M solution of allylzinc bromide (0.7 mL, 1 mmol, 1 equiv) was added to the solution of lithiated bis-oxazoline. After 30 min, ketone **56-c**[398] (187 mg, 0.9 mmol, 0.9 equiv) in THF (1.3 mL) was added at -100°C. As the reaction was complete, the mixture was quenched with 0.04 mL of MeOH/H_2O (1:1). The solvent was removed under vacuum and the crude was purified by flash chromatography on silica gel (pentane/dichloromethane, 7/3) to afford **56-d**[398] (105 mg, 47%). All the spectroscopic data were in agreement with a racemic sample. The determination of enantiomeric excess was determined by chiral gas chromatography (isotherm 110°C, CP-Chirasil-DEX CB – 25 m): enantiomer 1 (rt1 = 32.4 min) and enantiomer 2 (rt2 = 33.2 min), ee : 66%. $[\alpha]^{20}_D$ +7.5° (c 0.3, $CHCl_3$). Desilylation and acylation of enantio-enriched alcohol **56-d**, according to reported procedures, led to the formation of enantio-enriched **2**, $[\alpha]^{20}_D$ +3.2° (c 0.99, $CHCl_3$).

[398] For the synthesis and characterization of **56-a**, **56-c**, **56-d** and **56**, see Chapter II, section **V.D.1**.
[399] Nakamura, M.; Hirai, A.; Sogi, M; Nakamura, E. *J. Am. Chem. Soc.* **1998**, *120*, 5846–5847.

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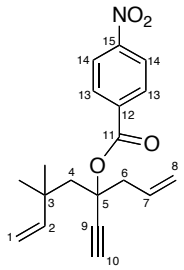
*Preparation of dienyne **56'***

4-Ethynyl-6,6-dimethylocta-1,7-dien-4-yl 4-nitrobenzoate (56')

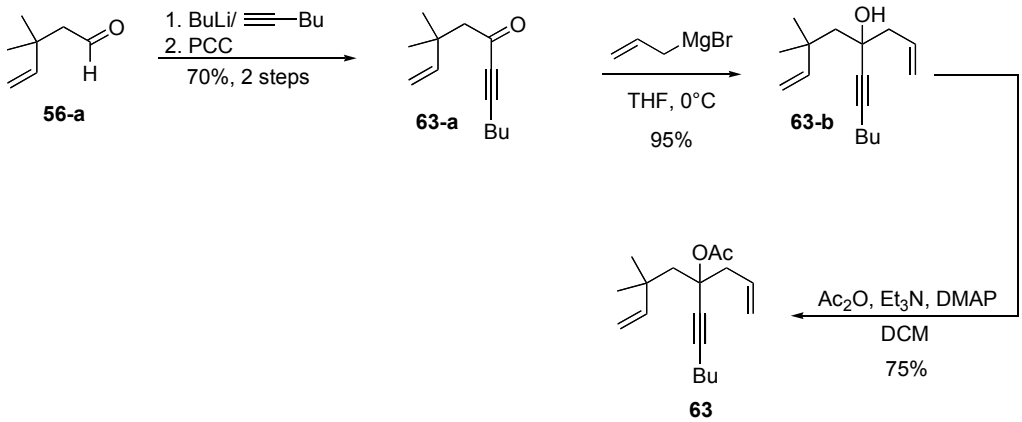


56'

To a solution of alcohol **55**[400] (0.5 g, 2.8 mmol, 1.0 equiv) in CH_2Cl_2 (9 mL), Et_3N (1.2 mL, 11.2 mmol, 4 equiv), DMAP (90 mg, 0.9 mmol, 0.3 equiv) and 4-nitrobenzoyl chloride (780 mg, 4.2 mmol, 1.5 equiv) were added and the mixture stirred at room temparature for 2 hours. The mixture was then quenched with a saturated NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated to give a crude oil, which was purified by flash chromatography on silica gel (pentane/Et_2O, 95/5), yielding 0.866 g (94%) of **56'**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 9.3 Hz, 2H, 2H^{14}), 8.12 (d, *J* = 9.3 Hz, 2H, 2H^{13}), 5.99-5.83 (m, 2H, H^2 + H^7), 5.16-5.10 (m, 2H, 2H^8), 4.90 (d, *J* = 17.6 Hz, 1H, H^1 *trans*), 4.81 (d, *J* = 10.7 Hz, 1H, H^1 *cis*), 3.01 (dd, *J* = 14.2, 7.3 Hz, 1H, 1H^6), 2.86 (dd, *J* = 14.2, 7.3 Hz, 1H, 1H^6), 2.73 (s, 1H, H^{10}), 2.36 (d, *J* = 14.7 Hz, 1H, 1H^4), 2.07 (d, *J* = 14.7 Hz, 1H, 1H^4), 1.19 (s, 3H, Me), 1.15 (s, 3H, Me). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 162.9 (C, C^{11}), 150.4 (C, C^{15}), 148.3 (CH, C^7), 136.4 (C, C^{12}), 132.0 (CH, C^2), 130.7 (CH, C^{14}), 123.5 (CH, C^{13}), 119.5 (CH_2, C^8), 110.3 (CH_2, C^1), 82.7 (C, C^9), 79.0 (C, C^5), 76.9 (CH, C^{10}), 49.1 (CH_2, C^6), 44.7 (CH_2, C^4), 36.8 (C, C^3), 28.9 (CH_3), 27.8 (CH_3).

*Preparation of dienyne **63***



[400] For the synthesis and characterization of **55**, see Chapter II, section **V.D.1**.

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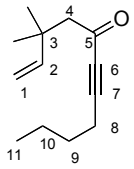
3,3-Dimethyl-undec-1-en-6-yn-5-one (63-a)



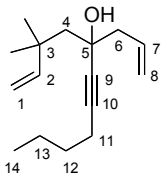
63-a

In an oven-dried round-bottom flask, 1-hexyne (1.5 mL, 13 mmol, 1.3 equiv) and BuLi (1.6 M in hexanes, 7.5 mL, 12 mmol, 1.2 equiv) were added to THF (20 mL) at -78ºC and stirred for 20 minutes under argon. To the reaction mixture, aldehyde **56-a**[398] (1.25 g, 10 mmol, 1.0 equiv) was added and the reaction stirred for 20 minutes. The reaction was then allowed to warm up to room temperature, quenched with a saturated aqueous NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give 3,3-dimethylundec-1-en-6-yn-5-ol **63-a** as a yellow oil that was engaged in the next step without further purification.

PCC (3.25 g, 15 mmol, 1.5 equiv) was mixed with 15.0 g of neutral alumina in CH_2Cl_2 (45 mL). A solution of **63-a** (2.0 g, 1 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was then added. The mixture was stirred at room temperature overnight, then filtered over Celite and concentrated, yielding the title compound as a crude oil, which, after flash chromatography on silica gel (pentane/Et_2O, 90/10), yielded 1.34 g (70% over 2 steps) of the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.89 (dd, *J* = 17.4, 10.6 Hz, 1H, H^2), 4.94 (dd, *J* = 17.4, 1.0 Hz, 1H, H^1 *trans*), 4.92 (dd, *J* = 10.6, 1.0 Hz, 1H, H^1 *cis*), 2.52 (s, 2H, H^4), 2.32 (t, *J* = 7.1 Hz, 2H, H^8), 1.56-1.49 (m, 2H, H^9), 1.35-1.45 (m, 2H, H^{10}), 1.13 (s, 6H, CH_3), 0.90 (t, *J* = 7.1 Hz, 3H, H^{11}). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 187.0 (C, C=O), 146.8 (CH, C^2), 111.0 (CH_2, C^1), 94.4 (C, C^6), 82.7 (C, C^7), 57.0 (CH_2, C^4), 37.0 (C, C^3), 29.7 (CH_2, C^9), 27.0 (CH_3), 22.0 (CH_2, C^8), 18.7 (CH_2, C^{10}), 13.5 (CH_3, C^{11}).

5-Allyl-3,3-dimethyl-undec-1-en-6-yn-5-ol (63-b)



63-b

63-a (1.34 g, 7 mmol, 1.0 equiv) was dissolved in THF (30 mL) under argon at -78°C. Allylmagnesium bromide (1.0 M, 8.4 mL, 8.4 mmol, 1.2 equiv) was added to the solution and the reaction mixture stirred at room temperature for 30 minutes. The reaction was then

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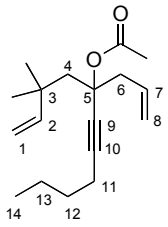
quenched with a saturated aqueous NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give the title compound as a crude oil that was engaged in the next step without further purification

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.08 (dd, *J* = 17.4, 10.9 Hz, 1H, H^2), 5.93 (ddt, *J* = 17.1, 9.8, 7.3 Hz, 1H, H^7), 5.15-5.06 (m, 2H, H^8), 5.02 (dd, *J* = 17.7, 1.2 Hz, 1H, H^1 *trans*), 4.96 (dd, *J* = 10.6, 1.2 Hz, 1H, H^1 *cis*), 2.49 (s, 1H, OH), 2.87 (m, 2H, H^6), 2.17 (t, *J* = 7.1 Hz, 2H, H^{11}), 1.71 (s, 2H, H^4), 1.49-1.33 (m, 4H, H^{12} + H^{13}), 1.25 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 0.89 (t, *J* = 7.1 Hz, 3H, H^{14}). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 149.4 (CH, C^2), 133.9 (CH, C^7), 118.7 (CH_2, C^1), 110.8 (CH_2, C^8), 86.3 (C, C^9), 83.4 (C, C^{10}), 69.4 (C, C^5), 53.1 (CH_2, C^4), 49.8 (CH_2, C^6), 37.0 (C, C^3), 30.7 (CH_2, C^{12}), 30.0 (CH_3, Me), 27.0 (CH_3, Me), 22.1 (CH_2, C^{11}), 18.5 (CH_2, C^{13}), 13.7 (CH_3, C^{14}). **IR (neat):** 3400, 3079, 2958, 2931, 2872, 2206, 1715, 1639, 1461, 1379 cm^{-1}.

5-Allyl-3,3-dimethylundec-1-en-6-yn-5-yl acetate (63)



63

Alcohol **63-b** (470 mg, 2 mmol, 1.0 equiv), DCE (6 mL), DMAP (52 mg, 0.6 mmol, 0.3 equiv), Et_3N (1.3 mL, 8 mmol, 4 equiv), and Ac_2O (0.36 mL, 4 mmol, 2 equiv) were added in turn in a round-bottom flask equipped with a condenser. The reaction mixture was heated overnight at 80°C. The reaction was then quenched with a saturated aqueous NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give a crude oil that was purified by flash chromatography on silica gel (pentane/MTBE, 90/10) affording 415 mg (75%) of the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.96 (dd, *J* = 17.4, 10.6 Hz, 1H, H^2), 5.83 (ddt, *J* = 16.6, 10.6, 7.3 Hz, 1H, H^7), 5.09-5.04 (m, 2H, H^8), 4.89 (dd, *J* = 17.4, 1.2 Hz, 1H, H^1 *trans*), 4.84 (dd, *J* = 10.6, 1.2 Hz, 1H, H^1 *cis*), 2.87 (ddt, *J* = 13.9, 7.3, 1.2 Hz, 1H, H^6), 2.67 (ddt, *J* = 13.6, 7.0, 1.3 Hz, 1H, H^6), 2.19 (t, *J* = 6.8 Hz, 2H, H^{11}), 2.18 (d, *J* = 14.9 Hz, 1H, H^4), 1.93 (s, 3H, OAc), 1.80 (d, *J* = 14.9 Hz, 1H, H^4), 1.52-1.35 (m, 4H, H^{12} + H^{13}), 1.15 (s, 3H, CH_3),

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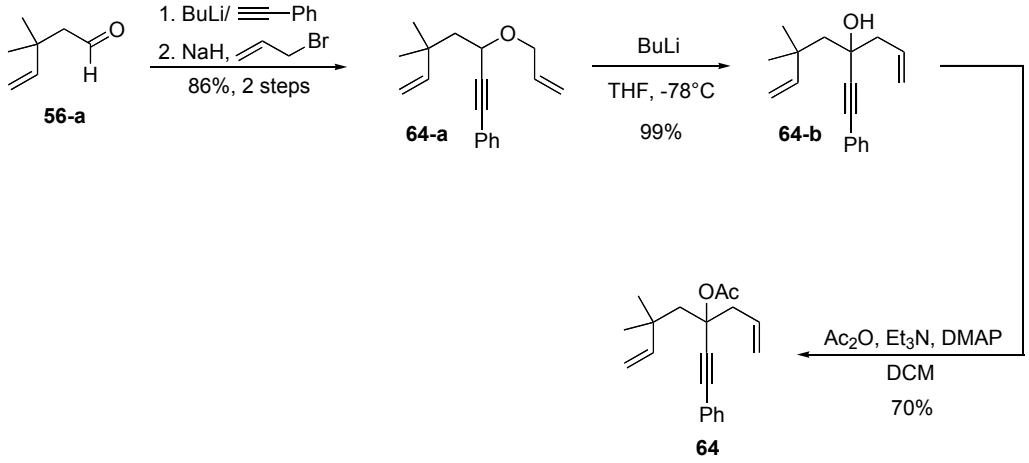
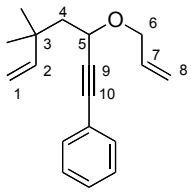
1.12 (s, 3H, CH_3), 0.89 (t, *J* = 7.3 Hz, 3H, H^{14}). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ 169.3 (C, *C*=O), 149.0 (CH, C^2), 133.1 (CH, C^7), 118.5 (CH_2, C^1), 109.2 (CH_2, C^8), 88.2 (C, C^9), 80.1 (C, C^{10}), 78.0 (C, C^5), 49.6 (CH_2, C^4), 45.2 (CH_2, C^6), 36.8 (C, C^3), 30.5 (CH_2, C^{12}), 28.6 (CH_3, Me), 28.0 (CH_3, Me), 22.3 (CH_3, OAc), 22.1 (CH_2, C^{11}), 18.6 (CH_2, C^{13}), 13.7 (CH_3, C^{14}). **Elemental analysis** calcd. (%) for $C_{18}H_{28}O_2$ (MW 276.41): C, 78.21; H, 10.21. Found: C, 78.37; H, 10.56.

*Preparation of dienyne **64***



(3-Allyloxy-3,5,5-trimethyl-hept-6-en-1-ynyl)-benzene (64-a)



64-a

In an oven-dried round-bottom flask, phenylacetylene (1.23 mL, 13 mmol, 1.3 equiv) and BuLi (1.6 M in hexanes, 7.5 mL, 12 mmol, 1.2 equiv) were added to THF (20 mL) at -78ºC and stirred for 20 minutes under argon. To the reaction mixture, aldehyde **56-a** (1.25 g, 10 mmol, 1.0 equiv) was added and the reaction stirred for 20 minutes. The reaction was then allowed to warm up to room temperature, quenched with a saturated aqueous NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give crude **64-a** as a yellow oil that was engaged in the next step without further purification.

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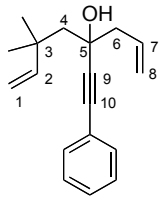
In an oven-dried round-bottom flask, the crude alcohol obtained above (10 mmol, 1.0 equiv) was added to a suspension of sodium hydride [60% in mineral oil] (0.48 g, 12 mmol, 1.2 equiv) in THF (20 mL) and stirred for 20 minutes at 0ºC under argon. To the reaction mixture, allylbromide (2.54 mL, 15 mmol, 1.5 equiv) was added and the reaction stirred for 20 minutes. The reaction was then allowed to warm up to room temperature, quenched with a saturated aqueous NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give **64-a** as a yellow oil that was purified by flash chromatography on silica gel (pentane/MTBE, 90/10) affording 2.18 g (86% over 2 steps) of the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.41 (m, 2H, H^{Ar}), 7.32-7.29 (m, 3H, H^{Ar}), 6.00-5.90 (m, 1H, H^7), 5.88 (dd, *J* = 17.4, 10.9, 1H, H^2), 5.33 (ddt, *J* = 17.1, 1.8, 1.5 Hz, 1H, H^8 *trans*), 5.19 (ddt, *J* = 10.3, 1.8, 1.5 Hz, 1H, H^8 *cis*), 4.98 (dd, *J* = 17.4, 1.3 Hz, 1H, H^1 *trans*), 4.97 (dd, *J* = 10.6, 1.3 Hz, 1H, H^1 *cis*), 4.32-4.27 (m, 2H, H^6), 3.98 (ddt, *J* = 12.6, 6.1, 1.3 Hz, 1H, H^5), 1.92 (dd, *J* = 14.1, 6.6 Hz, 1H, $1H^4$), 1.89 (dd, *J* = 14.1, 5.6 Hz, 1H, $1H^4$), 1.12 (s, 6H, CH_3). **IR (neat):** 3080, 2960, 2927, 2871, 2226, 1727, 1599, 1527, 1490, 1449, 1413, 1364 cm^{-1}.

6,6-Dimethyl-4-phenylethynyl-octa-1,7-dien-4-ol (64-b)



64-b

To a stirred solution of allylic ether **64-a** (510 mg, 2 mmol, 1.0 equiv) in THF (5 mL) at -78ºC, was added dropwise BuLi 1.6 M (1.25 mL, 1.0 equiv). After the addition was complete, the reaction mixture was quenched with brine and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give **64-b** as a yellow oil that was engaged in the next step without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.40 (m, 2H, H^{Ar}), 7.33-7.29 (m, 3H, H^{Ar}), 6.16 (dd, *J* = 17.7, 10.9 Hz, 1H, H^2), 6.05 (ddt, *J* = 17.4, 10.1, 7.1 Hz, 1H, H^7), 5.24-5.17 (m, 2H, H^8), 5.12 (dd, *J* = 17.4, 1.3 Hz, 1H, H^1 *trans*), 5.04 (dd, *J* = 10.6, 1.3 Hz, 1H, H^1 *cis*), 2.72 (s, 1H, OH), 2.56-2.44 (m, 2H, H^6), 1.88 (s, 2H, H^4), 1.36 (s, 3H, CH_3), 1.19 (s, 3H, CH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 149.2 (CH, C^2), 133.5 (CH, C^7), 131.4 (CH, C^{Ar}), 128.35 (CH, C^{Ar}),

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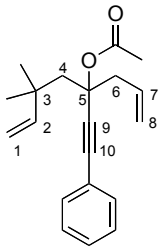
128.29 (CH, C^{Ar}), 123.1 (C, C^{Ar}), 119.2 (CH_2, C^1), 111.2 (CH_2, C^8), 92.6 (C, C^9), 85.8 (C, C^{10}), 69.8 (C, C^5), 53.0 (CH_2, C^4), 49.6 (CH_2, C^6), 37.1 (C, C^3), 30.0 (CH_3, Me), 27.1 (CH_3, Me). **IR (neat):** 3405, 3080, 2958, 2922, 2851, 2229, 1721, 1638, 1598, 1573, 1490, 1364 cm^{-1}.

6,6-Dimethyl-4-(phenylethynyl)octa-1,7-dien-4-yl acetate (64)



64

Alcohol **64-b** (509 mg, 2 mmol, 1.0 equiv), DCE (6 mL), DMAP (52 mg, 0.6 mmol, 0.3 equiv), Et_3N (1.3 mL, 8 mmol, 4 equiv), and Ac_2O (0.36 mL, 4 mmol, 2 equiv) were added in turn in a round-bottom flask equipped with a condenser. The reaction mixture was heated overnight at 80°C. The reaction was then quenched with a saturated aqueous NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give a crude oil that was purified by flash chromatography on silica gel (pentane/MTBE, 90/10) affording 415 mg (70%) of the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45-7.42 (m, 2H, H^{Ar}), 7.31-7.28 (m, 3H, H^{Ar}), 6.03 (dd, *J* = 17.4, 10.6 Hz, 1H, H^2), 5.93 (ddt, *J* = 17.4, 9.6, 7.3 Hz, 1H, H^7), 5.20-5.13 (m, 2H, H^8), 4.96 (dd, *J* = 17.4, 1.0 Hz, 1H, H^1 *trans*), 4.90 (dd, *J* = 10.6, 1.0 Hz, 1H, H^1 *cis*), 3.01 (dd, *J* = 13.9, 7.3 Hz, 1H, H^6), 2.83 (dd, *J* = 13.9, 7.1 Hz, 1H, H^6), 2.31 (d, *J* = 14.9 Hz, 1H, H^4), 2.00 (s, 3H, OAc), 1.94 (d, *J* = 14.9 Hz, 1H , H^4), 1.23 (s, 3H, CH_3), 1.20 (s, 3H, CH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 169.4 (C, C=O), 148.9 (CH, C^2), 132.8 (CH, C^7), 131.7 (CH, C^{Ar}), 128.5 (CH, C^{Ar}), 128.3 (CH, C^{Ar}), 122.9 (C, C^{Ar}), 119.0 (CH_2, C^1), 109.6 (CH_2, C^8), 89.3 (C, C^9), 87.5 (C, C^{10}), 78.0 (C, C^5), 49.6 (CH_2, C^4), 45.0 (CH_2, C^6), 37.0 (C, C^3), 28.6 (CH_3, Me), 28.2 (CH_3, Me), 22.4 (CH_3, OAc). **IR (neat):** 3080, 2961, 2926, 2870, 2234, 1741, 1639, 1598, 1573, 1490, 1364 cm^{-1}. **Elemental analysis** calcd. (%) for $C_{20}H_{24}O_2$ (MW 296.40): C, 81.04; H, 8.16. Found: 81.34; H, 8.16.

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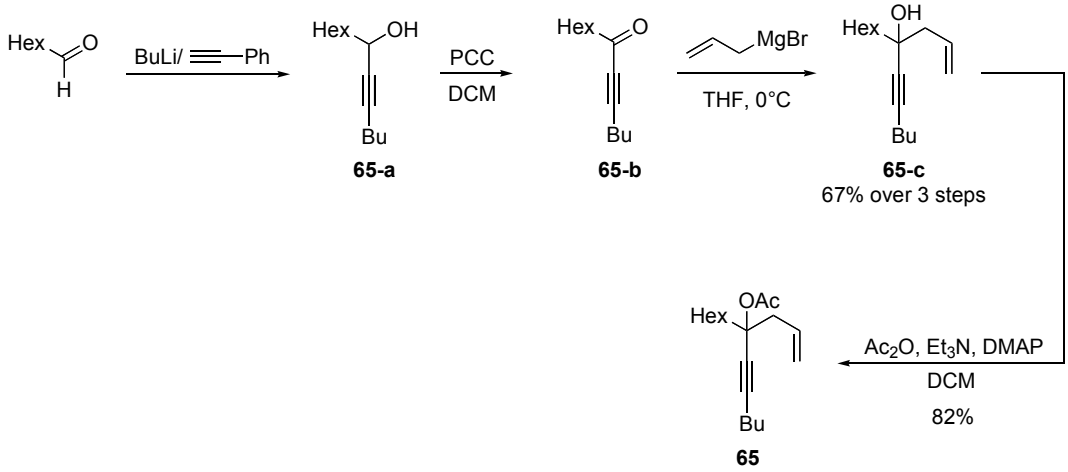
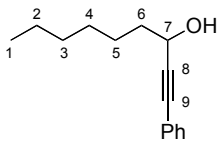
Preparation of enyne ***65***



1-Phenylnon-1-yn-3-ol (65-a)

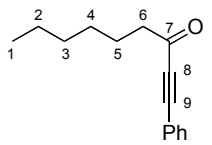


65-a

Phenylacetylene (4.3 mL, 39 mmol, 1.3 equiv) and BuLi (1.6 M in hexanes, 22.5 mL, 36 mmol, 1.2 equiv) were added to THF (70 mL) at -78ºC and stirred for 20 minutes under argon. To the reaction mixture, heptaldehyde (4.2 mL, 30 mmol, 1.0 equiv) was added and the reaction stirred at room temperature for 20 minutes. The reaction was then quenched with a saturated NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give crude **65-a** as a crude yellow oil that was engaged in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.41 (m, 2H, H^{Ar}), 7.32–7.24 (m, 3H, H^{Ar}), 4.58 (t, *J* = 6.6 Hz, H, H^7), 2.93 (s broad, 1H, -OH), 1.84–1.73 (m, 2H, H^6), 1.53–1.29 (m, 8H, H^5 + H^4 + H^3 + H^2), 0.88 (t, *J* = 6.5 Hz, 3H, H^1). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 132.2 (CH, C^{Ar}), 131.7 (CH, C^{Ar}), 128.3 (CH, C^{Ar}), 123.0 (C, C^{Ar}), 90.7 (C, C^8), 84.7 (C, C^9), 62.9 (CH, C^7), 38.0 (CH_2), 31.8 (CH_2), 29.1 (CH_2), 25.3 (CH_2), 22.6 (CH_2), 14.1 (CH_3, C^1).

1-Phenylnon-1-yn-3-one (65-b)



65-b

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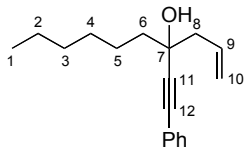
PCC (9.70 g, 45 mmol, 1.5 equiv) and neutral alumina (48.5 g) were added to a solution of DCM (90 mL) and 1-phenylnon-1-yn-3-ol **65-a** (30 mmol, 1.0 equiv) and the resulting suspension was refluxed overnight. The reaction was then allowed to cool down to room temperature, filtered through Celite and concentrated to give crude **65-b** as a crude yellow oil that was engaged in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, *J* = 5.4 Hz, 2H, H^{Ar}), 7.44–7.37 (m, 3H, H^{Ar}), 2.65 (t, *J* = 7.5 Hz, 2H, H^6), 1.73–1.71 (m, 2H, H^5), 1.36–1.28 (m, 6H, $H^4 + H^3 + H^2$), 0.89 (t, *J* = 6.6 Hz, 3H, H^1). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 188.2 (C, C^7), 133.1 (CH, C^{Ar}), 130.7 (CH, C^{Ar}), 128.7 (CH, C^{Ar}), 120.2 (C, C^{Ar}), 90.5 (C, C^8), 88.0 (C, C^9), 45.6 (CH_2, C^6), 31.6 (CH_2), 28.8 (CH_2), 24.3 (CH_2), 22.6 (CH_2), 14.1 (CH_3, C^1).

4-(Phenylethynyl)dec-1-en-4-ol (65-c)



65-c

1-Phenylnon-1-yn-3-one **65-b** (15.4 mmol, 1.0 equiv) in THF (60.8 mL) was stirred under argon at -78°C. Allylmagnesium bromide (2.0 M in diethyl ether, 9.25 mL, 18.5 mmol, 1.2 equiv) was added to the solution and the reaction mixture stirred at room temperature for 30 minutes. The reaction was then quenched with a saturated NH_4Cl solution and extracted with petroleum ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give a crude oil that was purified by flash chromatography on silica gel (pentane/diethyl ether, 9/10) affording 2.64 g (67% over 3 steps) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.40 (m, 2H, H^{Ar}), 7.32–7.24 (m, 3H, H^{Ar}), 6.01-5.98 (m, 1H, H^9), 5.21 (dt, *J* = 10.5, 6.9 Hz, 2H, H^{10}), 2.62-2.55 (m, 1H, H^8), 2.46-2.39 (m, 1H, H^8), 2.43 (s broad, 1H, OH), 1.76–1.71 (m, 2H, H^6), 1.61–1.54 (m, 2H, H^5), 1.38-1.33 (m, 6H, $H^2 + H^3 + H^4$), 0.89 (t, *J* = 6.0 Hz, 3H, H^1). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 137.4 (CH, C^9), 132.2 (CH, C^{Ar}), 131.7 (CH, C^{Ar}), 128.3 (CH, C^{Ar}), 123.0 (C, C^{Ar}), 116.8 (CH_2, C^{10}), 90.7 (C, C^{11}), 84.7 (C, C^{12}), 62.9 (C, C^7), 42.3 (CH_2, C^8), 38.0 (CH_2, C^6), 31.8 (CH_2), 29.1 (CH_2), 25.3 (CH_2), 22.6 (CH_2), 14.1 (CH_3, C^1).

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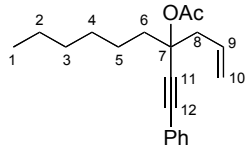
4-(Phenylethynyl)dec-1-en-4-yl acetate (65)



65

Alcohol **65-c** (512 mg, 2 mmol, 1.0 equiv), DCE (6 mL), DMAP (52 mg, 0.6 mmol, 0.3 equiv), Et_3N (1.3 mL, 8 mmol, 4 equiv), and Ac_2O (0.36 mL, 4 mmol, 2 equiv) were added in turn in a round-bottom flask equipped with a condenser. The reaction mixture was heated overnight at 80°C. The reaction was then quenched with a saturated aqueous NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give a crude oil that was purified by flash chromatography on silica gel (pentane/MTBE, 95/5) affording 489 mg (82%) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.40 (m, 2H, H^{Ar}), 7.29-7.24 (m, 3H, H^{Ar}), 5.96-5.86 (m, 1H, H^9), 519-5.14 (m, 2H, H^{10}), 2.91-2.79 (m, 2H, H^8), 2.10-2.02 (m, 1H, $1H^6$), 2.03 (s, 3H, OAc), 1.95-1.87 (m, 1H, $1H^6$), 1.56–1.49 (m, 2H, H^5), 1.38-1.24 (m, 6H, $H^2 + H^3 + H^4$), 0.89 (t, J = 6.6 Hz, 3H, H^1). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.2 (C, C=O), 132.4 (CH, C^9), 131.7 (CH, C^{Ar}), 128.2 (CH, C^{Ar}), 128.0 (CH, C^{Ar}), 122.5 (C, C^{Ar}), 118.6 (CH_2, C^{10}), 88.5 (C, C^{11}), 86.1 (C, C^{12}), 78.3 (C, C^7), 42.6 (CH_2, C^8), 38.2 (CH_2, C^6), 31.6 (CH_2), 29.0 (CH_2), 23.8 (CH_2), 22.5 (CH_2), 21.7 (CH_3, OAc), 13.9 (CH_3, C^1). **Elemental analysis** calcd. (%) for $C_{20}H_{26}O_2$ (MW 298.42): C, 80.50; H, 8.78. Found: 80.34; H, 8.76.

3. Synthesis and characterization of allenyl acetates 62 and 76

General procedure: To a suspension of $AgBF_4$ (5 mg, 0.05 mmol, 5 mol %) in DCM (10 mL) in a scintillation vial equipped with a stir bar, a 5 mL solution of propargylic acetate (1 mmol) in DCM was added, in the absence of light. When TLC analysis showed total consumption of the starting material, the solvent was removed. The resulting mixture was dissolved in pentane, filtered through Celite and concentrated. The crude oil was purified, when necessary, by flash chromatography on silica gel.

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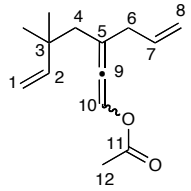
3-Allyl-5,5-dimethylhepta-1,2,6-trienyl acetate (62)

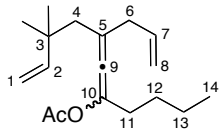


62

The general procedure, using propargylic acetate **56** (440 mg, 2.0 mmol), gave a crude oil that was purified by flash chromatography on silica gel (pentane/DCM, 90/10), yielding 408 mg (93%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (s, 1H, H^{10}), 5.83 (dd, *J* = 17.6, 10.8 Hz, 1H, H^{2}), 5.80-5.71 (m, 1H, H^{7}), 5.08-5.04 (m, 2H, $=CH_2$), 4.96-4.91 (m, 2H, $=CH_2$), 2.83 (m, 2H, $2H^{6}$), 2.13 (s, 3H, $3H^{12}$), 1.69 (m, 2H, $2H^{4}$), 1.063 (s, 3H, Me), 1.058 (s, 3H, Me). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 192.6 (C, C^{9}), 169.0 (C, C^{11}), 147.9 (CH, C^{7}), 135.2 (CH, C^{2}), 116.8 (CH_2, C^{8}), 115.7 (C, C^{5}), 111.02 (CH, C^{10}), 110.97 (CH_2, C^{1}), 46.3 (CH_2, C^{6}), 40.5 (CH_2, C^{4}), 37.7 (C, C^{3}), 27.1 (CH_3, Me), 27.0 (CH_3, Me), 21.1 (CH_3, C^{12}). **Elemental analysis** calcd. (%) for $C_{14}H_{20}O_2$ (MW 222.40): C, 76.33; H, 9.15. Found: C, 76.49; H, 9.22.

7-Allyl-9,9-dimethylundeca-5,6,10-trien-5-yl acetate (76)



76

The general procedure, using propargylic acetate **63** (442 mg, 1.6 mmol), yielded 420 mg (95%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 (dd, *J* = 17.4, 10.7 Hz, 1H, H^{2}), 5.86-5.75 (m, 1H, H^{7}), 5.05-5.00 (m, 2H, $2H^{8}$), 4.91 (dd, *J* = 17.5, 1.4 Hz, 1H, $1H^{1}$), 4.89 (dd, *J* = 11.4, 1.4 Hz, 1H, $1H^{1}$), 2.87-2.73 (m, 2H, $2H^{6}$), 2.25-2.13 (m, 2H, $2H^{11}$), 2.08 (s, 3H, OAc), 1.43-1.32 (m, 4H, $2H^{12}$ + $2H^{13}$), 1.04 (s, 3H, Me), 1.03 (s, 3H, Me), 0.89 (t, *J* = 7.1 Hz, 3H, $3H^{14}$). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 193.9 (C, C^{9}), 168.6 (C, C=O), 148.0 (CH, C^{7}), 135.6 (CH, C^{2}), 123.6 (C, C^{10}), 116.0 (CH_2, C^{8}), 111.7 (CH_2, C^{1}), 110.3 (C, C^{5}), 46.1 (CH_2, C^{6}), 40.3 (CH_2, C^{4}), 37.4 (C, C^{3}), 31.5 (CH_2, C^{11}), 28.5 (CH_2), 27.0 (CH_3), 26.8 (CH_3), 22.1 (CH_2), 21.0 (CH_3, OAc), 13.8 (CH_3, C^{14}). **Calcd. HMRS** for $C_{18}H_{28}O_2Na$ (M+Na): 299.1987. Found: 299.1990.

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4. Au-Catalyzed cycloisomerization reactions

General procedure: To a solution of gold catalyst (2 mol %) in DCM (5 mL) in a scintillation vial equipped with a stir bar, a silver(I) salt (*if required*) was added. The solution instantly became cloudy. A solution of enyne or allenyl acetate in DCM was then added (total volume of DCM calculated to obtain a 0.025 M solution). After consumption of the starting material (reaction monitored by TLC), the solvent was removed. The resulting mixture was dissolved in pentane, filtered through Celite and the filtrate reduced *in vacuo*. The crude oil was purified, when necessary, by flash chromatography on silica gel.

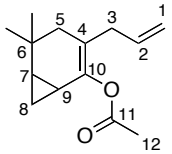
For the examination of the reaction parameters using **56** or **62** (Tables 23-28), yields are mixtures of isolated products, ratios are based on ^{1}H NMR integration.

*Cycloisomerized products **59-61***

A) The general procedure, employing dienyne **56** (222 mg, 1 mmol) and [(IPr)AuCl] **Au3**/$AgBF_4$ as catalytic system, yielded, after purification by flash chromatography on silica gel (pentane/Et_2O, 98/2), 67 mg (30%) of **59**, 27 mg (12%) of **60** and 93 mg (42%) of **61**.

B) The general procedure, employing allenyl acetate **62** (90 mg, 0.4 mmol) and [(IPr)AuCl] **Au3**/$AgBF_4$ as catalytic system, yielded, after filtration through a plug of Celite, 84 mg (93%) of a 1/1.4/9.3 mixture of **59**:**60**:**61**.

Acetic acid 3-allyl-5,5-dimethyl-bicyclo[4.1.0]hept-2-en-2-yl ester (59)[272]



59

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.56 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, H^2), 4.95 (d, *J* = 17.0 Hz, 1H, H^1 *trans*), 4.93 (d, *J* = 10.0 Hz, 1H, H^1 *cis*), 2.63 (dd, ***J* =** 14.8, 6.4 Hz, 1H, H^3), 2.50 (dd, ***J* =** 14.8, 6.4 Hz, 1H, H^3), 2.13 (s, 3H, OAc), 1.61 (m_{AB}, 2H, H^5), 1.21 (m, 1H, H^9), 1.05 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 0.96 (m, 1H, H^7), 0.77 (m, 1H, H^8), 0.66 (m, 1H, H^8). **^{13}C NMR (50 MHz, $CDCl_3$):** δ 169.4 (C, C^{11}), 143.4 (C, C^{10}), 135.4 (CH, C^2), 115.8 (CH_2, C^1), 114.6 (C, C^4), 37.9 (CH_2, C^3), 34.9 (CH_2, C^5), 29.5 (CH_3), 28.5 (CH_3), 28.0 (C, C^6), 26.6 (CH, C^7), 20.8 (CH_3, C^{12}), 13.6 (CH, C^9), 9.8 (CH_2, C^8). **Elemental analysis** calcd. (%) for $C_{14}H_{20}O_2$ (MW 222.40): C, 76.33; H, 9.15. Found: C, 76.29; H, 9.28.

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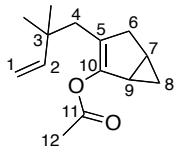
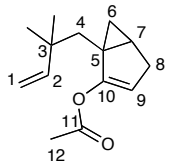
3-(2,2-Dimethylbut-3-enyl)bicyclo[3.1.0]hex-2-en-2-yl acetate (60)



60

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (dd, *J* = 17.6, 10.8 Hz, 1H, H^2), 4.89 (d, *J* = 17.6 Hz, 1H, H^1 *trans*), 4.87 (d, *J* = 10.8 Hz, 1H, H^1 *cis*), 2.60 (dd, *J* **=** 16.8, 7.6 Hz, 1H, H^6), 2.28 (d, *J* **=** 16.8 Hz, 1H, H^6), 2.17 (s, 3H, OAc), 1.90 (s, 2H, H^4), 1.54 (m, 1H, H^9), 1.02 (m, 1H, H^7), 0.97 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.82 (m, 1H, H^8), 0.25 (m, 1H, H^8). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.1 (C, C^{11}), 150.5 (C, C^{10}), 148.8 (CH, C^2), 120.6 (C, C^5), 110.3 (CH_2, C^1), 39.6 (CH_2, C^6), 37.9 (C, C^3), 36.4 (CH_2, C^4), 27.4 (CH_3), 27.3 (CH_3), 21.05 (CH, C^9), 20.97 (CH_3, C^{12}), 15.8 (CH_2, C^8), 12.9 (CH, C^7). **Elemental analysis** calcd. (%) for $C_{14}H_{20}O_2$ (MW 222.40): C, 76.33; H, 9.15. Found: C, 76.01; H, 9.06.

1-(2,2-Dimethylbut-3-enyl)bicyclo[3.1.0]hex-2-en-2-yl acetate (61)



61

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (dd, *J* = 17.6, 10.8 Hz, 1H, H^2), 5.08 (s, 1H, H^9), 4.91 (dd, *J* = 17.6, 1.2 Hz, 1H, H^1 *trans*), 4.85 (dd, *J* = 10.8, 1.2 Hz, 1H, H^1 *cis*), 2.61 (dd, *J* = 16.8, 6.8 Hz, 1H, $1H^8$), 2.30 (dd, *J* = 16.8, 2.0 Hz, 1H, $1H^8$), 2.19 (d, *J* = 14.8 Hz, 1H, $1H^4$), 2.18 (s, 3H, $3H^{12}$), 1.61-1.58 (m, 1H, H^7), 1.04 (s, 3H, Me), 1.03 (s, 3H, Me), 0.94 (d, *J* = 14.8 Hz, 1H, $1H^4$), 0.64 (dd, *J* = 8.4, 4.0 Hz, 1H, $1H^6$), 0.34-0.32 (m, 1H, $1H^6$). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 168.1 (C, C^{11}), 154.7 (C, C^{10}), 148.9 (CH, C^2), 109.6 (CH_2, C^1), 106.7 (CH, C^9), 43.4 (CH_2, C^8), 38.1 (C, C^5), 30.6 (CH_2, C^4), 30.1 (C, C^3), 27.6 (CH_3, Me), 26.9 (CH_3, Me), 21.8 (CH_2, C^6), 21.3 (CH_3, C^{12}), 19.5 (CH, C^7). **Elemental analysis** calcd. (%) for $C_{14}H_{20}O_2$ (MW 222.40): C, 76.33; H, 9.15. Found: C, 76.05; H, 8.94.

[The *p*-nitrobenzoate analogue of **61**, **61'**, was crystallized from a DCM/acetone/heptane solution. **CCDC-267108** contains the supplementary crystallographic data for this compound.]

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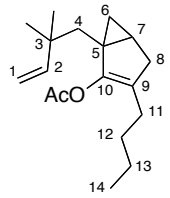
*Cycloisomerized product **67***

3-Butyl-1-(2,2-dimethylbut-3-enyl)bicyclo[3.1.0]hex-2-en-2-yl acetate (67)



67

A) The general procedure employing dienyne **66** (276 mg, 1 mmol) [(IPr)AuCl] **Au3**/$AgBF_4$ as catalytic system, yielded, after purification by flash chromatography on silica gel (pentane/MTBE, 95/5), 237 mg (0.86 mmol, 86% yield) of **67**.

B) The general procedure employing allenyl acetate **76** (138 mg, 0.5 mmol) [(IPr)AuCl] **Au3**/$AgBF_4$ as catalytic system, yielded, after filtration through a plug of silica, 137 mg (0.495 mmol, 99% yield) of **67**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.83 (dd, *J* = 17.1, 10.5 Hz, 1H, H^2), 4.86 (dd, *J* = 17.1, 10.5.2 Hz, 2H, H^1), 2.51 (dd, *J* = 16.8, 6.9 Hz, 1H, $1H^8$), 2.17 (s, 3H, OAc), 2.15 (d overlaping with OAc, 1H, $1H^8$), 1.97 (d, *J* = 15.0 Hz, 1H, $1H^4$), 1.91-1.52 (m, 2H, H^{11}), 1.58-1.51 (m, 1H, H^7), 1.28-1.21 (m, 4H, H^{12} + H^{13}), 1.03 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 0.93 (d, *J* = 14.8 Hz, 1H, $1H^4$), 0.86 (t, *J* = 6.6 Hz, 3H, H^{14}), 0.62 (dd, *J* = 7.8, 3.6 Hz, 1H, $1H^6$), 0.51-0.48 (m, 1H, $1H^6$). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 168.6 (C, C=O), 149.4 (CH, C^2), 148.9 (C, C^{10}), 122.0 (C, C^9), 109.5 (CH_2, C^1), 43.9 (CH_2, C^8), 38.2 (C, C^5), 33.0 (CH_2, C^4), 30.1 (C, C^3), 29.7 (CH_2, C^{11}), 28.2 (CH_3, Me), 26.8 (CH_3, Me), 26.1 (CH_2, C^{12}), 23.0 (CH_2, C^{13}), 22.4 (CH_2, C^6), 20.8 (CH_3, -OAc), 19.2 (CH, C^7), 14.0 (CH_3, C^{14}). **Elemental analysis** calcd. (%) for $C_{18}H_{28}O_2$ (MW 276.41): C, 78.21; H, 10.21. Found: C, 78.47; H, 10.31.

*Cycloisomerized products **69** and **70***

The general procedure, employing enyne **65** (298 mg, 1.0 mmol) and [(IPr)AuCl] **Au3**/$AgBF_4$ as catalytic system, yielded, after filtration through a plug of Celite, 295 mg (99%) of a 8/1mixture of **69**:**70**.

Structural assignment of **69** and **70** could be established after methanolysis of the vinyl acetate. The minor isomer displayed a triplet at δ = 3.38 ppm in the ^{1}H NMR spectrum, characteristic of a hydrogen in α-position of both a carbonyl function and an aryl.

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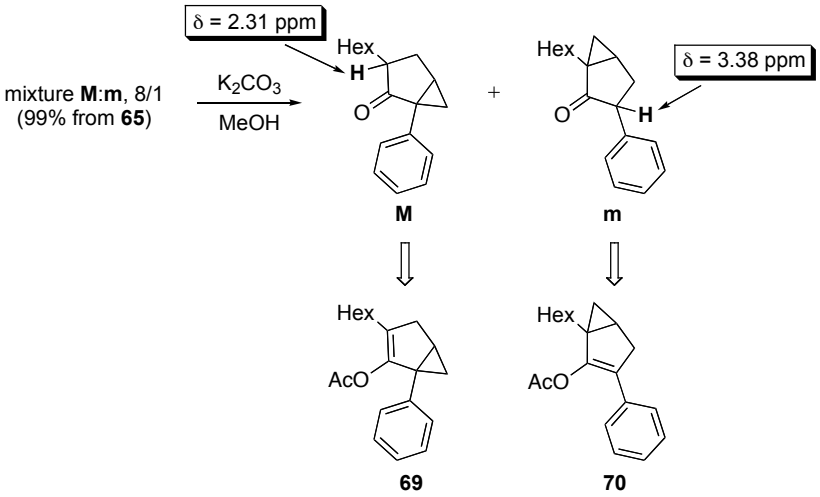
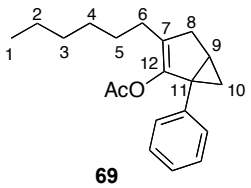


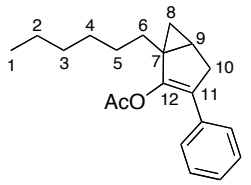
3-Hexyl-1-phenylbicyclo[3.1.0]hex-2-en-2-yl acetate (69)



69

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.23 (m, 4H, H^{Ar}), 7.19-7.17 (m, 1H, H^{Ar}), 2.70 (dd, *J* = 17.0, 8.4 Hz, 1H, $1H^8$), 2.29 (d, *J* = 17.0 Hz, 1H, $1H^8$), 2.02-1.89 (m, 2H, H^6), 1.95 (s, 3H, OAc), 1.69-1.64 (m, 1H, H^9), 1.57 (dd, *J* = 8.0, 4.4 Hz, 1H, $1H^{10}$), 1.37-1.23 (m, 8H, H^2 + H^3 H^4 + H^5), 0.95 (t, *J* = 4.4 Hz, 1H, H^{10}), 0.89 (t, *J* = 6.8 Hz, 3H, H^1). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 168.7 (C, C=O), 147.5 (C, C^{12}), 139.5 (C, C^7), 128.7 (CH, C^{Ar}), 128.3 (CH, C^{Ar}), 126.4 (CH, *p*-C^{Ar}), 124.7 (C, C^{Ar}), 37.1 (C, C^{11}), 33.6 (CH_2), 31.8 (CH_2), 29.2 (CH_2), 27.7 (CH_2), 26.6 (CH_2), 24.0 (CH, C^9), 22.8 (CH_2), 21.6 (CH_2), 20.6 (CH_3, OAc), 14.3 (CH_3, C^1). **Elemental analysis** calcd. (%) for $C_{20}H_{26}O_2$ (MW 298.42): C, 80.50; H, 8.78. Found: C, 80.27; H, 8.62.

1-Hexyl-3-phenylbicyclo[3.1.0]hex-2-en-2-yl acetate (70)



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.34 (m, 1H, H^{Ar}), 7.30-7.23 (m, 4H, H^{Ar}), 2.95 (dd, *J* = 16.2, 6.8 Hz, 1H, $1H^{10}$), 2.69 (d, *J* = 16.2 Hz, 1H, $1H^{10}$), 2.25 (s, 3H, OAc), 1.80-1.73 (m, 1H, H^6), 1.42-1.57 (m, 1H, H^9), 1.37-1.23 (m, 8H, H^{2-5}), 1,23-1,19 (m, 1H, H^6), 0.93-0.91

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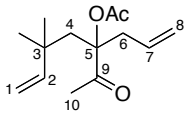
(m, 1H, H^8), 0.87 (t, *J* = 4.4 Hz, 3H, H^1), 0.72 (t, *J* = 4.0 Hz, 1H, H^8). **Elemental analysis** calcd. (%) for $C_{20}H_{26}O_2$ (MW 298.42): C, 80.50; H, 8.78. Found: C, 80.27; H, 8.62.

5. Characterization of compounds 74 and 75

4-Acetyl-6,6-dimethylocta-1,7-dien-4-yl acetate (74)

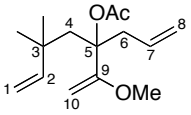


74

*Hydration of **56** in THF*. Following the general procedure for the cycloisomerization of **56** (1 mmol of **56** was engaged) in THF, and after purification by flash chromatography (pentane/*tert*-butylmethyl ether, 8:2), 164 mg (69% yield) of the title compound were isolated.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.72 (dd, *J* = 17.5, 10.8 Hz, 1H, H^2), 5.58-5.47 (m, 1H, H^7), 5.07-5.01 (m, 2H, H^8), 4.91-4.85 (m, 2H, H^1), 2.97 (dd, *J* = 14.4, 8.6 Hz, 1H, $1H^6$), 2.63 (dd, *J* = 14.4, 8.6 Hz, 1H, $1H^6$), 2.29 (d, *J* = 14.4, 1H, $1H^4$), 2.15 (s, 3H, H^{10}), 2.10 (d, *J* = 14.4, 1H, $1H^4$), 2.03 (s, 3H, OAc), 1.02 (s, 3H, CH_3), 0.97 (s, 3H, CH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 209.3 (C, C^9), 170.0 (C, O*C*(O)Me), 148.0 (CH, C^2), 131.3 (CH, C^7), 119.7 (CH_2, C^8), 110.6 (CH_2, C^1), 90.6 (C, C^5), 45.8 (CH_2, C^4), 41.2 (CH_2, C^6), 36.7 (C, C^3), 28.4 (CH_3, Me), 28.2 (CH_3, Me), 28.1 (CH_3, Me), 22.2 (CH_3, OAc). **Elemental analysis** calcd. (%) for $C_{14}H_{22}O_3$ (MW 238.32): C, 70.56; H, 9.30. Found: C, 70.60; H, 9.42.

4-Acetyl-6,6-dimethylocta-1,7-dien-4-yl acetate (75)



75

Trapping experiment in methanol. Following the general procedure for the cycloisomerization of **56** (1 mmol of **56** was engaged) in methanol, and after purification by flash chromatography (pentane/*tert*-butylmethyl ether, 8:2), 149 mg (59% yield) of the title compound were isolated.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.83 (dd, *J* = 17.6, 10.8 Hz, 1H, H^2), 5.62-5.51 (m, 1H, H^7), 5.01-4.96 (m, 2H, H^8), 4.84-4.77 (m, 2H, H^1), 4.38 (d, *J* = 2.0 Hz, 1H, $1H^{10}$), 4.04 (d, *J* = 2.0 Hz, 1H, $1H^{10}$), 3.50 (s, 3H, OMe), 3.07 (dd, *J* = 14.4, 8.8 Hz, 1H, $1H^6$), 2.54-2.47 (m, 2H, $1H^6$ + $1H^4$), 1.97 (s, 3H, OAc), 1.87 (d, *J* = 15.2 Hz, 1H, $1H^4$), 1.01 (s, 6H, $2CH_3$). **^{13}C NMR**

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($CDCl_3$, 100 MHz): δ 169.6 (C, O*C*(O)Me), 161.3 (C, *C*OMe), 148.4 (CH, C^2), 132.8 (CH, C^7), 117.9 (CH_2, C^8), 109.1 (CH_2, C^1), 85.3 (C, C^5), 82.2 (CH_2, C^{10}), 54.4 (CH_3, OMe), 44.8 (CH_2, C^4), 40.8 (CH_2, C^6), 37.0 (C, C^3), 27.8 (CH_3, Me), 27.4 (CH_3, Me), 22.7 (CH_3, OAc). **Elemental analysis** calcd. (%) for $C_{15}H_{24}O_3$ (MW 252.35): C, 71.39; H, 9.09. Found: C, 71.18; H, 9.15.

6. Computational details

All the Density Functional Theory (DFT) calculations were performed using the Gaussian03 package.[401] The BP86 GGA functional of Becke and Perdew was used.[402] The TZVP triple-ζ basis set with one polarization function was used for main group atoms,[403] while the relativistic SDD effective core potential in combination with a triple-ζ basis set was used for the Au atom.[404] All geometries were verified by frequency calculations that resulted in 0 and 1 imaginary frequency for intermediates and transition states, respectively. The reported energies include the vibrational gas-phase zero-point energy term. Solvent effects have been obtained through single-point calculations on the gas-phase optimized geometries. The polarizable continuous solvation model IEF-PCM as implemented in the Gaussian03 package has been used.[405] CH_2Cl_2 was chosen as model solvent, with a dielectric constant ε = 8.93. Standard non-electrostatic terms were also included.

[401] Gaussian 03; Gaussian, Inc.: Pittsburgh, PA, 2003.
[402] (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3100. (b) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822–8824. (c) Perdew, J. P. *Phys. Rev. B* **1986**, *34*, 7406.
[403] (a) Schaefer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571–2577. (b) Schaefer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829–5835.
[404] (a) Haeusermann, U.; Dolg, M.; Stoll, H.; Preuss, H. *Mol. Phys.* **1993**, *78*, 1211–1224. (b) Kuechle, W.; Dolg, M.; Stoll, H.; Preuss, H. *J. Chem. Phys.* **1994**, *100*, 7535. (c) Leininger, T.; Nicklass, A.; Stoll, H.; Dolg, M.; Schwerdtfeger, P. *J. Chem. Phys.* **1996**, *105*, 1052–1059.
[405] (a) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327–335. (b) Cancès, M. T.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032–3041. (c) Cossi, M.; Barone, V.; Mennucci, B.; Tomasi, J. *Chem. Phys. Lett.* **1998**, *286*, 253–260.

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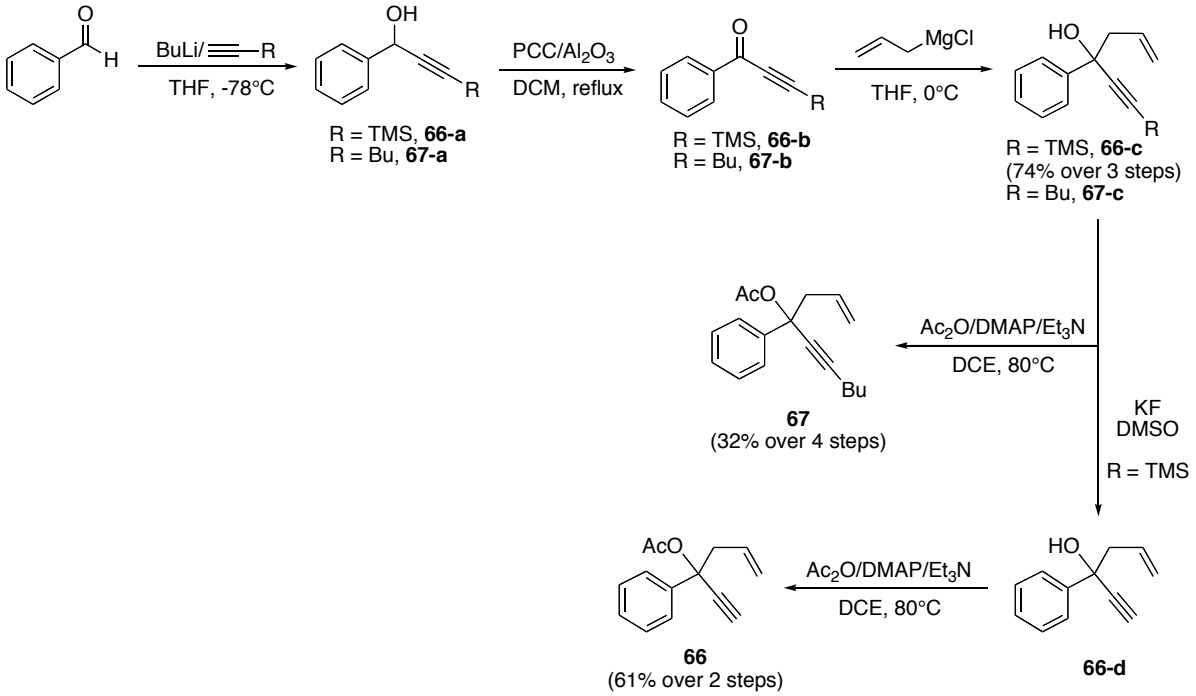
C. Formation of indenes from arylpropargyl acetates

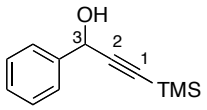
1. Synthesis and characterization of arylpropargyl acetates 66, 67, 77, 81-86, and 96

*Preparation of compounds **66** and **67***



*Synthesis of precursor **66***

1-Phenyl-3-trimethylsilyl-prop-2-yn-1-ol (66-a)



66-a

Trimethylsilylacetylene (5.5 mL, 39 mmol, 1.3 equiv) and BuLi 1.6 M (22.5 mL, 36 mmol, 1.2 equiv) were added to THF (70 mL) at -78ºC and stirred for 20 minutes under argon. Then, benzaldehyde (3.0 mL, 30 mmol, 1.0 equiv) was added and the reaction stirred at room temperature for 20 minutes. The reaction was then quenched with saturated NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give **66-a** as a pale yellow oil that was engaged in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.8 Hz, 2H, H^{Ar}), 7.35–7.27 (m, 3H, H^{Ar}), 5.39 (s, 1H, H^3), 3.18 (s broad, 1H, OH), 0.19 (s, 9H, TMS). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 140.6 (C, C^{Ar}), 128.6 (CH, C^{Ar}), 128.3 (CH, C^{Ar}), 126.8 (CH, C^{Ar}), 105.5 (C, C^2), 91.2 (C, C^1), 64.8 (CH, C^3), 0.12 (CH_3, TMS).

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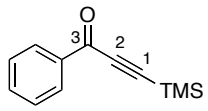
1-Phenyl-3-trimethylsilyl-propynone (66-b)

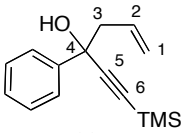


66-b

PCC (9.70 g, 45 mmol, 1.5 equiv) and neutral alumina (48.5 g) were added to a solution of DCM (90 mL) and 1-phenyl-3-trimethylsilylprop-2-yn-1-ol **66-a** (30 mmol, 1.0 equiv). The reaction mixture was refluxed overnight and then allowed to cool down to room temperature. The reaction mixture was filtered through Celite and concentrated to give **66-b** as a yellow oil that was engaged in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, *J* = 6.9 Hz, 2H, H^{Ar}), 7.62–7.45 (m, 3H, H^{Ar}), 0.32 (s, 9H, TMS). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 177.5 (C, C=O), 136.5 (C, C^{Ar}), 134.2 (CH, C^{Ar}), 129.6 (CH, C^{Ar}), 128.6 (CH, C^{Ar}), 100.9 (C, C^2), 100.4 (C, C^1), 0.02 (CH_3, TMS).

3-Phenyl-1-trimethylsilyl-hex-5-en-1-yn-3-ol (66-c)



66-c

To a solution of 1-phenyl-3-trimethylsilyl-propynone **66-b** (26.9 mmol, 1.0 equiv) in THF (57.7 mL) at -78°C, allylmagnesium bromide (1.8 M in diethyl ether, 18.3 mL, 32.3 mmol, 1.2 equiv) was added and the reaction mixture stirred at room temperature for 30 minutes. The reaction was then quenched with a saturated NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give **66-c** as an oil that was purified by flash chromatography on silica gel (pentane/MTBE, 90:10) affording 4.89 g (74% over 3 steps) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, *J* = 5.1 Hz, 2H, H^{Ar}), 7.37–7.24 (m, 3H, H^{Ar}), 5.91–5.82 (m, 1H, H^2), 5.12 (dt, *J* = 17.1, 8.7 Hz, 2H, H^1), 2.73 (s broad, 1H, OH), 2.62 (d, *J* = 3.0 Hz, 2H, H^3), 0.21 (s, 9H, TMS). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 144.1 (C, C^{Ar}), 133.2 (CH, C^2), 128.2 (CH, C^{Ar}), 127.8 (CH, C^{Ar}), 125.6 (CH, C^{Ar}), 119.7 (CH_2, C^1), 107.7 (C, C^5), 91.0 (C, C^6), 72.6 (C, C^4), 50.3 (CH_2, C^3), 0.1 (CH_3, TMS).

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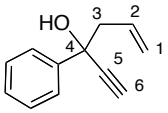
3-Phenylhex-5-en-1-yn-3-ol (66-d)

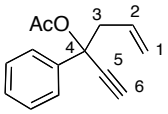


66-d

3-Phenyl-1-trimethylsilyl-hex-5-en-1-yn-3-ol **66-c** (20 mmol, 1.0 equiv), KF (2.18 g, 37.5 mmol, 1.5 equiv), DMSO (75 mL) and a few drops of water were stirred for 20 minutes. The reaction was then quenched with water and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give **66-d** as a pale yellow oil that was engaged in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, *J* = 3.2 Hz, 2H, H^{Ar}), 7.33–7.24 (m, 3H, H^{Ar}), 5.80-5.68 (m, 1H, H^{2}), 5.08-4.99 (m, 2H, H^{1}), 2.90 (dd, *J* = 13.6, 7.0 Hz, 1H, $1H^{3}$), 2.76 (s, 1H, H^{6}), 2.73 (dd, *J* = 13.6, 7.0 Hz, 1H, $1H^{3}$). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 140.3 (C, C^{Ar}), 131.9 (CH, C^{2}), 128.3 (CH, C^{Ar}), 127.3 (CH, C^{Ar}), 125.2 (CH, C^{Ar}), 118.7 (CH_2, C^{1}), 84.6 (C, C^{5}), 80.8 (C, C^{4}), 78.3 (CH, C^{6}), 47.9 (CH_2, C^{3}).

3-Phenylhex-5-en-1-yn-3-yl acetate (66)



66

In a round-bottom flask equipped with a condenser, 3-phenylhex-5-en-1-yn-3-ol **66-d** (19.2 mmol, 1.0 equiv), DCE (60 mL), DMAP (0.704 g, 5.76 mmol, 0.3 equiv), Et_3N (10.7 mL, 76.8 mmol, 4 equiv), and Ac_2O (3.6 mL, 38.4 mmol, 2 equiv) were added in turn and the reaction mixture was refluxed overnight at 80°C. The reaction was then quenched with a saturated NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give an oil that was purified by flash chromatography on silica gel (95:5, pentane/MTBE), affording 2.62 g (61% over 2 steps) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (dd, *J* = 3.3, 1.5 Hz, 2H, H^{Ar}), 7.35–7.20 (m, 3H, H^{Ar}), 5.76-5.67 (m, 1H, H^{2}), 5.09-5.00 (m, 2H, H^{1}), 2.90 (dd, *J* = 13.8, 6.9 Hz, 1H, $1H^{3}$), 2.82 (s, 1H, H^{6}), 2.74 (dd, *J* = 13.8, 6.9 Hz, 1H, $1H^{3}$), 2.04 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 168.3 (C, C=O), 140.6 (C, C^{Ar}), 131.6 (CH, C^{2}), 128.3 (CH, C^{Ar}), 127.9 (CH, C^{Ar}), 125.3 (CH, C^{Ar}), 119.4 (CH_2, C^{1}), 81.6 (C, C^{5}), 77.8 (C, C^{4}), 76.9 (CH, C^{6}), 48.4 (CH_2, C^{3}),

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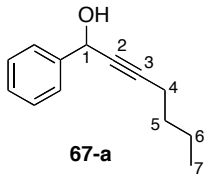
21.6 (CH_3, OAc). **Elemental analysis** calcd. (%) for $C_{14}H_{14}O_2$ (MW 214.26): C, 78.48; H, 6.59. Found: C, 78.50; H, 6.60.

*Synthesis of precursor **67***

1-Phenylhept-2-yn-1-ol (67-a)

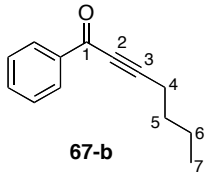


67-a

In an oven-dried round-bottom flask, 1-hexyne (1.5 mL, 13 mmol, 1.3 equiv) and BuLi (1.6 M in hexanes, 7.5 mL, 12 mmol, 1.2 equiv) were added to THF (20 mL) at -78ºC and stirred for 20 minutes under argon. To the reaction mixture, benzaldehyde (1.0 mL, 10 mmol, 1.0 equiv) was added and the reaction stirred for 20 minutes. The reaction was then allowed to warm up to room temperature, quenched with a saturated aqueous NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give **67-a** as a yellow oil that was engaged in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, *J* = 7.8 Hz, 2H, H^{Ar}), 7.38-7.24 (m, 3H, H^{Ar}), 5.41 (s, 1H, H^1), 2.75 (s broad, 1H, OH), 2.25 (dt, *J* = 6.9, 2.1 Hz, 2H, H^4), 1.57-1.35 (m, 4H, H^5 + H^6), 0.93 (t, *J* = 15.4 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 141.6 (C, C^{Ar}), 128.5 (CH, C^{Ar}), 128.1 (CH, C^{Ar}), 126.7 (CH, C^{Ar}), 87.4 (C, C^3), 80.2 (C, C^2), 64.7 (CH, C^1), 30.8 (CH_2, C^4), 22.1 (CH_2, C^5), 18.6 (CH_2, C^6), 13.7 (CH_3, C^7).

1-Phenylhept-2-yn-1-one (67-b)



67-b

PCC (3.25 g, 15 mmol, 1.5 equiv) and neutral alumina (16 g) were added to a solution of 1-phenylhept-2-yn-1-ol **67-a** (10 mmol, 1.0 equiv) in DCM (30 mL) and the resulting suspension was refluxed overnight. The reaction mixture was then allowed to cool down to room temperature, filtered through Celite and concentrated. The obtained brownish residue

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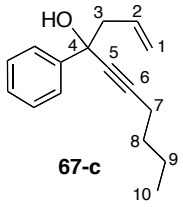
was dissolved in pentane, filtered through Celite and concentrated to give crude **67-b** as a pale yellow oil that was engaged in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.1 Hz, 2H, H^{Ar}), 7.57-7.43 (m, 3H, H^{Ar}), 2.48 (t, *J* = 7.1 Hz, 2H, H^4), 1.67-1.59 (m, 2H, H^5), 1.52–1.45 (m, 2H, H^6), 0.95 (t, *J* = 8.1 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 178.1 (C, C^1), 137.0 (C, C^{Ar}), 133.8 (CH, C^{Ar}), 129.5 (CH, C^{Ar}), 128.5 (CH, C^{Ar}), 96.7 (C, C^3), 79.7 (C, C^2), 29.9 (CH_2, C^4), 22.1 (CH_2, C^5), 18.9 (CH_2, C^6), 13.5 (CH_3, C^7).

4-Phenyldec-1-en-5-yn-4-ol (67-c)

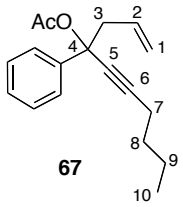


67-c

To a solution of 1-phenylhept-2-yn-1-one **67-b** (10 mmol, 1.0 equiv) in THF (40 mL) under argon at -78°C, allylmagnesium bromide (1.0 M in diethyl ether, 12.0 mL, 12 mmol, 1.2 equiv) was added and the reaction mixture stirred at room temperature for 30 minutes. The reaction was then quenched with a saturated aqueous NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give **67-c** as a crude yellow oil that was engaged in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, *J* = 5.4 Hz, 2H, H^{Ar}), 7.36-7.22 (m, 3H, H^{Ar}), 5.92-5.81 (m, 1H, H^2), 5.12 (dt, *J* = 15.7, 9.4 Hz, 2H, H^1), 2.63-2.61 (m, 3H, H^3 + OH), 2.28 (t, *J* = 7.1 Hz, 2H, H^7), 1.58-1.37 (m, 4H, H^8 + H^9), 0.92 (t, *J* = 7.2 Hz, 3H, H^{10}). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 144.9 (C, C^{Ar}), 133.5 (CH, C^2), 128.1 (CH, C^{Ar}), 127.6 (CH, C^{Ar}), 125.6 (CH, C^{Ar}), 119.3 (CH_2, C^1), 87.1 (C, C^5), 82.5 (C, C^6), 72.3 (C, C^4), 50.5 (CH_2, C^3), 30.9 (CH_2, C^7), 22.1 (CH_2, C^8), 18.5 (CH_2, C^9), 13.7 (CH_3, C^{10}).

1-Allyl-1-phenylhept-2-ynyl acetate (67)



67

4-Phenyldec-1-en-5-yn-4-ol **67-c** (10 mmol, 1.0 equiv), DCE (30 mL), DMAP (0.360 g, 3.0

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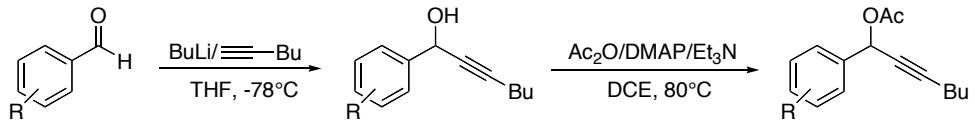
mmol, 0.3 equiv), Et_3N (5.6 mL, 40 mmol, 4 equiv), and Ac_2O (1.8 mL, 20 mmol, 2 equiv) were added in turn in a round-bottom flask equipped with a condenser. The reaction mixture was heated overnight at 80°C. The reaction was then quenched with a saturated aqueous NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give **67** as a crude oil that was purified by flash chromatography on silica gel (pentane/MTBE, 90/10) affording 1.43 g (53% over 4 steps) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.1 Hz, 2H, H^{12}), 7.34-7.22 (m, 3H, H^{13} + H^{14}), 5.79-5.66 (m, 1H, H^9), 5.03 (dt, *J* = 16.5, 8.4 Hz, 2H, H^{10}), 2.91-2.84 (m, 1H, H^8), 2.73-2.66 (m, 1H, H^8), 2.33 (t, *J* = 6.9 Hz, 2H, H^4), 2.04 (3H, OAc), 1.61-1.39 (m, 4H, H^2 + H^3), 0.93 (t, *J* = 7.4 Hz, 3H, H^1). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 168.5 (C, C=O), 141.8 (C, C^{Ar}), 132.4 (CH, C^2), 128.2 (CH, C^{Ar}), 127.7 (CH, C^{Ar}), 125.5 (CH, C^{Ar}), 118.9 (CH_2, C^1), 89.7 (C, C^5), 78.6 (C, C^6), 72.3 (C, C^4), 49.0 (CH_2, C^3), 30.9 (CH_2, C^7), 22.1 (CH_2, C^8), 18.7 (CH_2, C^9), 13.7 (CH_3, C^{10}). **Elemental analysis** calcd. **(%)** for $C_{18}H_{22}O_2$ (MW 270.37): C, 79.96; H, 8.20. Found: C, 79.70; H, 8.10.

*Preparation of arylpropargyl acetates **77**, and **81-86***



77, **81-86**

Representative Procedure: **1-Phenylhept-2-ynyl acetate (77)**

In an oven-dried round-bottom flask, 1-hexyne (1.5 mL, 13 mmol, 1.3 equiv) and BuLi (1.6 M in hexanes, 7.5 mL, 12 mmol, 1.2 equiv) were added to THF (20 mL) at -78ºC and stirred for 20 minutes under argon. Then, benzaldehyde (1.0 mL, 10 mmol, 1.0 equiv) was added and the reaction was stirred for 20 minutes. The reaction was then allowed to warm up to room temperature, quenched with a saturated aqueous NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give crude **66-c** as a yellow oil that was engaged in the next step without further purification.

1-Phenyl-hept-2-yn-1-ol **66-c** (10 mmol, 1.0 equiv), 1,2-dichloroethane (DCE) (30 mL), DMAP (0.360 g, 3.0 mmol, 0.3 equiv), Et_3N (5.6 mL, 40 mmol, 4 equiv), and Ac_2O (1.8 mL,

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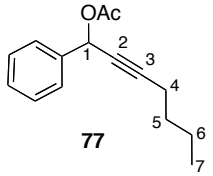
20 mmol, 2 equiv) were added in turn to a round-bottom flask equipped with a condenser. The reaction mixture was heated overnight at 80°C, then quenched with a saturated aqueous NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give a crude oil that was purified by flash chromatography on silica gel (pentane/MTBE, 95/5) affording 1.75 g (76% over 2 steps) of the title compound.

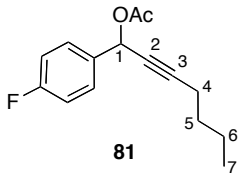
1-Phenylhept-2-ynyl acetate (77)



77

The above general procedure yielded, after flash chromatography on silica gel (pentane/MTBE, 95/5), 1.75 g (76% over 2 steps) of the title compound as a pale yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (t, *J* = 8.1 Hz, 2H, H^{Ar}), 7.40-7.33 (m, 3H, H^{Ar}), 6.46 (s, 1H, H^1), 2.26 (dt, *J* = 6.6, 1.8 Hz, 2H, H^4), 2.08 (s, 3H, OAc), 1.55-1.47 (m, 2H, H^5), 1.44-1.36 (m, 2H, H^6), 0.90 (t, *J* = 7.5 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.7 (C, C=O), 137.8 (C, C^{Ar}), 128.7 (CH, C^{Ar}), 128.6 (CH, C^{Ar}), 127.7 (CH, C^{Ar}), 88.3 (C, C^2), 76.9 (C, C^3), 66.1 (CH, C^1), 30.5 (CH_2, C^4), 22.0 (CH_2, C^5), 21.1 (CH_3, OAc), 18.5 (CH_2, C^6), 13.6 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{15}H_{18}O_2$ (MW 230.30): C, 78.23; H, 7.88. Found: C, 78.00; H, 8.04.

1-(4-Fluorophenyl)hept-2-ynyl acetate (81)



81

The above general procedure yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 2.06 g (83% over 2 steps) of the title compound as a pale yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53-7.49 (m, 2H, H^{Ar}), 7.08-7.03 (m, 2H, H^{Ar}), 6.44 (t, *J* = 2.0 Hz, 1H, H^1), 2.28 (dt, *J* = 6.9, 2.0 Hz, 2H, H^4), 2.09 (s, 3H, OAc), 1.58-1.48 (m, 2H, H^5), 1.44-1.35 (m, 2H, H^6), 0.91 (t, *J* = 7.5 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.0 (C, C=O), 163.1 (d, *J* = 246 Hz, C, C–F), 133.8 (C, C^{Ar}), 129.8 (d, *J* = 8.4 Hz, CH, C^{Ar}), 115.6

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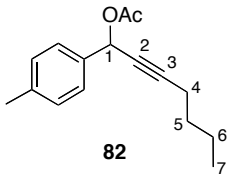
(d, J = 21.6 Hz, CH, C^{Ar}), 88.8 (C, C^3), 76.7 (C, C^2), 65.5 (CH, C^1), 30.6 (CH_2, C^4), 22.1 (CH_2, C^5), 21.3 (CH_3, OAc), 18.7 (CH_2, C^6), 13.7 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{15}H_{17}FO_2$ (MW 248.29): C, 72.56; H, 6.90. Found: C, 72.62; H, 7.05.

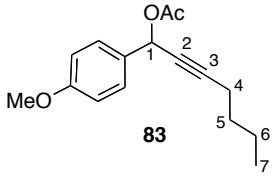
1-*p*-Tolylhept-2-ynyl acetate (82)



82

The above general procedure yielded, after flash chromatography on silica gel (pentane/MTBE, 95/5), 2.17 g (89% over 2 steps) of the title compound as a pale yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, J = 8.0 Hz, 2H, H^{Ar}), 7.17 (d, J = 8.0 Hz, 2H, H^{Ar}), 6.43 (t, J = 2.0 Hz, 1H, H^1), 2.35 (s, 3H, C^{Ar}–CH_3), 2.26 (dt, J = 7.0, 2.0 Hz, 2H, H^4), 2.07 (s, 3H, OAc), 1.57-1.46 (m, 2H, H^5), 1.45-1.34 (m, 2H, H^6), 0.90 (t, J = 7.2 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.1 (C, C=O), 138.8 (C, C^{Ar}), 135.0 (C, C^{Ar}), 129.4 (CH, C^{Ar}), 127.9 (CH, C^{Ar}), 88.3 (C, C^2), 77.0 (C, C^3), 66.1 (CH, C^1), 30.7 (CH_2, C^4), 22.1 (CH_2, C^5), 21.4 (CH_3 (2 peaks overlaping), OAc + C^{Ar}–CH_3), 18.7 (CH_2, C^6), 13.8 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{16}H_{20}O_2$ (MW 244.33): C, 78.65; H, 8.25. Found: C, 78.67; H, 7.99.

1-(4-Methoxyphenyl)hept-2-ynyl acetate (83)



83

The above general procedure yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 1.46 g (56% over 2 steps) of the title compound as a pale yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, J = 8.8 Hz, 2H, H^{Ar}), 6.86 (d, J = 8.8 Hz, 2H, H^{Ar}), 6.42 (t, J = 1.9 Hz, 1H, H^1), 3.76 (s, 3H, OMe), 2.25 (dt, J = 6.9, 1.9 Hz, 2H, H^4), 2.03 (s, 3H, OAc), 1.53-1.46 (m, 2H, H^5), 1.43-1.36 (m, 2H, H^6), 0.90 (t, J = 6.9 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.7 (C, C=O), 160.0 (C, *C*–OMe), 130.0 (C, C^{Ar}), 129.2 (C, C^{Ar}), 113.8 (CH, C^{Ar}), 87.9 (C, C^3), 77.0 (C, C^2), 65.7 (CH, C^1), 55.1 (CH_3, OMe), 30.5 (CH_2, C^4), 21.9 (CH_2, C^5), 21.0 (CH_3, OAc), 18.5 (CH_2, C^6), 13.5 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{16}H_{20}O_3$ (MW 260.33): C, 73.82; H, 7.74. Found: C, 73.89; H, 7.68.

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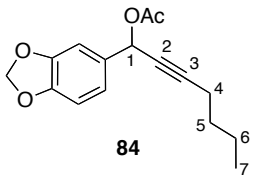
1-(Benzo[1,3]dioxol-5-yl)hept-2-ynyl acetate (84)

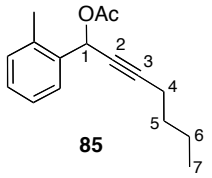


84

The above general procedure yielded, after flash chromatography on silica gel (pentane/MTBE, 90/10), 1.84 g (67% over 2 steps) of the title compound as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (d, *J* = 2.0 Hz, 1H, H^{Ar}), 7.00 (dd, *J* = 8.0, 2.0 Hz, 1H, H^{Ar}), 6.78 (d, *J* = 8.0 Hz, 1H, H^{Ar}), 6.37 (t, *J* = 2.0 Hz, 1H, H^1), 5.97 (s, 2H, OCH_2O), 2.27 (dt, *J* = 6.9, 2.0 Hz, 2H, H^4), 1.57-1.48 (m, 2H, H^5), 1.47-1.34 (m, 2H, H^6), 0.91 (t, *J* = 7.2 Hz, 3H, H^7). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.8 (C, C=O), 155.1 (C, C^{Ar}), 147.9 (C, C^{Ar}), 147.7 (C, C^{Ar}), 121.7 (CH, C^{Ar}), 108.3 (CH, C^{Ar}), 108.0 (CH, C^{Ar}), 101.2 (CH_2, OCH_2O), 88.1 (C, C^3), 77.1 (C, C^2), 65.8 (CH, C^1), 30.4 (CH_2, C^4), 21.9 (CH_2, C^5), 21.1 (OAc), 18.5 (CH_2, C^6), 13.5 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{16}H_{18}O_4$ (MW 274.31): C, 70.06; H, 6.61. Found: C, 69.83; H, 6.38.

1-*o*-Tolylhept-2-ynyl acetate (85)



85

The above general procedure yielded, after flash chromatography on silica gel (pentane/MTBE, 95/5), 2.13 g (87% over 2 steps) of the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62-7.59 (m, 1H, H^{Ar}), 7.23-7.20 (m, 2H, H^{Ar}), 7.17-7.14 (m, 1H, H^{Ar}), 6.55 (t, *J* = 2.1 Hz, 1H, H^1), 2.39 (s, 3H, C^{Ar}–CH_3), 2.23 (dt, *J* = 6.9, 2.1 Hz, 2H, H^4), 2.07 (s, 3H, OAc), 1.52-1.45 (m, 2H, H^5), 1.43-1.34 (m, 2H, H^6), 0.89 (t, *J* = 7.2 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.8 (C, C=O), 136.2 (C, C^{Ar}), 135.8 (C, C^{Ar}), 130.8 (CH, C^{Ar}), 128.8 (CH, C^{Ar}), 127.9 (CH, C^{Ar}), 126.2 (CH, C^{Ar}), 88.2 (C, C^3), 76.7 (C, C^2), 64.2 (CH, C^1), 30.6 (CH_2, C^4), 22.1 (CH_2, C^5), 21.1 (CH_3, OAc), 19.1 (CH_3, C^{Ar}–CH_3), 18.7 (CH_2, C^6), 13.6 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{16}H_{20}O_2$ (MW 244.33): C, 78.65; H, 8.25. Found: C, 78.88; H, 8.00.

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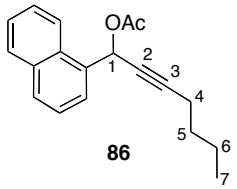
1-(Naphthalen-1-yl)hept-2-ynyl acetate (86)

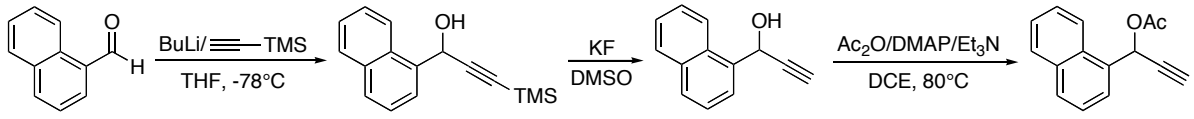


86

The above general procedure yielded, after flash chromatography on silica gel (pentane/MTBE, 80/20), 2.36 g (84% over 2 steps) of the title compound as a pale yellow oil.

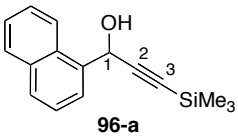
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.0 Hz, 1H, H^{Ar}), 7.96-7.78 (m, 3H, H^{Ar}), 7.62-7.43 (m, 3H, H^{Ar}), 7.11 (t, *J* = 1.7 Hz, 1H, H^1), 2.29 (dt, *J* = 6.8, 1.7 Hz, 2H, H^4), 2.12 (s, 3H, OAc), 1.59-1.48 (m, 2H, H^5), 1.48-1.36 (m, 2H, H^6), 0.91 (t, *J* = 7.2 Hz, 3H, H^7). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.9 (C, C=O), 133.8 (C, C^{Ar}), 132.9 (C, C^{Ar}), 130.5 (C, C^{Ar}), 129.6 (CH, C^{Ar}), 128.7 (CH, C^{Ar}), 126.4 (CH, C^{Ar}), 126.3 (CH, C^{Ar}), 125.8 (CH, C^{Ar}), 125.1 (CH, C^{Ar}), 123.8 (CH, C^{Ar}), 88.8 (C, C^3), 76.6 (C, C^2), 64.4 (CH, C^1), 30.4 (CH_2, C^4), 21.9 (CH_2, C^5), 21.0 (CH_3, OAc), 18.5 (CH_2, C^6), 13.5 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{19}H_{20}O_2$ (MW 280.36): C, 81.40; H, 7.19. Found: C, 81.13; H, 7.10.

*Preparation of arylpropargyl acetate **96***



96-a **96-b** **96** (75% over 3 steps)

1-(Naphthalen-1-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (96-a)



96-a

In an oven-dried round-bottom flask, trimethylsilyl acetylene (2.0 mL, 15 mmol, 1.5 equiv) and BuLi 1.6 M (4.1 mL, 12 mmol, 1.2 equiv) were added to THF (15 mL) at -78ºC and stirred for 20 minutes under argon. Then, naphthaldehyde (1.4 mL, 10 mmol, 1.0 equiv) was added and the reaction stirred for 20 minutes. The reaction was then allowed to warm up to room temperature, quenched with a saturated aqueous NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium

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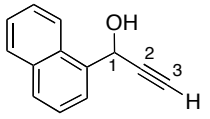
sulfate, filtered and concentrated to give **96-a** as a yellow oil that was engaged in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 8.8 Hz, 1H, H^{Ar}), 7.93-7.78 (m, 3H, H^{Ar}), 7.61-7.41 (m, 1H, 3H, H^{Ar}), 6.11 (s, 1H, H^1), 2.90 (s broad, 1H, OH), 0.23 (s, 9H, TMS). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 135.4 (C, C^{Ar}), 133.9 (C, C^{Ar}), 130.6 (C, C^{Ar}), 129.2 (CH, C^{Ar}), 128.6 (CH, C^{Ar}), 126.1 (CH, C^{Ar}), 125.8 (CH, C^{Ar}), 125.2 (CH, C^{Ar}), 124.6 (CH, C^{Ar}), 124.0 (CH, C^{Ar}), 104.9 (C, C^3), 92.1 (C, C^2), 63.1 (CH, C^1), -0.2 (CH_3, TMS).

1-(Naphthalen-1-yl)prop-2-yn-1-ol (96-b)

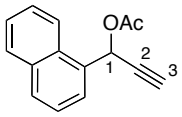


96-b

To crude alcohol **96-a** (10 mmol, 1.0 equiv) dissolved in DMSO (17 mL), KF (480 mg, 8.3 mmol, 1.5 equiv) and a few drops of water were added. After 45 min, the reaction mixture was quenched with water and extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give **96-b** as a yellow oil that was engaged in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.4 Hz, 1H, H^{Ar}), 7.98-7.78 (m, 3H, H^{Ar}), 7.64-7.40 (m, 1H, 3H, H^{Ar}), 6.11 (s, 1H, H^1), 2.09 (s broad, 1H, OH), 2.74 (s, 1H, H^3). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 135.0 (C, C^{Ar}), 133.9 (C, C^{Ar}), 130.4 (C, C^{Ar}), 129.4 (CH, C^{Ar}), 128.7 (CH, C^{Ar}), 126.4 (CH, C^{Ar}), 125.8 (CH, C^{Ar}), 125.1 (CH, C^{Ar}), 124.5 (CH, C^{Ar}), 123.8 (CH, C^{Ar}), 83.5 (C, C^2), 75.4 (C, C^3), 62.5 (CH, C^1).

1-(Naphthalen-1-yl)prop-2-ynyl acetate (96)



96

1-(Naphthalen-1-yl)prop-2-yn-1-ol **96-b** (10 mmol, 1.0 equiv), DCE (30 mL), DMAP (0.360 g, 3.0 mmol, 0.3 equiv), Et_3N (5.6 mL, 40 mmol, 4 equiv), and Ac_2O (1.8 mL, 20 mmol, 2 equiv) were added in turn in a round-bottom flask equipped with a condenser and was heated overnight at 80°C. The reaction was then quenched with a saturated aqueous NH_4Cl solution and extracted with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give a crude oil that was purified by flash

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chromatography on silica gel (pentane/MTBE, 90/10) affording 1.68 g (7.5 mmol, 75% over 3 steps) of the title compound as a pale yellow oil.

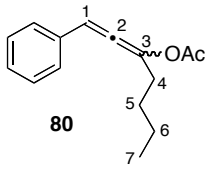
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.4 Hz, 1H, H^{Ar}), 7.98-7.82 (m, 3H, H^{Ar}), 7.66-7.44 (m, 1H, 3H, H^{Ar}), 7.11 (d, *J* = 2.0 Hz, 1H, H^1), 2.74 (d, *J* = 2.0 Hz, 1H, H^3), 2.15 (s, 3H, OAc). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.7 (C, C=O), 133.9 (C, C^{Ar}), 131.6 (C, C^{Ar}), 130.4 (C, C^{Ar}), 130.0 (CH, C^{Ar}), 128.8 (CH, C^{Ar}), 126.7 (CH, C^{Ar}), 126.5 (CH, C^{Ar}), 126.0 (CH, C^{Ar}), 125.1 (CH, C^{Ar}), 123.5 (CH, C^{Ar}), 80.1 (C, C^2), 75.9 (C, C^3), 63.6 (CH, C^1), 20.9 (CH_3, OAc). **Elemental analysis** calcd. (%) for $C_{15}H_{12}O_2$ (MW 224.25): C, 80.34; H, 5.39. Found: C, 80.24; H, 5.03.

2. Synthesis and characterization of allenes 80, 90, and 98

Representative Procedure: **1-Phenylhepta-1,2-dien-3-yl acetate (80)**

In an oven-dried round-bottom flask, 1-phenylhept-2-ynyl acetate **77** (230 mg, 1 mmol, 1.0 equiv) and anhydrous DCM (40 mL) were introduced. The solution was degassed with nitrogen for 15 minutes before silver hexafluoroantimonate (17.2 mg, 0.05 mmol, 0.05 equiv) was added. The reaction mixture was heated to 40°C until it was complete (TLC monitoring) and then diluted with diethyl ether, washed twice with water and with a saturated aqueous NH_4Cl solution. The organic layer was dried over magnesium sulfate and concentrated to give 205 mg (89% yield) of **80** as a pale yellow oil.

1-Phenylhepta-1,2-dien-3-yl acetate (80)



80

The general procedure yielded 205 mg (89%) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.40 (m, 2H, H^{Ar}), 7.35-7.29 (m, 2H, H^{Ar}), 7.26-7.20 (m, 1H, H^{Ar}), 6.58 (t, *J* = 3.1 Hz, 1H, H^1), 2.37-2.23 (m, 2H, H^4), 2.13 (s, 3H, OAc), 1.52-1.34 (m, 4H, H^5 + H^6), 0.89 (t, *J* = 7.1 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 196.8 (C, C^2), 168.7 (C, C=O), 134.0 (C, C^{Ar}), 128.8 (CH, C^{Ar}), 128.1 (CH, C^{Ar}), 127.9 (CH, C^{Ar}), 127.0 (C, C^3), 104.6 (CH, C^1), 31.6 (CH_2, C^4), 28.4 (CH_2, C^5), 22.3 (CH_2, C^6), 21.1 (CH_3, OAc), 14.0 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{15}H_{18}O_2$ (MW 230.30): C, 78.23; H, 7.88. Found: C, 78.05; H, 8.27.

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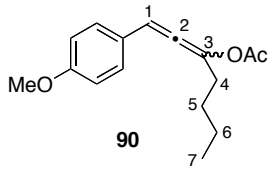
1-(4-Methoxyphenyl)hepta-1,2-dien-3-yl acetate (90)

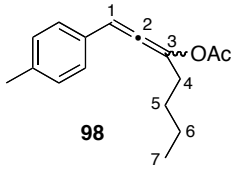


90

The above general procedure yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 203 mg (78%) of the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.8 Hz, 2H, H^{Ar}), 6.87 (d, *J* = 8.8 Hz, 2H, H^{Ar}), 6.55 (t, *J* = 3.1 Hz, 1H, H^1), 3.81 (s, 3H, OMe), 2.36-2.30 (m, 2H, H^4), 2.14 (s, 3H, OAc), 1.49-1.32 (m, 4H, H^5 + H^6), 0.89 (t, *J* = 7.1 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 195.5 (C, C^2), 169.0 (C, C=O), 159.8 (C, C^{Ar}–OMe), 129.3 (CH, C^{Ar}), 126.8 (C, C^{Ar}), 126.5 (C, C^3), 114.3 (CH, C^{Ar}), 104.3 (CH, C^1), 55.5 (CH_3, OMe), 31.8 (CH_2, C^4), 28.5 (CH_2, C^5), 22.4 (CH_2, C^6), 21.3 (CH_3, OAc), 14.1 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{16}H_{20}O_3$ (MW 260.33): C, 73.82; H, 7.74. Found: C, 74.14; H, 7.53.

1-*p*-Tolylhepta-1,2-dien-3-yl acetate (98)



98

The general procedure yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 230 mg (94%) of the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (d, *J* = 7.8 Hz, 2H, H^{Ar}), 7.14 (d, *J* = 7.8 Hz, 2H, H^{Ar}), 6.56 (t, *J* = 3.1 Hz, 1H, H^1), 2.35-2.21 (m, 2H, H^4), 2.33 (s, 3H, C^{Ar}–CH_3), 2.14 (s, 3H, OAc), 1.51-1.24 (m, 4H, H^5 + H^6), 0.89 (t, *J* = 7.1 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 196.2 (C, C^2), 169.0 (C, C=O), 138.1 (C, C^{Ar}–C^1), 131.2 (C, C^{Ar}–CH_3), 129.6 (CH, C^{Ar}), 127.9 (CH, C^{Ar}), 126.9 (C, C^3), 104.6 (CH, C^1), 31.7 (CH_2, C^4), 28.5 (CH_2, C^5), 22.4 (CH_2, C^6), 21.5 (CH_3, C^{Ar}–CH_3), 21.1 (CH_3, OAc), 14.1 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{16}H_{20}O_2$ (MW 244.33): C, 78.65; H, 8.25. Found: C, 78.93; H, 8.36.

3. Au-Catalyzed formation of indene derivatives 71-73, 78, 87-95, and 97

General Procedure: To a solution of [(IPr)AuCl] (12.4 mg, 0.02 mmol) in anhydrous DCM (35 mL) in a round-bottom flask equipped with a septum, $AgBF_4$ (2 mg, 0.02 mmol) was

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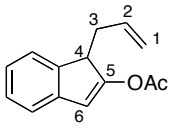
added in the absence of light. The solution instantly became cloudy. A 5 mL solution of arylpropargyl acetate (1 mmol) in anhydrous DCM was then injected through the septum. When TLC analysis showed total consumption of the starting material, the solvent was removed. The resulting mixture was dissolved in pentane, filtered through Celite and concentrated. The crude oil was purified by flash chromatography on silica gel.

1-Allyl-1*H*-inden-2-yl acetate (71)

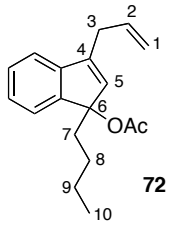


71

The general procedure employing arylpropargyl acetate **66** (214 mg) yielded, after flash chromatography on silica gel (pentane/MTBE, 95/5), 159 mg (74%) of the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, *J* = 7.2 Hz, 1H, H^{Ar}), 7.27-7.18 (m, 2H, H^{Ar}), 7.15-7.10 (m, 1H, H^{Ar}), 6.63 (s, 1H, H^6), 5.71-5.58 (m, 1H, H^2), 5.07-4.95 (m, 2H, H^1), 3.66 (t, *J* = 6.3 Hz, 1H, H^4), 2.70-2.61 (m, 1H, $1H^3$), 2.51-2.41 (m, 1H, $1H^3$), 2.24 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 168.1 (C, C=O), 158.0 (C, C^5), 142.3 (C, C^{Ar}), 140.9 (C, C^{Ar}), 134.7 (CH, C^6), 127.1 (CH, C^2), 124.6 (CH, C^{Ar}), 123.1 (CH, C^{Ar}), 121.2 (CH, C^{Ar}), 117.1 (CH_2, C^1), 114.5 (CH, C^{Ar}), 47.8 (CH, C^4), 34.2 (CH_2, C^3), 21.4 (CH_3, OAc). **Elemental analysis** calcd. (%) for $C_{14}H_{14}O_2$ (MW 214.26): C, 78.48; H, 6.59. Found: C, 78.24; H, 6.53.

3-Allyl-1-butyl-1*H*-inden-1-yl acetate (72)



72

The general procedure employing arylpropargyl acetate **67** (270 mg) yielded, after flash chromatography on silica gel (pentane/MTBE, 95/5), 181 mg (67%) of the title compound along with 49 mg (18%) of **73** as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.4 Hz, 1H, H^{Ar}), 7.29-7.25 (m, 1H, H^{Ar}), 7.21-7.18 (m, 2H, H^{Ar}), 6.32 (s, 1H, H^5), 6.04-5.96 (m, 1H, H^2), 5.19 (dd, *J* = 16.8, 1.6 Hz, 1H, H^1 *trans*), 5.13 (d, *J* = 10.4 Hz, 1H, H^1 *cis*), 3.23 (d, *J* = 9.6 Hz, 2H, H^3), 2.25 (dt, *J* = 12.4, 3.6 Hz, 1H, $1H^7$), 2.00 (s, 3H, OAc), 1.96 (dt, *J* = 12.4, 3.6 Hz, 1H, $1H^7$), 1.35-1.15 (m, 4H, H^8 +

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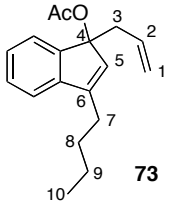
H^9), 0.82 (t, *J* = 6.8 Hz, 3H, H^{10}). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.3 (C, C=O), 146.5 (C, C^{Ar}), 143.6 (C, C^{Ar}), 143.0 (C, C^4), 134.8 (CH, C^{Ar}), 132.6 (CH, C^2), 128.6 (CH, C^{Ar}), 126.4 (CH, C^{Ar}), 122.3 (CH, C^{Ar}), 119.9 (CH, C^5), 117.1 (CH_2, C^1), 90.3 (C, C^6), 35.5 (CH_2, C^7), 32.2 (CH_2, C^3), 26.4 (CH_2, C^8), 23.1 (CH_2, C^9), 22.1 (CH_3, OAc), 14.1 (CH_3, C^{10}). **Elemental analysis** calcd. (%) for $C_{18}H_{22}O_2$ (MW 270.37): C, 79.96; H, 8.20. Found: C, 79.95; H, 8.21.

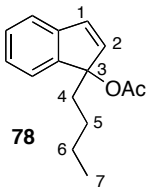
1-Allyl-3-butyl-1*H*-inden-1-yl acetate (73)



73

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.39 (m, 1H, H^{Ar}), 7.31-7.25 (m, 1H, H^{Ar}), 7.21-7.16 (m, 2H, H^{Ar}), 6.30 (s, 1H, H^5), 5.69-5.55 (m, 1H, H^2), 5.04-4.98 (m, 2H, H^1), 2.93 (dd, *J* = 13.8, 7.5 Hz, 1H, $1H^3$), 2.82 (dd, *J* = 13.8, 7.5 Hz, 1H, $1H^3$), 2.45 (t, *J* = 8.1 Hz, 2H, H^7), 2.00 (s, 3H, OAc), 1.68-1.57 (m, 2H, H^8), 1.47-1.35 (m, 2H, H^9), 0.94 (t, *J* = 7.2 Hz, 3H, H^{10}). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.4 (C, C=O), 146.1 (C, C^{Ar}), 146.0 (C, C^{Ar}), 143.5 (C, C^6), 132.8 (CH, C^2), 131.0 (CH, C^{Ar}), 128.7 (CH, C^{Ar}), 126.2 (CH, C^{Ar}), 122.8 (CH, C^{Ar}), 119.6 (CH, C^5), 118.7 (CH_2, C^1), 89.3 (C, C^4), 40.0 (CH_2, C^3), 29.8 (CH_2, C^7), 27.2 (CH_2, C^8), 22.8 (CH_2, C^9), 22.1 (CH_3, OAc), 14.1 (CH_3, C^{10}). **Elemental analysis** calcd. (%) for $C_{18}H_{22}O_2$ (MW 270.37): C, 79.96; H, 8.20. Found: C, 80.10; H, 8.12.

1-Butyl-1*H*-inden-1-yl acetate (78)



78

The general procedure employing arylpropargyl acetate **77** (230 mg) yielded, after flash chromatography on silica gel (pentane/MTBE, 95/5), 212 mg (92%) of the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.2 Hz, 1H, H^{Ar}), 7.24-7.14 (m, 3H, H^{Ar}), 7.21-7.18 (m, 2H, H^{Ar}), 6.70 (d, *J* = 5.7 Hz, 1H, H^1), 6.56 (d, *J* = 5.7 Hz, 1H, H^2), 2.22 (dt, *J* = 12.6, 4.5 Hz, 1H, $1H^4$), 1.99 (s, 3H, OAc), 1.93 (dt, *J* = 12.6, 4.5 Hz, 1H, $1H^4$), 1.32-1.19 (m,

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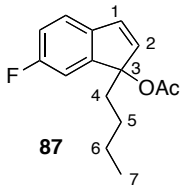
4H, H^5 + H^6), 0.83 (t, *J* = 7.5 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.0 (C, C=O), 145.8 (C, C^{Ar}), 142.4 (C, C^{Ar}), 137.9 (CH, C^{Ar}), 132.4 (CH, C^1), 128.7 (CH, C^{Ar}), 126.2 (CH, C^2), 122.2 (CH, C^{Ar}), 121.7 (CH, C^{Ar}), 91.0 (C, C^3), 35.7 (CH_2, C^4), 26.4 (CH_2, C^5), 23.1 (CH_2, C^6), 21.9 (CH_3, OAc), 14.0 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{15}H_{18}O_2$ (MW 230.30): C, 78.23; H, 7.88. Found: C, 78.15; H, 7.94.

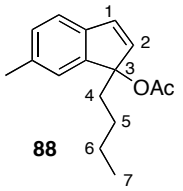
1-Butyl-6-fluoro-1*H*-inden-1-yl acetate (87)



The general procedure employing arylpropargyl acetate **81** (248 mg) yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 201 mg (81%) of the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14 (dd, *J* = 8.1, 5.0 Hz, 1H, H^{Ar}), 7.07 (dd, *J* = 8.4, 2.3 Hz, 1H, H^{Ar}), 6.93 (ddd, *J* = 9.3, 8.1, 2.4 Hz, 1H, H^{Ar}), 6.67 (d, *J* = 5.6 Hz, 1H, H^1), 6.50 (d, *J* = 5.6 Hz, 1H, H^2), 2.23-2.13 (m, 1H, 1H^4), 2.01 (s, 3H, OAc), 1.90-1.82 (m, 1H, 1H^4), 1.35-1.21 (m, 4H, H^5 + H^6), 0.84 (t, *J* = 7.0 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.9 (C, C=O), 162.3 (d, *J* = 244 Hz, C, C–F), 148.2 (d, *J* = 7.9 Hz, C, C^{Ar}), 138.1 (d, *J* = 2.6 Hz, C, C^{Ar}), 137.8 (d, *J* = 4.2 Hz, CH, C^1), 131.6 (CH, C^2), 122.4 (d, *J* = 8.5 Hz, CH, C^{Ar}), 115.0 (d, *J* = 22.5 Hz, CH, C^{Ar}), 110.5 (d, *J* = 24.0 Hz, CH, C^{Ar}), 90.5 (C, C^3), 35.9 (CH_2, C^4), 26.3 (CH_2, C^5), 23.1 (CH_2, C^6), 21.9 (CH_3, OAc), 14.1 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{15}H_{17}FO_2$ (MW 248.29): C, 72.56; H, 6.90. Found: C, 72.39; H, 6.88.

1-Butyl-6-methyl-1*H*-inden-1-yl acetate (88)



The general procedure employing arylpropargyl acetate **82** (244 mg) yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 191 mg (78%) of the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (s, 1H, H^{Ar}), 7.09 (d, *J* = 7.5 Hz, 1H, H^{Ar}), 7.04 (d, *J* = 7.5 Hz, 1H, H^{Ar}), 6.67 (d, *J* = 5.7 Hz, 1H, H^1), 6.49 (d, *J* = 5.7 Hz, 1H, H^2), 2.36 (s, 3H,

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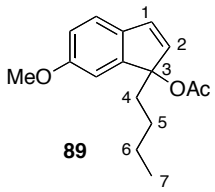
C^{Ar}–CH_3), 2.27-2.17 (m, 1H, $1H^4$), 2.00 (s, 3H, OAc), 1.94-1.84 (m, 1H, $1H^4$), 1.36-1.18 (m, 4H, H^5 + H^6), 0.83 (t, *J* = 7.1 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.1 (C, C=O), 146.1 (C, C^{Ar}), 139.7 (C, C^{Ar}), 136.8 (CH, C^2), 136.1 (C, C^{Ar}), 132.3 (CH, C^1), 129.2 (CH, C^{Ar}), 123.2 (CH, C^{Ar}), 121.4 (CH, C^{Ar}), 91.0 (C, C^3), 35.8 (CH_2, C^4), 26.4 (CH_2, C^5), 23.1 (CH_2, C^6), 22.0 (CH_3, OAc), 21.8 (CH_3, C^{Ar}–*C*H_3), 14.1 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{16}H_{20}O_2$ (MW 244.33): C, 78.65; H, 8.25. Found: C, 78.47; H, 8.22.

1-Butyl-6-methoxy-1*H*-inden-1-yl acetate (89)

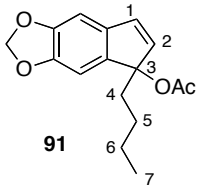


89

The above general procedure employing arylpropargyl acetate **83** (260 mg) yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 145 mg (63%) of the title compound as a pale yellow oil along with 30 mg (13%) of allenyl acetate **90** (see above for complete characterization).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (d, *J* = 8.1 Hz, 1H, H^{Ar}), 6.93 (d, *J* = 2.4 Hz, 1H, H^{Ar}), 6.75 (dd, *J* = 8.1, 2.4 Hz, 1H, H^{Ar}), 6.66 (d, *J* = 5.7 Hz, 1H, H^1), 6.42 (d, *J* = 5.7 Hz, 1H, H^2), 3.82 (s, 3H, OMe), 2.26-2.14 (m, 1H, $1H^4$), 2.01 (s, 3H, OAc), 1.92-1.82 (m, 1H, $1H^4$), 1.34-1.19 (m, 4H, H^5 + H^6), 0.83 (t, *J* = 7.4 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.0 (C, C=O), 159.0 (C, *C*^{Ar}–OMe), 147.8 (C, C^{Ar}), 135.8 (CH, C^1), 135.2 (C, C^{Ar}), 129.4 (CH, C^{Ar}), 122.1 (CH, C^2), 112.5 (CH, C^{Ar}), 110.0 (CH, C^{Ar}), 90.9 (C, C^3), 55.7 (CH_3, OMe), 36.0 (CH_2, C^4), 26.3 (CH_2, C^5), 23.1 (CH_2, C^6), 22.0 (CH_3, OAc), 14.1 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{16}H_{20}O_3$ (MW 260.33): C, 73.82; H, 7.74. Found: C, 73.76; H, 7.74.

5-Butyl-5*H*-indeno[5,6-*d*][1,3]dioxol-5-yl acetate (91)



91

The above general procedure employing arylpropargyl acetate **84** (274 mg) yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 247 mg (90%) of the title compound as a pale yellow oil.

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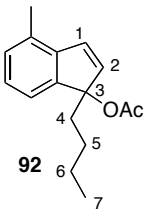
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 (s, 1H, H^{Ar}), 6.71 (s, 1H, H^{Ar}), 6.58 (d, *J* = 5.8 Hz, 1H, H^1), 6.46 (d, *J* = 5.8 Hz, 1H, H^2), 5.96 (d, *J* = 1.4 Hz, 1H, O–CH_2–O), 5.93 (d, *J* = 1.4 Hz, 1H, O–CH_2–O), 2.43-2.15 (m, 1H, $1H^4$), 2.00 (s, 3H, OAc), 1.90-1.78 (m, 1H, $1H^4$), 1.35-1.18 (m, 4H, H^5 + H^6), 0.84 (t, *J* = 7.3 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.0 (C, C=O), 147.8 (C, O–C^{Ar}), 146.6 (C, O–C^{Ar}), 139.8 (C, C^{Ar}), 136.9 (CH, C^1), 136.2 (C, C^{Ar}), 131.8 (CH, C^2), 104.4 (CH, C^{Ar}), 103.2 (CH, C^{Ar}), 101.4 (CH_2, O–CH_2–O), 90.5 (C, C^3), 35.9 (CH_2, C^4), 26.3 (CH_2, C^5), 23.1 (CH_2, C^6), 22.0 (CH_3, OAc), 14.1 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{16}H_{18}O_4$ (MW 274.31): C, 70.06; H, 6.61. Found: C, 70.03; H, 6.66.

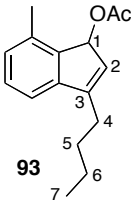
1-Butyl-4-methyl-1*H*-inden-1-yl acetate (92)



The above general procedure employing arylpropargyl acetate **85** (244 mg) yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 217 mg (89%) of the title compound along with 22 mg (9%) of indene **93** as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18-7.16 (m, 1H, H^{Ar}), 7.11-7.03 (m, 2H, H^{Ar}), 6.82 (dd, *J* = 5.8, 0.7 Hz, 1H, H^1), 6.56 (d, *J* = 5.8 Hz, 1H, H^2), 2.36 (s, 3H, C^{Ar}–CH_3), 2.21 (ddt, *J* = 10.9, 4.5, 0.7 Hz, 1H, $1H^4$), 2.00 (s, 3H, OAc), 1.90 (ddt, *J* = 10.9, 4.5, 0.7 Hz, 1H, $1H^4$), 1.39-1.18 (m, 2H, H^5), 1.08-0.95 (m, 2H, H^6), 0.83 (t, *J* = 7.0 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.1 (C, C=O), 145.7 (C, C^{Ar}), 140.9 (C, C^{Ar}), 137.2 (CH, C^{Ar}), 131.0 (C, C^{Ar}), 130.6 (CH, C^1), 130.1 (CH, C^2), 126.4 (CH, C^{Ar}), 119.6 (CH, C^{Ar}), 91.3 (C, C^3), 35.8 (CH_2, C^4), 26.4 (CH_2, C^5), 23.1 (CH_2, C^6), 22.0 (CH_3, OAc), 18.3 (CH_3, C^{Ar}–*C*H_3), 14.1 (CH_3, C^7). **Elemental analusis** calcd. (%) for $C_{16}H_{20}O_2$ (MW 244.33): C, 78.65; H, 8.25. Found: C, 78.24; H, 7.93.

3-Butyl-7-methyl-1*H*-inden-1-yl acetate (93)



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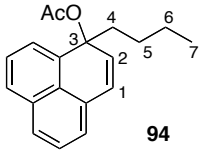
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (t, *J* = 7.5 Hz, 1H, H^{Ar}), 7.08 (d, *J* = 7.5 Hz, 1H, H^{Ar}), 7.01 (d, *J* = 7.5 Hz, 1H, H^{Ar}), 6.23-6.22 (m, 1H, H^1), 6.07-6.05 (m, 1H, H^2), 2.48-2.42 (m, 2H, H^4), 2.31 (s, 3H, C^{Ar}–CH_3), 2.13 (s, 3H, OAc), 1.66-1.58 (m, 2H, H^5), 1.46-1.36 (m, 2H, H^6), 0.95 (t, *J* = 7.3 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 171.6 (C, C=O), 148.5 (C, C^{Ar}), 144.4 (C, C^{Ar}), 140.2 (C, C^3), 134.4 (C, C^{Ar}), 129.2 (CH, C^{Ar}), 128.2 (CH, C^{Ar}), 126.6 (CH, C^{Ar}), 117.4 (CH, C^2), 76.5 (CH, C^1), 29.7 (CH_2, C^4), 27.5 (CH_2, C^5), 22.8 (CH_2, C^6), 22.0 (CH_3, OAc), 18.1 (CH_3, C^{Ar}–*C*H_3), 14.2 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{16}H_{20}O_2$ (MW 244.33): C, 78.65; H, 8.25. Found: C, 78.93; H, 8.18.

1-Butyl-1*H*-phenalen-1-yl acetate (94)

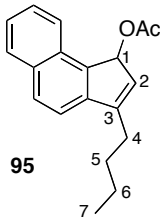


94

The above general procedure employing arylpropargyl acetate **86** (280 mg) yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 219 mg (78%) of the title compound along with 31 mg (11%) of indene **95** as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.2 Hz, 1H, H^{Ar}), 7.85 (d, *J* = 7.6 Hz, 1H, H^{Ar}), 7.73 (d, *J* = 8.2 Hz, 1H, H^{Ar}), 7.54-7.42 (m, 3H, H^{Ar}), 7.28 (d, *J* = 5.8 Hz, 1H, H^1), 6.75 (d, *J* = 5.8 Hz, 1H, H^2), 2.31 (dt, *J* = 12.3, 4.1 Hz, 1H, 1H^4), 2.02 (s, 3H, OAc), 1.96 (dt, *J* = 12.3, 4.1 Hz, 1H, 1H^4), 1.31-1.18 (m, 2H, H^5), 1.06-0.94 (m, 2H, H^6), 0.80 (t, *J* = 7.1 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.1 (C, C=O), 143.2 (C, C^{Ar}), 138.4 (C, C^{Ar}), 138.3 (CH, C^2), 134.2 (C, C^{Ar}), 129.4 (CH, C^{Ar}), 128.7 (CH, C^{Ar}), 127.8 (C, C^{Ar}), 126.7 (CH, C^{Ar}), 126.3 (CH, C^{Ar}), 125.9 (CH, C^{Ar}), 124.1 (CH, C^{Ar}), 120.2 (CH, C^1), 91.6 (C, C^3), 35.5 (CH_2, C^4), 26.5 (CH_2, C^5), 23.1 (CH_2, C^6), 22.0 (CH_3, OAc), 14.1 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{19}H_{20}O_2$ (MW 280.36): C, 81.40; H, 7.19. Found: C, 81.72; H, 7.33.

3-Butyl-1*H*-cyclopenta[*a*]naphthalen-1-yl acetate (95)



95

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.4 Hz, 2H, H^{Ar}), 7.80 (d, *J* = 8.4 Hz, 1H, H^{Ar}), 7.52-7.38 (m, 3H, H^{Ar}), 6.53 (d, *J* = 1.6 Hz, 1H, H^2), 6.20-6.18 (m, 1H, H^1), 2.56 (t, *J* = 7.1

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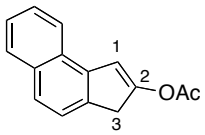
Hz, 2H, H^4), 2.20 (s, 3H, OAc), 1.75-1.58 (m, 2H, H^5), 1.52-1.40 (m, 2H, H^6), 0.97 (t, J = 7.4 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 171.7 (C, C=O), 148.5 (C, C^{Ar}), 142.4 (C, C^{Ar}), 137.7 (C, C^{Ar}), 132.8 (C, C^{Ar}), 130.0 (CH, C^{Ar}), 129.5 (C, C^{Ar}), 129.1 (CH, C^{Ar}), 127.1 (CH, C^{Ar}), 126.8 (CH, C^{Ar}), 125.2 (CH, C^{Ar}), 123.6 (CH, C^{Ar}), 118.6 (CH, C^2), 76.4 (CH, C^1), 29.8 (CH_2, C^4), 27.7 (CH_2, C^5), 22.8 (CH_2, C^6), 21.5 (CH_3, OAc), 14.2 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{19}H_{20}O_2$ (MW 280.36): C, 81.40; H, 7.19. Found: C, 81.06; H, 7.55.

3*H*-Cyclopenta[*a*]naphthalen-2-yl acetate (97)



97

The above general procedure employing arylpropargyl acetate **96** (224 mg) yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 173 mg (77%) of the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82-7.80 (m, 2H, H^{Ar}), 7.75 (d, J = 8.3 Hz, 1H, H^{Ar}), 7.50-7.44 (m, 2H, H^{Ar}), 7.39-7.33 (m, 1H, H^{Ar}), 6.71 (t, J = 1.4 Hz, 1H, H^1), 3.90 (s, 2H, H^3), 2.29 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 168.4 (C, C=O), 155.7 (C, C^{Ar}), 140.5 (C, C^2), 132.9 (C, C^{Ar}), 131.5 (C, C^{Ar}), 129.2 (CH, C^{Ar}), 127.6 (CH, C^{Ar}), 126.6 (CH, C^{Ar}), 124.5 (CH, C^{Ar}), 123.1 (CH, C^{Ar}), 120.7 (CH, C^{Ar}), 115.4 (CH, C^1), 39.3 (CH_2, C^3), 21.6 (CH_3, OAc). **Elemental analysis** calcd. (%) for $C_{15}H_{12}O_2$ (MW 224.25): C, 80.34; H, 5.39. Found: C, 80.20; H, 5.29.

4. Au-Catalyzed formation of indenes from allenyl acetates

General Procedure: To a solution of [(IPr)AuCl] (12 mg, 0.02 mmol) in anhydrous DCM (35 mL) in a round-bottom flask equipped with a septum, $AgBF_4$ (2 mg, 0.02 mmol) was added in the absence of light. The solution instantly became cloudy. A 5 mL solution of allenyl acetate (1 mmol) in anhydrous DCM was then injected through the septum. When TLC analysis showed total consumption of the starting material, the solvent was removed. The resulting residue was dissolved in pentane, filtered through Celite and concentrated. The crude oil was purified by column chromatography on silica gel.

The reported yields are isolated yields. Indene derivatives **78**, **88**, and **89** were isolated as mixtures containing **79**, **99**, and **100** respectively, and further assigned thanks to 2

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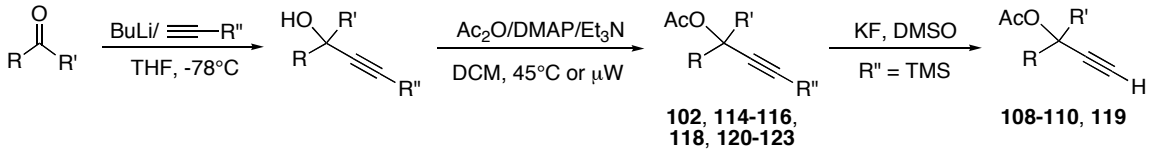
characteristic signals in the ^{1}H NMR spectrum (vinylic and allylic ^{1}H). The ratios given in Scheme 55 (p 230) are based on integration of NMR signals.

D. Formation of conjugated enones and enals from propargylic acetates

1. Synthesis and characterization of propargylic acetates 77, 81-83, 85, 102, 108-110, 114-116, and 118-123

The synthesis and characterization of propargylic acetates **77**, **81-83**, and **85** are described in section **VIII.C**.

*Preparation of propargylic acetates **102**, **108-110**, **114-116**, and **118-123***



General procedures

Alkynylation: In an oven-dried round-bottom flask, the alkyne (13 mmol, 1.3 equiv) and BuLi (1.6 M in hexanes, 12 mmol, 1.2 equiv) were added to THF (20 mL) at -78ºC and stirred for 20 minutes under nitrogen. To this solution, the aldehyde or the ketone (10 mmol, 1.0 equiv) was added and the reaction was stirred for 20 minutes. The reaction was then allowed to warm up to room temperature, and further stirred until completion (TLC monitoring). Then, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give the crude propargylic alcohol that was engaged in the next step without further purification.

Acylation: The propargylic alcohol (10 mmol, 1.0 equiv), DCM (30 mL), DMAP (0.360 g, 3.0 mmol, 0.3 equiv), Et_3N (5.6 mL, 40 mmol, 4 equiv), and Ac_2O (1.8 mL, 20 mmol, 2 equiv) were added in turn in a round-bottom flask equipped with a condenser. The reaction mixture was heated overnight at 45°C. The reaction was then quenched with a saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give a crude product that was purified by flash chromatography on silica gel.

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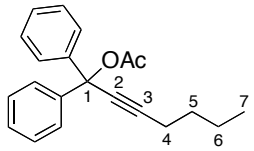
Alternatively, the acylation of propargylic alcohols could be carried out using microwave-heating conditions described as follow. The propargylic alcohol (10 mmol, 1.0 equiv), DMAP (0.360 g, 3.0 mmol, 0.3 equiv), Et_3N (5.6 mL, 40 mmol, 4 equiv), and Ac_2O (1.8 mL, 20 mmol, 2 equiv) were added in turn in a microwave-designed vial fitted with a sealed cap. The reaction mixture was heated under microwave irradiation at 100°C for 12 min. The reaction was then quenched with a saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give a crude product that was purified by flash chromatography on silica gel when necessary.

Desilylation: Compounds **108-110** and **119** were obtained by desilylation of the corresponding alkyne (propargylic acetate **115** being the precursor of **108** for example). The silylated alkyne (10 mmol, 1.0 equiv) was diluted in DMSO (17 mL). KF (480 mg, 8.3 mmol, 1.5 equiv) and few drops of water were added. After 45 min, the reaction mixture was quenched with water and extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give a crude product purified by flash chromatography on silica gel.

1,1-Diphenylhept-2-ynyl acetate (102)



102

The general procedure yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 2.21 g (83% over 2 steps) of the title compound as a yellow solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.34 (m, 2H, H^{Ar}), 7.23-7.20 (m, 8H, H^{Ar}), 2.16 (dt, J = 6.9, 2.0 Hz, 2H, H^4), 2.03 (s, 3H, OAc), 1.48-1.42 (m, 2H, CH_2), 1.40-1.34 (m, 2H, CH_2), 0.89 (t, J = 7.2 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.1 (C, C=O), 140.2 (C, C^{Ar}), 129.8 (CH, C^{Ar}), 127.9 (CH, C^{Ar}), 127.5 (CH, C^{Ar}), 87.2 (C, C^3), 82.7 (C, C^1), 78.2 (CH, C^2), 31.6 (CH_2), 22.3 (CH_2), 21.0 (CH_3, OAc), 18.7 (CH_2), 13.1 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{21}H_{22}O_2$ (MW 306.40): C, 82.32; H, 7.24. Found: C, 82.04; H, 7.27.

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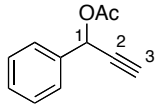
1-Phenylprop-2-ynyl acetate (108)[406]

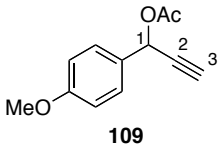


108

The general procedure yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 1.11 g (64% over 3 steps) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52-7.49 (m, 2H, H^{Ar}), 7.33-7.30 (m, 3H, H^{Ar}), 6.45 (d, *J* = 2.0 Hz, 1H, H^1), 2.66 (d, *J* = 2.0 Hz, 1H, H^3), 1.99 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.3 (C, C=O), 136.5 (C, C^{Ar}), 128.9 (CH, C^{Ar}), 128.6 (CH, C^{Ar}), 127.6 (CH, C^{Ar}), 80.2 (C, C^2), 75.5 (CH, C^1), 65.1 (CH, C^3), 20.7 (CH_3, OAc).

1-(4-Methoxyphenyl)prop-2-ynyl acetate (109)

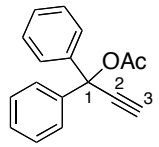


109

The general procedure yielded, after filtration through a plug of silica (pentane), 1.59 g (78% over 3 steps) of the title compound as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.7 Hz, 2H, H^{Ar}), 6.90 (d, *J* = 8.7 Hz), 6.40 (s, 1H, H^1), 3.80 (s, 3H, OMe), 2.65 (d, *J* = 2.3 Hz, 1H, H^3), 2.08 (s, 3H, OAc). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.9 (C, C=O), 160.4 (C, C^{Ar}), 129.5 (CH, C^{Ar}), 128.9 (C, C^{Ar}), 114.2 (CH, C^{Ar}), 80.7 (C, C^2), 75.3 (CH, C^3), 65.2 (CH, C^1), 55.5 (CH_3, OMe), 21.2 (CH_3, OAc). **Calcd. HRMS** for $C_{12}H_{12}O_3Na$ (M+Na): 227.0684. Found: 227.0686.

1,1-Diphenylprop-2-ynyl acetate (110)



110

The corresponding alcohol was purchased and acylated as described above to yield, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 1.80 g (72%) of the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.43 (m, 2H, H^{Ar}), 7.23-7.17 (m, 8H, H^{Ar}), 2.72 (s, 1H, H^3), 2.04 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.1 (C, C=O), 146.4 (C, C^{Ar}),

[406] Trahanovsky, W. S.; Mullen, P. W. *J. Am. Chem. Soc.* **1972**, *94*, 5086–5087.

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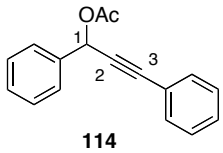
129.6 (CH, C^{Ar}), 128.4 (CH, C^{Ar}), 126.9 (CH, C^{Ar}), 86.4 (C, C^2), 84.2 (C, C^1), 75.2 (CH, C^3), 21.2 (CH_3, OAc). **Elemental analysis** calcd. (%) for $C_{16}H_{20}O_2$ (MW 244.33): C, 81.58; H, 5.64. Found: C, 81.36; H, 5.77.

1,3-Diphenylprop-2-yn-1-yl acetate (114)[407]

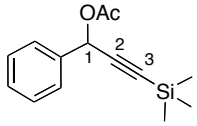


114

The general procedure yielded, after filtration through a plug of Celite, 2.05 g (82% over 2 steps) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.58 (m, 2H, H^{Ar}), 7.49-7.46 (m, 2H, H^{Ar}), 7.43-7.28 (m, 6H, H^{Ar}), 6.70 (s, 1H, H^1), 2.12 (s, 3H, OAc). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.0 (C, C=O), 137.4 (C, C^{Ar}), 132.1 (CH, C^{Ar}), 129.1 (CH, C^{Ar}), 129.0 (CH, C^{Ar}), 128.9 (CH, C^{Ar}), 128.5 (CH, C^{Ar}), 128.0 (CH, C^{Ar}), 122.3 (C, C^{Ar}), 87.2 (C, C^2), 85.8 (C, C^3), 66.3 (CH, C^1), 21.3 (CH_3, OAc).

1-Phenyl-3-(trimethylsilyl)prop-2-ynyl acetate (115)[408]

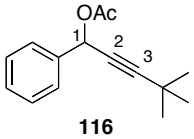


115

The general procedure yielded, after filtration through a plug of Celite (pentane), 1.90 g (77% over 2 steps) of the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.34 (m, 2H, H^{Ar}), 7.23-7.20 (m, 3H, H^{Ar}), 6.26 (s, 1H, H^1), 1.99 (s, 3H, OAc), 0.03 (s, 9H, TMS). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.1 (C, C=O), 142.5 (C, C^{Ar}), 128.9 (CH, C^{Ar}), 127.6 (CH, C^{Ar}), 127.3 (CH, C^{Ar}), 103.8 (C, C^3), 83.2 (C, C^2), 72.1 (CH, C^1), 20.1 (CH_3, OAc), 0.13 (CH_3, TMS).

4,4-Dimethyl-1-phenylpent-2-ynyl acetate (116)



116

[407] Mahrwald, R.; Quint, S. *Tetrahedron* **2000**, *56*, 7463–7468.
[408] Allevi, P.; Ciuffreda, P.; Anastasia, M. *Tetrahedron: Asymmetry* **1997**, *8*, 93–99.

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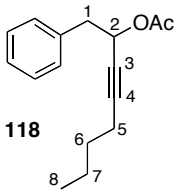
The general procedure yielded, after filtration through a plug of Celite (pentane), 1.72 g (75% over 2 steps) of the title compound as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.8, 1.8 Hz, 2H, H^{Ar}), 7.39-7.33 (m, 3H, H^{Ar}), 6.49 (s, 1H, H^1), 2.08 (s, 3H, OAc), 1.25 (s, 9H, *t*-Bu). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.1 (C, C^{Ar}), 138.1 (C, C^{Ar}), 128.9 (CH, C^{Ar}), 128.7 (CH, C^{Ar}), 128.0 (CH, C^{Ar}), 96.5 (C, C^3), 75.4 (C, C^2), 66.1 (CH, C^1), 31.0 (CH_3, *t*-Bu), 27.7 (C, *t*-Bu), 21.5 (CH_3, OAc). **Calcd. HMRS** for $C_{21}H_{22}O_2Na$ (M+Na): 253.1204. Found: 253.1206.

1-Phenyloct-3-yn-2-yl acetate (118)

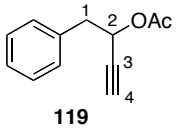


118

The general procedure yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 2.12 g (87% over 2 steps) of the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.22 (m, 5H, H^{Ar}), 5.56 (tt, *J* = 6.8, 2.0 Hz, 1H, H^2), 3.05 (m, 2H, H^1), 2.19 (dt, *J* = 6.9, 2.0 Hz, 2H, H^5), 2.05 (s, 3H, OAc), 1.51-1.41 (m, 2H, H^6), 1.40-1.29 (m, 2H, H^7), 0.90 (t, *J* = 7.2 Hz, 3H, H^8). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.1 (C, C=O), 136.4 (C, C^{Ar}), 129.9 (CH, C^{Ar}), 128.4 (CH, C^{Ar}), 127.0 (CH, C^{Ar}), 87.4 (C, C^3), 77.2 (C, C^4), 65.2 (CH, C^2), 41.7 (CH_2, C^1), 30.6 (CH_2, C^5), 22.0 (CH_2, C^6), 21.2 (CH_3, OAc), 18.5 (CH_2, C^7), 13.8 (CH_3, C^8). **Elemental analysis** calcd. (%) for $C_{16}H_{20}O_2$ (MW 244.33): C, 78.65; H, 8.25. Found: C, 78.86; H, 8.07.

1-Phenylbut-3-yn-2-yl acetate (119)



119

The general procedure yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 1.51 g (80% over 3 steps) of the title compound as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.23 (m, 5H, H^{Ar}), 5.53 (td, *J* = 6.8, 2.2 Hz 1H, H^2), 3.07-3.04 (m, 2H, H^1), 2.44 (d, *J* = 2.2 Hz, 1H, H^4), 2.00 (s, 3H, OAc). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.7 (C, C=O), 135.7 (C, C^{Ar}), 129.7 (CH, C^{Ar}), 128.4 (CH, C^{Ar}), 127.1 (CH, C^{Ar}), 80.8 (C, C^3), 74.5 (CH, C^4), 64.3 (CH, C^2), 41.0 (CH_2, C^1), 20.8 (CH_3, OAc).

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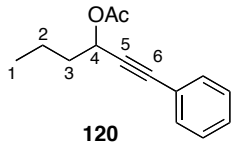
Elemental analysis calcd. (%) for $C_{12}H_{12}O_2$ (MW 188.22): C, 78.01; H, 5.87. Found: C, 77.89; H, 5.68.

1-Phenylhex-1-yn-3-yl acetate (120)

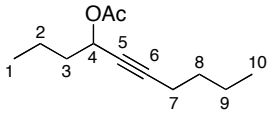


120

The general procedure yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 1.67 g (77% over 2 steps) of the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.42 (m, 2H, H^{Ar}), 7.30-7.27 (m, 3H, H^{Ar}), 5.61 (t, *J* = 6.7 Hz, 1H, H^4), 2.09 (s, 3H, OAc), 1.87-1.79 (m, 2H, H^3), 1.59-1.47 (m, 2H, H^2), 0.98 (t, *J* = 7.4 Hz, 3H, H^1). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.0 (C, C=O), 131.9 (CH, C^{Ar}), 128.6 (CH, C^{Ar}), 128.3 (CH, C^{Ar}), 122.4 (C, C^{Ar}), 86.7 (C, C^5), 85.2 (C, C^6), 64.4 (CH, C^4), 37.0 (CH_2, C^3), 21.1 (CH_3, OAc), 18.5 (CH_2, C^2), 13.7 (CH_3, C^1). **Elemental analysis** calcd. (%) for $C_{14}H_{16}O_2$ (MW 216.28): C, 77.75; H, 7.46. Found: C, 77.89; H, 7.38.

Dec-5-yn-4-yl acetate (121)[409]

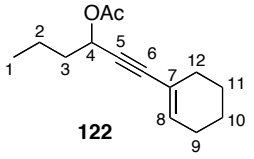


121

The general procedure yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 0.94 g (48% over 2 steps) of the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.36 (t, *J* = 6.6 Hz, 1H, H^4), 2.20 (td, *J* = 6.5, 1.2 Hz, 2H, H^7), 2.06 (s, 3H, OAc), 1.75-1.67 (m, 2H, H^3), 1.54-1.33 (m, 6H, H^2 + H^8 + H^9), 0.94 (t, *J* = 7.4 Hz, 3H, CH_3), 0.91 (t, *J* = 7.1 Hz, 3H, CH_3). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.2 (C, C=O), 86.2 (C, C^5), 77.7 (C, C^6), 64.5 (CH, C^4), 37.3 (CH_2, C^3), 30.7 (CH_2, C^8), 22.0 (CH_2, C^7), 21.2 (CH_3, OAc), 18.5 (CH_2), 13.74 (CH_3), 13.67 (CH_3).

1-Cyclohexenylhex-1-yn-3-yl acetate (122)



122

[409] Mahrwald, R.; Quint, S.; Scholtis, S. *Tetrahedron* **2002**, *58*, 9847–9851.

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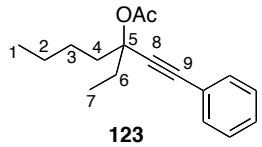
The general procedure yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 1.89 g (86% over 2 steps) of the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.13-6.11 (m, 1H, H^8), 5.50 (t, *J* = 6.6 Hz, 1H, H^4), 2.10-2.07 (m, 7H, OAc + H^9 + H^{12}), 1.78-1.70 (m, 2H, H^3), 1.66-1.53 (m, 4H, H^{10} + H^{11}), 1.50-1.40 (m, 2H, H^2), 0.95 (t, *J* = 7.4 Hz, 3H, H^1). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.6 (C, C=O), 135.9 (CH, C^8), 120.0 (C, C^7), 87.1 (C, C^6), 83.9 (C, C^5), 64.6 (CH, C^4), 37.2 (CH_2, C^3), 29.1 (CH_2, C^{12}), 25.7 (CH_2, C^9), 23.3 (CH_2), 21.5 (CH_2), 21.2 (CH_3, OAc), 18.5 (CH_2, C^2), 13.7 (CH_3, C^1). **Elemental analysis** calcd. (%) for $C_{14}H_{20}O_2$ (MW 220.31): C, 76.33; H, 9.15. Found: C, 76.35; H, 9.28.

3-Ethyl-1-phenylhept-1-yn-3-yl acetate (123)



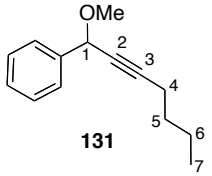
123

The general procedure yielded, after flash chromatography on silica gel (pentane/Et_2O, 99/1), 1.73 g (67% over 2 steps) of the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.41 (m, 2H, H^{Ar}), 7.31-7.26 (m, 3H, H^{Ar}), 2.20-1.90 (m, 7H, OAc + H^4 + H^6), 1.53-1.30 (m, 4H, H^2 + H^3), 1.04 (t, *J* = 7.4 Hz, 3H, CH_2–CH_3), 0.94 (t, *J* = 7.2 Hz, 3H, CH_2–CH_3). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.5 (C, C=O), 132.0 (CH, C^{Ar}), 128.4 (CH, C^{Ar}), 128.3 (CH, C^{Ar}), 123.0 (C, C^{Ar}), 89.0 (C, C^8), 85.9 (C, C^9), 80.1 (C, C^5), 37.8 (CH_2, C^4), 31.5 (CH_2, C^6), 26.5 (CH_2, C^3), 22.9 (CH_2, C^2), 22.2 (CH_3, OAc), 14.3 (CH_3, C^1), 8.7 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{17}H_{22}O_2$ (MW 258.36): C, 79.03; H, 8.58. Found: C, 79.28; H, 8.47.

2. Synthesis and characterization of propargylic methylether 131

(1-Methoxyhept-2-ynyl)benzene (131)



131

A suspension of NaH (60% in mineral oil, 400 mg, 10.5 mmol, 2.1 equiv) was introduced in a dry round-bottom flask and washed with hexane. Dry THF (15 mL), MeI (3.1 mL, 50 mmol, 3.3 equiv) and a solution of alcohol **67-a** (940 mg, 5 mmol, 1 equiv) in dry THF (5

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mL) were added in turn. The mixture was heated to 35°C for 1 h and then quenched with a saturated NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated to give a crude oil, which was purified by flash chromatography on silica gel (pentane/Et_2O, 95/5), yielding 698 mg (69%) of the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.45 (m, 2H, H^{Ar}), 7.36-7.22 (m, 3H, H^{Ar}), 5.06 (s, 1H, H1), 3.38 (s, 3H, OMe), 2.27 (t, *J* = 6.6 Hz, 2H, H4), 1.62-1.35 (m, 4H, H^5 + H^6), 0.91 (t, *J* = 6.9 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 139.3 (C, C^{Ar}), 128.4 (CH, C^{Ar}), 128.2 (CH, C^{Ar}), 127.5 (CH, C^{Ar}), 88.6 (C, C^3), 77.8 (C, C^2), 73.3 (C, C^1), 55.6 (CH_3, OMe), 30.9 (CH_2, C^5), 22.1 (CH_2, C^6), 18.6 (CH_2, C^4), 13.6 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{14}H_{18}O$ (MW 202.29): C, 83.12; H, 8.97. Found: C, 83.00; H, 8.84.

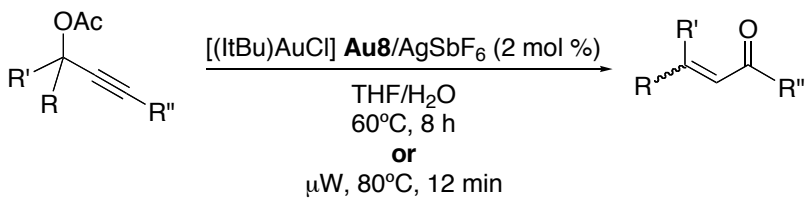
3. Optimization of the catalytic cystem

General Procedure

To a solvent "S" solution (2.5 mL) of [(NHC)AuCl] (0.01 mmol, 2 mol %) in a screw-cap vial, AgX (0.01 mmol, 2 mol %) was added. The solution instantly became cloudy and distilled water (0.5 mL) was added. The reaction mixture was stirred for 1 min before a solvent "S" solution (2.5 mL) of propargylic acetate **77** (0.5 mmol, 1.0 equiv) was added. The vial was then placed in an oil bath at the indicated temperature and the reaction mixture stirred for the indicated time and allowed to cool down to room temperature. The resulting mixture was dissolved in pentane, filtered through Celite and concentrated. ^{1}H NMR analysis relies on characteristic propargylic or vinylic signals for **77**, **78**, **101** and **80** [δ, ppm: 6.46 (s, 1H); 6.58 (t, 1H); 6.75 (d, 1H); 6.70 (d, 1H) respectively].

4. Au-Catalyzed formation of a,b-unsaturated carbonyl compounds

General procedure



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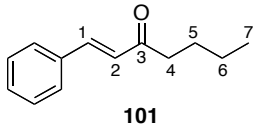
Conventional heating (A). To a THF solution (5 mL) of [(ItBu)AuCl] **Au8** (8 mg, 0.02 mmol, 2 mol %) in a screw-cap vial, $AgSbF_6$ (7 mg, 0.02 mmol, 2 mol %) was added. The solution instantly became cloudy and distilled water (1 mL) was added. The reaction mixture was stirred for 1 min before a THF solution (5 mL) of propargylic acetate (1 mmol, 1.0 equiv) was added. The vial was then placed in an oil bath at 60ºC and the reaction mixture stirred for 8 h and allowed to cool down to room temperature. The resulting mixture was dissolved in pentane, filtered through Celite and concentrated. The crude product was purified by flash chromatography on silica gel.

Microwave heating (B). To a THF solution (5 mL) of [(ItBu)AuCl] **Au8** (8.2 mg, 0.02 mmol, 2 mol %) in a screw-cap vial, $AgSbF_6$ (6.8 mg, 0.02 mmol, 2 mol %) was added. The solution instantly became cloudy and distilled water (1 mL) was added. The reaction mixture was stirred for 1 min before a THF solution (5 mL) of propargylic acetate (1 mmol, 1.0 equiv) was added. The vial was then closed and placed in a microwave reactor and heated at 80ºC for 12 min. The resulting mixture was dissolved in pentane, filtered through Celite and concentrated. The crude product was purified by flash chromatography on silica gel when necessary.

*Characterization of α,β-unsaturated carbonyl compounds **101**, **103-107**, **111-113**, **117**, and **124-129***

(*E*)-1-Phenylhept-1-en-3-one (101)[410]



101

A) The general procedure, using propargylic acetate **77** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 185 mg (98%) of the title compound.

B) The general procedure, using propargylic acetate **77** under microwave heating, yielded, after filtration over a plug of Celite (pentane), 185 mg (98%) of the title compound.

C) The general procedure, using propargylic alcohol **130**[411] under conventional heating, afforded 25% of the title compound as estimated by ^{1}H NMR integration of the signals of the starting alcohol and the formed enone.

[410] Dimmock, J. R.; Carter, P. L.; Ralph, P. D. *J. Chem. Soc. B* **1968**, 698–703.

[411] Alcohol **130** is an intermediate in the synthesis of arylpropargyl acetate **67** and its synthesis and characterization are described in section **VII.C.1** of this chapter under **67-a**.

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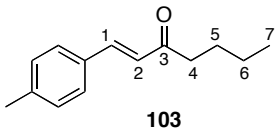
D) The general procedure, using propargylic methylether **131** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 117 mg (62%) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57-7.54 (m, 2H, H^{Ar}), 7.55 (d, *J* = 16.2 Hz, 1H, H^1), 7.41-7.38 (m, 3H, H^{Ar}), 6.75 (d, *J* = 16.2 Hz, 1H, H^2), 2.67 (t, *J* = 7.3 Hz, 2H, H^4), 1.72-1.62 (m, 2H, H^5), 1.45-1.33 (m, 2H, H^6), 0.95 (t, *J* = 7.3 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 200.9 (C, C^3), 142.5 (C, C^1), 134.8 (C, C^{Ar}), 130.6 (CH, C^{Ar}), 129.1 (CH, C^{Ar}), 128.4 (CH, C^{Ar}), 126.5 (CH, C^2), 40.9 (CH_2, C^4), 26.7 (CH_2, C^5), 22.7 (CH_2, C^6), 14.1 (CH_3, C^7).

(*E*)-1-*p*-Tolylhept-1-en-3-one (103)[410]

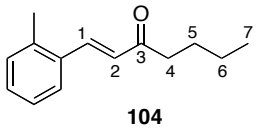


103

The general procedure, using propargylic acetate **82** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 196 mg (97%) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, *J* = 16.2 Hz, 1H, H^1), 7.45 (d, *J* = 8.2 Hz, 2H, H^{Ar}), 7.20 (d, *J* = 8.2 Hz, 2H, H^{Ar}), 6.70 (d, *J* = 16.2 Hz, 1H, H^2), 2.66 (t, *J* = 7.3 Hz, 2H, H^4), 2.38 (s, 3H, C^{Ar}–CH_3), 1.71-1.61 (m, 2H, H^5), 1.45-1.32 (m, 2H, H^6), 0.94 (t, *J* = 7.3 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 201.0 (C, C^3), 142.6 (C, C^1), 141.1 (C, C^{Ar}), 132.0 (C, C^{Ar}), 129.9 (CH, C^{Ar}), 128.5 (CH, C^{Ar}), 125.6 (CH, C^2), 40.8 (CH_2, C^4), 26.8 (CH_2, C^5), 22.7 (CH_2, C^6), 21.7 (CH_3, C^{Ar}–CH_3), 14.1 (CH_3, C^7).

(*E*)-1-*o*-Tolylhept-1-en-3-one (104)



104

A) The general procedure, using propargylic acetate **85** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 198 mg (98%) of the title compound.

B) The general procedure, using propargylic acetate **85** under microwave heating, yielded, after filtration over a plug of Celite (pentane), 200 mg (99%) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 16.0 Hz, 1H, H^1), 7.58 (d, *J* = 7.0 Hz, 1H, H^{Ar}), 7.29-7.19 (m, 3H, H^{Ar}), 6.67 (d, *J* = 16.0 Hz, 1H, H^2), 2.66 (t, *J* = 7.2 Hz, 2H, H^4), 2.45 (s,

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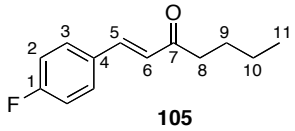
3H, C^{Ar}–CH_3), 1.73-1.63 (m, 2H, H^5), 1.45-1.33 (m, 2H, H^6), 0.95 (t, *J* = 7.4 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 200.9 (C, C^3), 140.0 (C, C^1), 138.2 (C, C^{Ar}–CH_3), 133.7 (C, C^{Ar}), 131.0 (CH, C^{Ar}), 130.3 (CH, C^{Ar}), 127.4 (CH, C^{Ar}), 126.6 (CH, C^{Ar}), 126.5 (CH, C^2), 41.2 (CH_2, C^4), 26.7 (CH_2, C^5), 22.7 (CH_2, C^6), 20.0 (CH_3, C^{Ar}–CH_3), 14.1 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{14}H_{18}O$ (MW 202.29): C, 83.12; H, 8.97. Found: C, 83.00; H, 9.10.

(*E*)-1-(4-Fluorophenyl)hept-1-en-3-one (105)



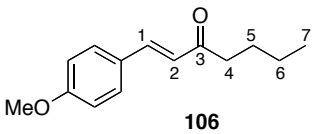
105

A) The general procedure, using propargylic acetate **81** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 188 mg (91%) of the title compound.

B) The general procedure, using propargylic acetate **81** under microwave heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 186 mg (90%) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56-7.49 (m, 3H, $2H^2 + H^5$), 7.11-7.05 (m, 2H, H^3), 6.68 (d, *J* = 16.2 Hz, 1H, H^6), 2.65 (t, *J* = 7.3 Hz, 2H, H^8), 1.71-1.61 (m, 2H, H^9), 1.44-1.32 (m, 2H, H^{10}), 0.94 (t, *J* = 7.3 Hz, 3H, H^{11}). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 200.6 (C, C^7), 164.1 (d, *J* = 250 Hz, C, C^1), 141.1 (CH, C^5), 131.0 (d, *J* = 3.3 Hz, C, C^4), 130.3 (d, *J* = 8.5 Hz, CH, C^3), 126.1 (CH, C^6), 116.2 (d, *J* = 21.8 Hz, CH, C^2), 40.9 (CH_2, C^8), 26.6 (CH_2, C^9), 22.6 (CH_2, C^{10}), 14.1 (CH_3, C^{11}). **Elemental analysis** calcd. (%) for $C_{13}H_{15}FO$ (MW 206.26): C, 75.70; H, 7.33. Found: C, 75.52; H, 7.61.

(*E*)-1-(4-Methoxyphenyl)hept-1-en-3-one (106)



106

The general procedure, using propargylic acetate **83** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 194 mg (89%) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56-7.52 (m, 3H, $2H^{Ar} + H^1$), 6.95 (d, *J* = 8.8 Hz, 2H, H^{Ar}), 6.66 (d, *J* = 16.0 Hz, 1H, H^2), 3.87 (s, 3H, OMe), 2.66 (t, *J* = 7.6 Hz, 2H, H^4), 1.72-1.65 (m, 2H, H^5), 1.46-1.36 (m, 2H, H^6), 0.97 (t, *J* = 6.8 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ

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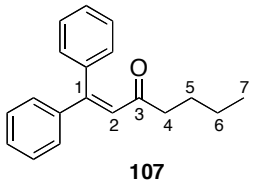
200.9 (C, C^3), 161.7 (C, *C*–OMe), 142.3 (CH, C^1), 130.1 (CH, C^{Ar}), 127.5 (C, C^{Ar}), 124.4 (CH, C^2), 114.6 (CH, C^{Ar}), 55.6 (CH_3, OMe), 40.8 (CH_2, C^4), 26.9 (CH_2, C^5), 22.7 (CH_2, C^6), 14.1 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{14}H_{18}O_2$ (MW 218.29): C, 77.03; H, 8.31. Found: C, 77.12; H, 8.61.

1,1-Diphenylhept-1-en-3-one (107)

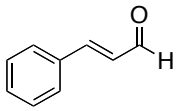


107

The general procedure, using propargylic acetate **102** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 233 mg (88%) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.36 (m, 3H, H^{Ar}), 7.35-7.28 (m, 5H, H^{Ar}), 7.22-7.18 (m, 2H, H^{Ar}), 6.58 (s, 1H, H^2), 2.23 (t, *J* = 7.3 Hz, 2H, H^4), 1.52-1.43 (m, 2H, H^5), 1.24-1.12 (m, 2H, H^6), 0.80 (t, *J* = 7.3 Hz, 3H, H^7). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 202.8 (C, C^3), 153.3 (C, C^1), 141.2 (C, C^{Ar}), 139.3 (C, C^3), 129.7 (CH, C^{Ar}), 129.5 (CH, C^{Ar}), 128.7 (CH, C^{Ar}), 128.6 (CH, C^{Ar}), 128.5 (CH, C^{Ar}), 126.9 (CH, C^2), 43.1 (CH_2, C^4), 26.6 (CH_2, C^5), 22.5 (CH_2, C^6), 14.0 (CH_3, C^7). **Elemental analysis** calcd. (%) for $C_{19}H_{20}O$ (MW 264.36): C, 86.32; H, 7.63. Found: C, 86.15; H, 7.51.

Cinnamaldehyde (111)[412]



111

A) The general procedure, using propargylic acetate **108** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 130 mg (98%) of the title compound.

B) The general procedure, using propargylic acetate **108** under microwave heating, yielded, after filtration over a plug of Celite (pentane), 129 mg (98%) of the title compound.

[412] Cinnamaldehyde is a commercially available product, CAS # [104-55-2].

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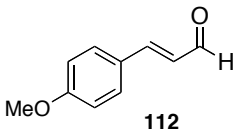
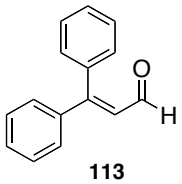
(*E*)-3-(4-Methoxyphenyl)acrylaldehyde (112)[413]



112

The general procedure, using propargylic acetate **109** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 157 mg (97%) of the title compound.

3,3-Diphenylacrylaldehyde (113)[414]

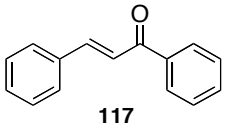


113

The general procedure, using propargylic acetate **110** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 200 mg (96%) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.53 (d, *J* = 8.0 Hz, 1H, CHO), 7.49-7.29 (m, 10H, H^{Ar}), 6.60 (d, *J* = 8.0 Hz, 1H, =CH). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 193.7 (CH, C=O), 162.5 (C, *C*=CH), 139.9 (C, C^{Ar}), 136.8 (C, C^{Ar}), 130.9 (CH, C^{Ar}), 130.7 (CH, C^{Ar}), 129.6 (CH, C^{Ar}), 128.9 (CH, C^{Ar}), 128.83 (CH, C^{Ar}), 128.80 (CH, C^{Ar}), 128.5 (CH, C^{Ar}), 127.4 (C, C=*C*H).

(*E*)-Chalcone (117)[415]



117

The general procedure, using propargylic acetate **114** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 192 mg (92%) of the title compound.

[413] (*E*)-3-(4-Methoxyphenyl)acrylaldehyde is a commercially available product, CAS # [1963-36-6].
[414] Cadierno, V.; Diez, S. E.; Garcia-Garrido, J. Gimeno, *Chem. Commun.* **2004**, 2716–2717.
[415] (*E*)-Chalcone is a commercially available product, CAS # [614-47-1].

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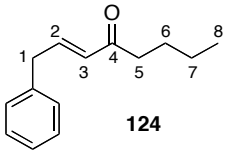
(*E*)-1-Phenyloct-2-en-4-one (124)



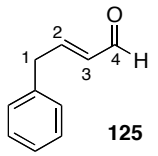
124

A) The general procedure, using propargylic acetate **118** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 176 mg (87%) of the title compound.

B) The general procedure, using propargylic acetate **118** under microwave heating yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 188 mg (93%) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.29 (m, 2H, H^{Ar}), 7.27-7.21 (m, 1H, H^{Ar}), 7.19-7.16 (m, 2H, H^{Ar}), 6.38 (dt, *J* = 15.8, 6.8 Hz, 1H, H^2), 6.09 (dt, *J* = 15.8, 1.6 Hz, 1H, H^3), 5.52 (dd, *J* = 6.8, 1.6 Hz, 2H, H^1), 2.53 (t, *J* = 7.3 Hz, 2H, H^5), 1.63-1.53 (m, 2H, H^6), 1.38-1.26 (m, 2H, H^7), 0.90 (t, *J* = 7.3 Hz, 3H, H^8). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 200.9 (C, C^4), 145.2 (CH, C^2), 137.9 (C, C^{Ar}), 131.3 (CH, C^3), 129.0 (CH, C^{Ar}), 128.9 (CH, C^{Ar}), 126.9 (CH, C^{Ar}), 40.0 (CH_2, C^1), 38.9 (CH_2, C^5), 26.4 (CH_2, C^6), 22.6 (CH_2, C^7), 14.1 (CH_3, C^8). **Elemental analysis** calcd. (%) for $C_{14}H_{18}O$ (MW 202.29): C, 83.12; H, 8.97. Found: C, 83.05; H, 8.98.

(*E*)-4-Phenylbut-2-enal (125)



125

A) The general procedure, using propargylic acetate **119** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 137 mg (94%) of the title compound.

B) The general procedure, using propargylic acetate **119** under microwave heating, yielded, after filtration over a plug of Celite (pentane), 135 mg (93%) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.53 (d, *J* = 7.9 Hz, 1H, H^4), 7.33-7.23 (m, 3H, H^{Ar}), 7.19-7.17 (m, 2H, H^{Ar}), 6.95 (dt, *J* = 15.5, 6.7 Hz, 1H, H^2), 6.09 (ddt, *J* = 15.5, 7.9, 1.5 Hz, 1H, H^3), 3.64 (d, *J* = 6.7 Hz, 2H, H^1). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 193.9 (CH, C^4), 156.6 (CH, C^2), 137.2 (C, C^{Ar}), 133.6 (CH, C^3), 129.0 (CH, C^{Ar}), 128.9 (CH, C^{Ar}), 127.1 (CH, C^{Ar}), 39.1

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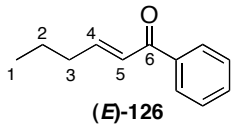
(CH_2, C^1). **Elemental analysis** calcd. (%) for $C_{10}H_{10}O$ (MW 146.19): C, 82.16; H, 6.89. Found: C, 82.28; H, 7.07.

(*E*)-1-Phenylhex-2-en-1-one (126)

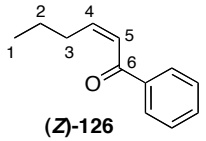


(*E*)-126

The general procedure, using propargylic acetate **120** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 143 mg (82%) of the title compound. The product was collected in two fractions. The second one (33 mg) was a mixture (*E*:*Z*, 2:1) of the two isomers of the title compound while the first one (110 mg) contained only the (*E*)-olefin.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95-7.91 (m, 2H, H^{Ar}), 7.55 (tt, *J* = 7.2, 1.4 Hz, 1H, H^{Ar}), 7.49-7.43 (m, 2H, H^{Ar}), 7.07 (dt, *J* = 15.4, 6.9 Hz, 1H, H^4), 6.88 (dt, *J* = 15.4, 1.3 Hz, 1H, H^5), 2.34-2.26 (m, 2H, H^3), 1.62-1.47 (m, 2H, H^2), 0.98 (t, *J* = 7.4 Hz, 3H, H^1). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 191.1 (C, C^6), 150.1 (CH, C^4), 138.2 (C, C^{Ar}), 132.8 (CH, C^{Ar}), 128.70 (CH, C^{Ar}), 128.68 (CH, C^{Ar}), 126.2 (CH, C^5), 35.0 (CH_2, C^3), 21.6 (CH_2, C^2), 13.9 (CH_3, C^1). **Elemental analysis** calcd. (%) for $C_{12}H_{14}O$ (MW 174.24): C, 82.72; H, 8.10. Found: C, 82.78; H, 8.07.

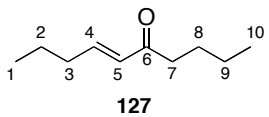
(*Z*)-1-Phenylhex-2-en-1-one ((*Z*)-126)[416]



(*Z*)-126

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93-7.91 (m, 2H, H^{Ar}), 7.58-7.54 (m, 1H, H^{Ar}), 7.50-7.43 (m, 2H, H^{Ar}), 6.81 (dt, *J* = 11.6, 1.7 Hz, 1H, H^5), 6.33 (dt, *J* = 11.6, 7.4 Hz, 1H, H^4), 2.65-2.57 (m, 2H, H^3), 1.58-1.45 (m, 2H, H^2), 0.95 (t, *J* = 7.4 Hz, 3H, H^1).

(*E*)-Dec-6-en-5-one (127)[417]



127

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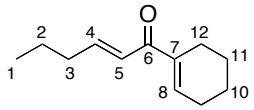
A) The general procedure, using propargylic acetate **121** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 99/1), 145 mg (94%) of the title compound.

B) The general procedure, using propargylic acetate **121** under microwave heating, yielded, after filtration over a plug of Celite (pentane), 147 mg (95%) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83 (dt, *J* = 15.9, 6.9 Hz, 1H, H^4), 6.10 (dt, *J* = 15.9, 1.5 Hz, 1H, H^5), 2.54 (t, *J* = 7.3 Hz, 2H, H^7), 2.23-2.16 (m, 2H, H^3), 1.64-1.44 (m, 4H, H^2 + H^8), 1.40-1.28 (m, 2H, H^9), 0.97-0.89 (m, 6H, H^1 + H^{10}). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 201.2 (C, C^6), 147.3 (CH, C^4), 130.7 (CH, C^5), 40.0 (CH_2, C^7), 34.6 (CH_2, C^3), 26.6 (CH_2, C^8), 22.6 (CH_2, C^9), 21.6 (CH_2, C^2), 14.1 (CH_3, C^{10}), 14.1 (CH_3, C^1).

(*E*)-1-Cyclohexenylhex-2-en-1-one (128)



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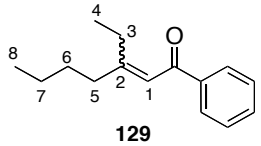
The general procedure, using propargylic acetate **122** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 99/1), 159 mg (89%) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 (dt, *J* = 15.6, 7.0 Hz, 1H, H^4), 6.64-6.60 (m, 1H, H^8), 6.48 (dt, *J* = 15.6, 1.3 Hz, 1H, H^5), 1.98-1.86 (m, 6H, H^3 + H^9 + H^{12}), 1.68-1.61 (m, 4H, H^{10} + H^{11}), 1.52-1.45 (m, 2H, H^2), 0.95 (t, *J* = 7.4 Hz, 3H, H^1). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 190.3 (C, C^6), 155.1 (CH, C^4), 146.2 (CH, C^8), 137.8 (C, C^7), 127.7 (CH, C^5), 35.0 (CH_2, C^3), 26.6 (CH_2), 25.8 (CH_2), 24.0 (CH_2), 23.7 (CH_2), 23.2 (CH_2), 13.7 (CH_3, C^1). **Elemental analysis** calcd. (%) for $C_{12}H_{18}O$ (MW 178.27): C, 80.85; H, 10.18. Found: C, 80.69; H, 10.26.

3-Ethyl-1-phenylhept-2-en-1-one (129)



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The general procedure, using propargylic acetate **123** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 98/2), 195 mg (90%) of the title compound.

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^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81-7.75 (m, 3H, H^{Ar}), 7.48-7.43 (m, 2H, H^{Ar}), 6.70 (s broad, 1H, H^1), 2.03-1.92 (m, 4H, H^3 + H^5), 1.33-1.27 (m, 4H, H^6 + H^7), 1.01 (t, *J* = 7.3 Hz, 3H, CH_2–CH_3), 0.91 (t, *J* = 7.4 Hz, 3H, CH_2–CH_3). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 191.0 (C, C=O), 163.1 (C, C^2), 139.2 (C, C^{Ar}), 138.7 (C, C^{Ar}), 134.8 (CH, C^{Ar}), 134.7 (CH, C^{Ar}), 129.8 (CH, C^{Ar}), 128.7 (CH, C^{Ar}), 128.6 (CH, C^{Ar}), 118.2 (CH, C^1), 33.0 (CH_2), 32.8 (CH_2), 31.6 (CH_2), 21.9 (CH_2), 21.7 (CH_2), 21.6 (CH_2), 21.2 (CH_2), 13.9 (CH_3), 9.3 (CH_3), 9.1 (CH_3). **Elemental analysis** calcd. (%) for $C_{15}H_{20}O$ (MW 216.32): C, 83.28; H, 9.32. Found: C, 83.40; H, 9.07.

5. Computational details

In the computational model, the acetate of reactant **R1** was represented by a formate. A methyl group was used as the alkyne substituent. The NHC ligand was represented by IDM (*N*,*N*'-dimethylimidazol-2-ylidene). The stationary points for the uncatalyzed and the Au-catalyzed reaction were fully optimized at the DFT-Becke3LYP[418,419] level of theory. The Au-atom is described using the LANL2DZ basis set;[420] this basis set includes the Los Alamos effective core potential for the inner electrons, and a double-ζ basis for the outer electrons. To improve the basis set for the Au-atom, a f-polarization shell was added (exponent 1.050).[421] The 6-31+G(d) basis set[422] was used for all remaining atoms. All stationary points were characterized by frequency calculations, transition states were identified by having a single negative eigenvalue in the Hessian matrix. All calculations were performed using the Gaussian03 suite of programs.[423]

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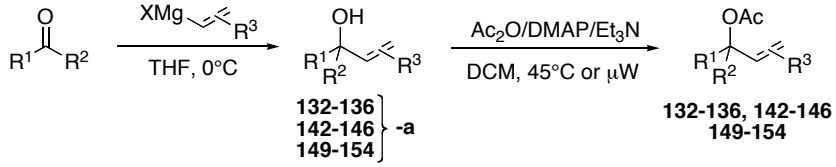
E. Rearrangement of allylic acetates

1. Synthesis and characterization of allylic acetates (57), (132-136), (142-146), and (149-154)

The synthesis and characterization of allylic acetate **57** is described in Chapter II, section **V.E.1**.

*Preparation of allylic acetates **132-136**, **142-146**, and **149-154***



General procedures

Alkenylation: In an oven-dried round-bottom flask, to a solution of aldehyde/ketone (10 mmol, 1.0 equiv) in THF (20 mL) under nitrogen at 0ºC, the Grignard reagent (12 mmol, 1.2 equiv) was added and the reaction mixture was stirred for 20 minutes. The reaction was then allowed to warm up to room temperature, further stirred until completion (TLC monitoring) and quenched with a saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give the crude allylic alcohol "**-a**" that was engaged in the next step without further purification.

Acylation: The allylic alcohol (10 mmol, 1.0 equiv), DCE (30 mL), DMAP (0.360 g, 3.0 mmol, 0.3 equiv), Et_3N (5.6 mL, 40 mmol, 4 equiv), and Ac_2O (1.8 mL, 20 mmol, 2 equiv) were added in turn in a round-bottom flask equipped with a condenser and heated overnight at 80°C. The reaction was then quenched with a saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give a crude product that was purified by flash chromatography on silica gel.

Alternatively, the acylation of allylic alcohols could be carried out using microwave-assisted heating conditions described as follow. The allylic alcohol (10 mmol, 1.0 equiv), DMAP (0.360 g, 3.0 mmol, 0.3 equiv), Et_3N (5.6 mL, 40 mmol, 4 equiv), and Ac_2O (1.8 mL, 20 mmol, 2 equiv) were added in turn in a microwave-designed vial. The reaction mixture was heated under microwave-assisted heating at 100°C for 12 min, then quenched with a

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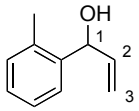
saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give a crude product that was purified by flash chromatography on silica gel when necessary.

*Characterization of allylic acetates **132-136**, **142-146**, and **149-154***

1-*o*-Tolylallyl acetate (132)

The general procedure yielded, after flash chromatography on silica gel (gradient pentane/Et_2O, from 95/5 to 80/20), 1.87 g (98% over 2 steps) of the title compound as a colorless oil.

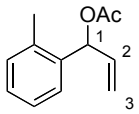
1-*o*-Tolylprop-2-en-1-ol (132-a)



132-a

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 7.4, 1.5 Hz, 1H, H^{Ar}), 7.21-7.08 (m, 3H, H^{Ar}), 5.99 (ddd, *J* = 17.2, 10.4, 6.0 Hz, 1H, H^2), 5.35 (d, *J* = 5.7 Hz, 1H, H^1), 5.27 (dt, *J* = 17.2, 1.5 Hz, 1H, $1H^3$), 5.17 (dt, *J* = 10.4, 1.5 Hz, 1H, $1H^3$), 2.54 (s broad, 1H, OH), 2.32 (s, 3H, Me). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 140.7 (C, C^{Ar}), 139.6 (CH, C^2), 135.4 (C, C^{Ar}), 130.6 (CH, C^{Ar}), 127.6 (CH, C^{Ar}), 126.4 (CH, C^{Ar}), 126.0 (CH, C^{Ar}), 115.2 (CH_2, C^3), 72.0 (CH, C^1), 19.2 (CH_3, Me).

1-*o*-Tolylallyl acetate (132)



132

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.35 (m, 1H, H^{Ar}), 7.23-7.14 (m, 3H, H^{Ar}), 6.44 (d, *J* = 5.7 Hz, 1H, H^1), 5.99 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1H, H^2), 5.23 (dt, *J* = 17.0, 1.3 Hz, 1H, $1H^3$), 5.20 (dt, *J* = 10.5, 1.3 Hz, 1H, $1H^3$), 2.37 (s, 3H, Me), 2.11 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.2 (C, C=O), 137.2 (C, C^{Ar}), 135.92 (C, C^{Ar}), 135.86 (CH, C^2), 130.7 (CH, C^{Ar}), 128.2 (CH, C^{Ar}), 127.0 (CH, C^{Ar}), 126.4 (CH, C^{Ar}), 117.1 (CH_2, C^3), 73.6 (CH, C^1), 21.4 (CH_3, OAc), 19.4 (CH_3, Me). **Calcd. HMRS** for $C_{12}H_{14}O_2Na$ (M+Na): 213.0891. Found: 213.0896.

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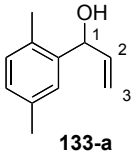
1-(2,5-Dimethylphenyl)allyl acetate (133)

The general procedure yielded, after filtration over a plug of silica (pentane), 2.04 g (99% over 2 steps) of the title compound as a colorless oil.

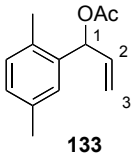
1-(2,5-Dimethylphenyl)prop-2-en-1-ol (133-a)



133-a

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (s, 1H, H^{Ar}), 7.01 (d, *J* = 7.7 Hz, 1H, H^{Ar}), 6.97 (d, *J* = 7.7 Hz, 1H, H^{Ar}), 5.98 (ddd, *J* = 17.3, 10.3, 5.6 Hz, 1H, H^{2}), 5.32 (d, *J* = 5.6 Hz, 1H, H^{1}), 5.27 (d, *J* = 17.3 Hz, 1H, $1H^{3}$), 5.16 (d, *J* = 10.3 Hz, 1H, $1H^{3}$), 2.30 (s, 3H, Me), 2.28 (s, 3H, Me), 2.22 (s, 1H, OH). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 140.4 (C, C^{Ar}), 139.6 (CH, C^{2}), 135.9 (C, C^{Ar}), 132.2 (C, C^{Ar}), 130.6 (CH, C^{Ar}), 128.4 (CH, C^{Ar}), 126.6 (CH, C^{Ar}), 115.1 (CH_2, C^{3}), 72.1 (CH, C^{1}), 21.2 (CH_3, Me), 18.8 (CH_3, Me).

1-(2,5-Dimethylphenyl)allyl acetate (133)



133

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (s, 1H, H^{Ar}), 7.05-6.98 (m, 2H, H^{Ar}), 6.42 (dt, *J* = 5.6, 1.5 Hz, 1H, $1H^{3}$), 6.03-5.92 (m, 1H, H^{2}), 5.23 (d, *J* = 1.5 Hz, 1H, H^{1}), 5.18 (dt, *J* = 6.9, 1.5 Hz, 1H, $1H^{3}$), 2.32 (s, 3H, Me), 2.31 (s, 3H, Me), 2.10 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.0 (C, C=O), 136.8 (C, C^{Ar}), 135.9 (CH, C^{2}), 135.7 (C, C^{Ar}), 132.7 (C, C^{Ar}), 130.6 (CH, C^{Ar}), 128.9 (CH, C^{Ar}), 127.6 (CH, C^{Ar}), 116.8 (CH_2, C^{3}), 73.6 (CH, C^{1}), 21.3 (CH_3, Me), 21.2 (CH_3, Me), 18.9 (CH_3, OAc). **Calcd. HMRS** for $C_{13}H_{16}O_2Na$ (M+Na): 227.1048. Found: 227.1039.

1-(4-Fluorophenyl)allyl acetate (134)

The general procedure yielded, after flash chromatography on silica gel (gradient pentane/Et_2O, from 98/2 to 80/20), 1.55 g (80% over 2 steps) of the title compound as a colorless oil.

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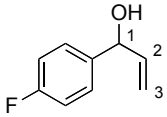
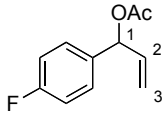
1-(4-Fluorophenyl)prop-2-en-1-ol (134-a)



134-a

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.31 (m, 2H, H^{Ar}), 7.04-7.00 (m, 2H, H^{Ar}), 6.00 (ddd, *J* = 17.1, 10.3, 6.0 Hz, 1H, H^2), 5.31 (dt, *J* = 17.1, 1.4 Hz, 1H, $1H^3$), 5.18 (dt, *J* = 10.3, 1.4 Hz, 1H, $1H^3$), 5.15 (d, *J* = 6.0 Hz, 1H, H^1), 2.91 (s broad, 1H, OH). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 162.4 (d, *J* = 243.8 Hz, C, C–F), 140.5 (CH, C^2), 138.7 (d, *J* = 3.1 Hz, C, C^{Ar}), 128.2 (d, *J* = 8.1 Hz, CH, C^{Ar}), 115.4 (d, *J* = 21.3 Hz, CH, C^{Ar}), 115.2 (CH_2, C^3), 74.7 (CH, C^1).

1-(4-Fluorophenyl)allyl acetate (134)



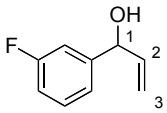
134

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.31 (m, 2H, H^{Ar}), 7.07-7.01 (m, 2H, H^{Ar}), 6.24 (d, *J* = 6.0 Hz, 1H, H^1), 5.98 (ddd, *J* = 17.1, 10.4, 6.0 Hz, 1H, H^2), 5.28 (dt, *J* = 17.1, 1.3 Hz, 1H, $1H^3$), 5.25 (dt, *J* = 10.4, 1.3 Hz, 1H, $1H^3$), 2.10 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.1 (C, C=O), 162.7 (d, *J* = 245.2 Hz, C, C–F), 136.2 (CH, C^2), 134.9 (d, *J* = 3.2 Hz, C, C^{Ar}), 129.2 (d, *J* = 8.2 Hz, CH, C^{Ar}), 117.2 (CH_2, C^3), 115.6 (d, *J* = 21.4 Hz, CH, C^{Ar}), 75.6 (CH, C^1), 21.4 (CH_3, OAc). **Calcd. HMRS** for $C_{11}H_{11}FO_2Na$ (M+Na): 217.0641. Found: 217.0650.

1-(3-Fluorophenyl)allyl acetate (135)

The general procedure yielded, after flash chromatography on silica gel (gradient pentane/Et_2O, from 98/2 to 80/20), 1.23 g (64% over 2 steps) of the title compound as a colorless oil.

1-(3-Fluorophenyl)prop-2-en-1-ol (135-a)



135-a

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.26 (m, 1H, H^{Ar}), 7.12-7.07 (m, 2H, H^{Ar}), 6.96-6.92

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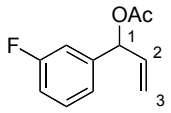
(m, 1H, H^{Ar}), 5.98 (ddd, *J* = 17.1, 10.3, 5.9 Hz, 1H, H^2), 5.32 (dt, *J* = 17.1, 1.3 Hz, 1H, $1H^3$) 5.18 (dt, *J* = 10.3, 1.3 Hz, 1H, $1H^3$), 5.14 (d, *J* = 5.9 Hz, 1H, H^1), 3.40 (s broad, 1H, OH). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 163.1 (d, *J* = 244.3 Hz, C, C–F), 145.7 (d, *J* = 6.6 Hz, C, C^{Ar}), 140.1 (CH, C^2), 130.0 (d, *J* = 8.1 Hz, CH, C^{Ar}), 122.0 (d, *J* = 2.7 Hz, CH, C^{Ar}), 115.5 (CH_2, C^3), 114.4 (d, *J* = 21.0 Hz, C, C^{Ar}), 113.2 (d, *J* = 21.8 Hz, C, C^{Ar}), 74.6 (CH, C^1).

1-(3-Fluorophenyl)allyl acetate (135)



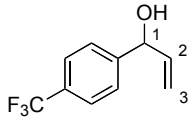
135

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (td, *J* = 8.0, 5.8 Hz, 1H, H^{Ar}), 7.12 (d, *J* = 7.7 Hz, 1H, H^{Ar}), 7.06 (dt, *J* = 9.6, 2.1 Hz, 1H, H^{Ar}), 6.99 (tdd, *J* = 8.4, 2.6, 0.9 Hz, 1H, H^{Ar}), 6.24 (d, *J* = 6.0 Hz, 1H, H^1), 5.97 (ddd, *J* = 17.1, 10.5, 6.0 Hz, 1H, H^2), 5.33-5.25 (m, 2H, H^3), 2.12 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.0 (C, C=O), 163.0 (d, *J* = 244.7 Hz, C, C–F), 141.6 (d, *J* = 7.1 Hz, C, C^{Ar}), 135.9 (CH, C^2), 130.3 (d, *J* = 8.0 Hz, CH, C^{Ar}), 122.8 (d, *J* = 2.9 Hz, CH, C^{Ar}), 117.3 (CH_2, C^3), 115.2 (d, *J* = 21.0 Hz, CH, C^{Ar}), 114.1 (d, *J* = 22.1 Hz, CH, C^{Ar}), 75.6 (d, *J* = 1.8 Hz, CH, C^1), 21.0 (CH_3, OAc). **Calcd. HMRS** for $C_{11}H_{11}FO_2Na$ (M+Na): 217.0641. Found: 217.0633.

1-(4-(Trifluoromethyl)phenyl)allyl acetate (136)

The general procedure yielded, after filtration over a plug of silica (pentane), 1.89 g (77% over 2 steps) of the title compound as a colorless oil.

1-(4-(Trifluoromethyl)phenyl)prop-2-en-1-ol (136-a)



136-a

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.2 Hz, 2H, H^{Ar}), 7.47 (d, *J* = 8.2 Hz, 2H, H^{Ar}), 6.02-5.93 (m, 1H, H^2), 5.35 (d, *J* = 17.7 Hz, 1H, H^1), 5.24-5.17 (m, 2H, H^3), 2.74 (s broad, 1H, OH). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 146.6 (C, CF_3), 139.8 (CH, C^2), 129.6 (C, *C*–CF_3), 126.72 (CH, C^{Ar}), 126.69 (CH, C^{Ar}), 125.6 (C, C^{Ar}), 116.2 (CH_2, C^3), 74.9 (CH, C^1).

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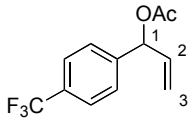
1-(4-(Trifluoromethyl)phenyl)allyl acetate (136)



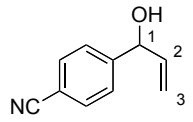
136

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.3 Hz, 2H, H^{Ar}), 7.47 (d, *J* = 8.3 Hz, 2H, H^{Ar}), 6.30 (d, *J* = 6.0 Hz, 1H, H^1), 5.98 (ddd, *J* = 17.1, 10.4, 6.0 Hz, 1H, H^2), 5.35-5.26 (m, 2H, H^3), 2.12 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.9 (C, C=O), 143.1 (C, C^{Ar}), 135.7 (CH, C^2), 127.6 (CH, C^{Ar}), 130.2 (q, *J* = 32.3 Hz, C, *C*–CF_3), 127.4 (CH, C^{Ar}), 125.6 (q, *J* = 3.7 Hz, C, CF_3), 117.9 (CH_2, C^3), 75.6 (CH, C^1), 21.1 (CH_3, OAc). **Calcd. HMRS** for $C_{12}H_{11}F_3O_2Na$ (M+Na): 267.0609. Found: 267.0614.

1-(4-Cyanophenyl)allyl acetate (142)

The general procedure (starting with 5.3 mmol of the corresponding aldehyde) yielded, after flash chromatography on silica gel (gradient hexane/Et_2O, from 95/5 to 80/20), 0.64 g (60% over 2 steps) of the title compound as a yellow oil.

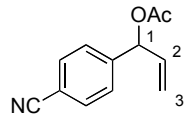
4-(1-Hydroxyallyl)benzonitrile (142-a)



142-a

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63-7.61 (m, 2H, H^{Ar}), 7.50-7.48 (m, 2H, H^{Ar}), 5.99-5.92 (m, 1H, H^2), 5.35 (d, *J* = 17.1 Hz, 1H, $1H^3$), 5.23-5.21 (m, 2H, $1H^3$ + H^1). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 148.3 (C, C^{Ar}), 139.6 (CH, C^2), 132.3 (CH, C^{Ar}), 127.0 (CH, C^{Ar}), 119.0 (C, CN) 116.3 (CH_2, C^3), 111.1 (C, C^{Ar}), 74.5 (CH, C^1).

1-(4-Cyanophenyl)allyl acetate (142)



142

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, 2H, H^{Ar}), 7.47 (d, *J* = 8.3 Hz, 2H, H^{Ar}), 6.26 (d, *J* = 6.1 Hz, 1H, H^1), 5.98 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1H, H^2), 5.36-5.29 (m, 2H, H^3), 2.14 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.8 (C, C=O), 144.2 (C, C^{Ar}), 135.2 (CH, C^2), 132.5 (CH, C^{Ar}), 127.5 (CH, C^{Ar}), 118.7 (C, CN), 118.4 (CH_2, C^3), 112.0 (C,

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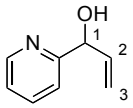
C^{Ar}), 75.4 (CH, C^{1}), 21.2 (CH_3, OAc). **Calcd. HMRS** for $C_{12}H_{11}NO_2Na$ (M+Na): 224.0687. Found: 217.0697.

1-(Pyridin-2-yl)allyl acetate (143)

The general procedure yielded, after flash chromatography on silica gel (gradient hexane/Et_2O, from 90/10 to 70/30), 0.84 g (47% over 2 steps) of the title compound as a dark yellow oil.

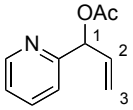
1-(Pyridin-2-yl)prop-2-en-1-ol (143-a)



143-a

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54-8.52 (m, 1H, H^{Ar}), 7.69 (td, *J* = 7.7, 1.7 Hz, 1H, H^{Ar}), 7.34-7.31 (m, 1H, H^{Ar}), 7.22-7.19 (m, 1H, H^{Ar}), 5.98 (ddd, *J* = 17.0, 10.3, 6.9 Hz, 1H, H^{2}), 5.46 (dt, *J* = 17.1, 1.3 Hz, 1H, $1H^{3}$), 5.23 (dt, *J* = 10.3, 1.3 Hz, 1H, $1H^{3}$), 5.19 (d, *J* = 6.9, 1H, H^{1}). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 160.3 (C, C^{Ar}), 148.3 (CH, C^{Ar}), 139.6 (CH, C^{2}), 137.0 (CH, C^{Ar}), 123.8 (CH, C^{Ar}), 121.0 (CH, C^{Ar}), 116.4 (CH_2, C^{3}), 74.5 (CH, C^{1}).

1-(Pyridin-2-yl)allyl acetate (143)



143

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H, H^{Ar}), 7.70 (td, *J* = 7.7, 1.8 Hz, 1H, H^{Ar}), 7.37 (d, *J* = 7.7 Hz, 1H, H^{Ar}), 7.22 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H, H^{Ar}), 6.32-6.29 (m, 1H, H^{1}), 6.12 (ddd, *J* = 17.1, 10.4, 6.0 Hz, 1H, H^{2}), 5.39 (dt, *J* = 17.1, 1.2 Hz, 1H, $1H^{3}$), 5.30 (dt, *J* = 10.4, 1.2 Hz, 1H, $1H^{3}$), 2.16 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.0 (C, C=O), 158.2 (C, C^{Ar}), 149.6 (CH, C^{Ar}), 137.0 (CH, C^{Ar}), 135.1 (CH, C^{2}), 123.0 (CH, C^{Ar}), 121.4 (CH, C^{Ar}), 117.9 (CH_2, C^{3}), 77.1 (CH, C^{1}), 21.3 (CH_3, OAc). **Calcd. HMRS** for $C_{10}H_{11}NO_2Na$ (M+Na): 200.0687. Found: 200.0691.

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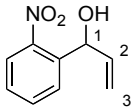
1-(2-Nitrophenyl)allyl acetate (144)

The general procedure yielded, after filtration over a plug of Celite (pentane), 0.56 g (25% over 2 steps) of the title compound as a dark yellow oil.

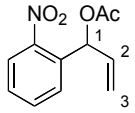
1-(2-Nitrophenyl)prop-2-en-1-ol (144-a)



144-a

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, *J* = 7.8 Hz, 1H, H^{Ar}), 7. 74 (d, *J* = 7.8 Hz, 1H, H^{Ar}), 7.62 (t, *J* = 7.8 Hz, 1H, H^{Ar}), 7.42 (t, *J* = 7.8 Hz, 1H, H^{Ar}), 6.04 (ddd, *J* = 17.1, 10.5, 5.0 Hz, 1H, H^2), 5.76 (d, *J* = 5.0 Hz, 1H, H^1), 5.37 (dt, *J* = 17.1, 1.3 Hz, 1H, $1H^3$), 5.21 (dt, *J* = 10.5, 1.3 Hz, 1H, $1H^3$), 3.23 (s broad, 1H, OH). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 148.2 (C, C^{Ar}), 138.1 (CH, C^2), 137.7 (C, C^{Ar}), 133.7 (CH, C^{Ar}), 128.9 (CH, C^{Ar}), 128.5 (CH, C^{Ar}), 124.6 (CH, C^{Ar}), 116.2 (CH_2, C^3), 69.9 (CH, C^1).

1-(2-Nitrophenyl)allyl acetate (144)



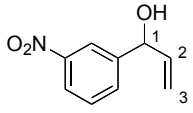
144

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96-7.93 (m, 1H, H^{Ar}), 7.67-759 (m, 2H, H^{Ar}), 7.50-7.42 (m, 1H, H^{Ar}), 6.82 (dt, *J* = 5.6, 1.3 Hz, 1H, H^1), 6.08 (ddd, *J* = 17.2, 10.5, 5.6 Hz, 1H, H^2), 5.36 (dt, *J* = 17.2, 1.3 Hz, 1H, $1H^3$), 5.34 (dt, *J* = 10.5, 1.3 Hz, 1H, $1H^3$), 2.11 (s, 3H, OAc). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 169.7 (C, C=O), 134.72 (C, C^{Ar}), 134.71 (CH, C^2), 133.6 (CH, C^{Ar}), 128.9 (CH, C^{Ar}), 128.5 (CH, C^{Ar}), 124.7 (CH, C^{Ar}), 118.1 (CH_2, C^3), 71.2 (CH, C^1), 21.1 (CH_3, OAc). **Calcd. HMRS** for $C_{11}H_{11}NO_4Na$ (M+Na): 221.0688. Found: 221.0696.

1-(3-Nitrophenyl)allyl acetate (145)

The general procedure yielded, after filtration over a plug of Celite (pentane), 0.84 g (38% over 2 steps) of the title compound as a dark yellow oil.

1-(3-Nitrophenyl)prop-2-en-1-ol (145-a)



145-a

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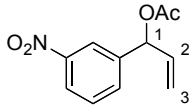
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27-8.26 (m, 1H, H^{Ar}), 8.16-8.12 (m, 1H, H^{Ar}), 7.73-7.71 (m, 1H, H^{Ar}), 7.55-7.51 (m, 1H, H^{Ar}), 6.05-5.98 (m, 1H, H^2), 5.42 (dt, *J* = 17.1, 1.2 Hz, 1H, H^3), 5.31 (d, *J* = 6.9 Hz, 1H, H^1), 5.29 (dt, *J* = 10.2, 1.2 Hz, 1H, $1H^3$), 2.37 (s broad, 1H, OH). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 148.2 (C, C^{Ar}), 138.1 (CH, C^2), 137.7 (C, C^{Ar}), 133.7 (CH, C^{Ar}), 128.9 (CH, C^{Ar}), 128.5 (CH, C^{Ar}), 124.6 (CH, C^{Ar}), 118.7 (C, CN), 116.2 (CH_2, C^3), 69.9 (CH, C^1).

1-(3-Nitrophenyl)allyl acetate (145)



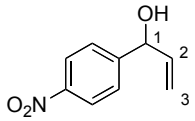
145

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24-8.15 (m, 2H, H^{Ar}), 7.69 (d, *J* = 7.8 Hz, 1H, H^{Ar}), 7.55 (t, *J* = 7.8 Hz, 1H, H^{Ar}), 6.33 (d, *J* = 6.1 Hz, 1H, H^1), 5.99 (ddd, *J* = 17.1, 10.4, 6.1 Hz, 1H, H^2), 5.36 (dt, *J* = 17.1, 1.0 Hz, 1H, $1H^3$), 5.34 (dt, *J* = 10.4, 1.0 Hz, 1H, $1H^3$), 2.16 (s, 3H, OAc). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 169.9 (C, C=O), 148.6 (C, C^{Ar}), 135.3 (CH, C^2), 133.4 (CH, C^{Ar}), 129.7 (CH, C^{Ar}), 123.2 (CH, C^{Ar}), 122.1 (CH, C^{Ar}), 118.5 (CH_2, C^3), 75.2 (CH, C^1), 21.3 (CH_3, OAc). **Calcd. HMRS** for $C_{11}H_{11}NO_4Na$ (M+Na): 221.0688. Found: 221.0680.

1-(4-Nitrophenyl)allyl acetate (146)

The general procedure yielded, after filtration over a plug of silica (pentane), 0.61 g (28% over 2 steps) of the title compound as a yellow oil.

1-(4-Nitrophenyl)prop-2-en-1-ol (146-a)



146-a

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (dt, *J* = 8.9, 2.4 Hz, 2H, H^{Ar}), 7.58-7.54 (m, 2H, H^{Ar}), 6.00 (ddd, *J* = 17.0, 10.2, 6.5 Hz, 1H, H^2), 5.41 (dt, *J* = 17.0, 1.1 Hz, 1H, $1H^3$), 5.32 (d, *J* = 6.5 Hz, 1H, H^1), 5.28 (dt, *J* = 10.2, 1.1 Hz, 1H, $1H^3$), 1.99 (s broad, 1H, OH). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 150.0 (C, C^{Ar}), 147.4 (C, C^{Ar}), 139.4 (CH, C^2), 127.1 (CH, C^{Ar}), 123.8 (CH, C^{Ar}), 116.8 (CH_2, C^3), 74.6 (CH, C^1).

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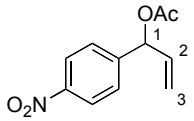
1-(3-Nitrophenyl)allyl acetate (146)



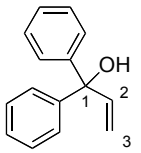
146

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (dt, *J* = 8.8, 2.3 Hz, 2H, H^{Ar}), 7.53 (dt, *J* = 8.8, 2.3 Hz, 2H, H^{Ar}), 6.32 (d, *J* = 6.1 Hz, 1H, H^1), 5.97 (ddd, *J* = 17.1, 10.2, 6.3 Hz, 1H, H^2), 5.38-5.31 (m, 2H, H^3), 2.16 (s, 3H, OAc). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 169.9 (C, C=O), 146.2 (C, C^{Ar}), 135.2 (CH, C^2), 127.9 (CH, C^{Ar}), 124.0 (CH, C^{Ar}), 118.6 (CH_2, C^3), 75.3 (CH, C^1), 21.2 (CH_3, OAc). **Calcd. HMRS** for $C_{11}H_{11}NO_4Na$ (M+Na): 221.0688. Found: 221.0683.

1,1-Diphenylallyl acetate (149)

The general procedure yielded, after crystallization from Et_2O/hexane and washings with hexane, 1.70 g (68% over 2 steps) of the title compound as a pale yellow solid.

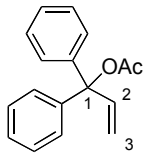
1,1-Diphenylprop-2-en-1-ol (149-a)



149-a

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.35 (m, 4H, H^{Ar}), 7.30-7.27 (m, 4H, H^{Ar}), 7.24-7.20 (m, 2H, H^{Ar}), 6.47 (dd, *J* = 17.1, 10.6 Hz, 1H, H^2), 5.30-5.28 (m, 1H, $1H^3$), 5.26-5.27 (m, 1H, $1H^3$), 2.88 (s, 1H, OH). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 146.0 (C, C^{Ar}), 143.7 (CH, C^2), 128.2 (CH, C^{Ar}), 127.3 (CH, C^{Ar}), 127.1 (CH, C^{Ar}), 114.0 (CH_2, C^3), 79.4 (C, C^1).

1,1-Diphenylallyl acetate (149)



149

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.23 (m, 10H, H^{Ar}), 7.06 (dd, *J* = 17.6, 10.8 Hz, 1H, H^2), 5.41 (dd, *J* = 10.8, 1.0 Hz, 1H, H^3), 4.80 (dd, *J* = 17.6, 1.0 Hz, 1H, $1H^3$), 2.14 (s, 3H, OAc). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.2 (C, C=O), 143.2 (C, C^{Ar}), 139.6 (CH, C^2), 128.2 (CH, C^{Ar}), 127.6 (CH, C^{Ar}), 127.3 (CH, C^{Ar}), 119.9 (CH_2, C^3), 87.7 (C, C^1), 22.5 (CH_3, OAc). **Calcd. HMRS** for $C_{17}H_{16}O_2Na$ (M+Na): 275.1048. Found: 275.1036.

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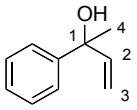
2-Phenylbut-3-en-2-yl acetate (150)

The general procedure yielded, after filtration over a plug of silica (pentane), 0.95 g (57% over 2 steps) of the title compound as a colorless oil.

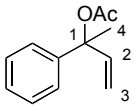
2-Phenylbut-3-en-2-ol (150-a)



150-a

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47-7.45 (m, 2H, H^{Ar}), 7.33-7.30 (m, 2H, H^{Ar}), 7.24-7.22 (m, 1H, H^{Ar}), 6.15 (dd, *J* = 17.5, 10.8 Hz, 1H, H^2), 5.27 (dt, *J* = 17.5, 1.4 Hz, 1H, $1H^3$), 5.11 (dt, *J* = 10.8, 2.5 Hz, 1H, $1H^3$), 2.67 (s broad, 1H, OH), 1.63 (s, 3H, H^4). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 146.8 (C, C^{Ar}), 145.1 (CH, C^2), 128.3 (CH, C^{Ar}), 127.0 (CH, C^{Ar}), 125.3 (CH, C^{Ar}), 112.3 (CH_2, C^3), 74.7 (C, C^1), 29.4 (CH_3, C^4).

2-Phenylbut-3-en-2-yl acetate (150)



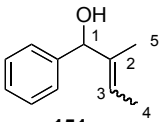
150

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.29 (m, 4H, H^{Ar}), 7.21-7.26 (m, 1H, H^{Ar}), 6.26 (dd, *J* = 17.4, 10.8 Hz, 1H, H^2), 5.26 (dd, *J* = 17.4, 1.0 Hz, 1H, H^3), 5.22 (dd, *J* = 10.8, 1.0 Hz, 1H, $1H^3$), 2.06 (s, 3H, OAc), 1.87 (s, 3H, H^4). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.5 (C, C=O), 143.8 (C, C^{Ar}), 141.6 (CH, C^2), 128.3 (CH, C^{Ar}), 127.3 (CH, C^{Ar}), 125.3 (CH, C^{Ar}), 114.5 (CH_2, C^3), 83.2 (C, C^1), 25.5 (CH_3), 22.3 (CH_3). **Calcd. HMRS** for $C_{12}H_{14}O_2Na$ (M+Na): 213.0891. Found: 213.0887.

2-Methyl-1-phenylbut-2-enyl acetate (151)

The general procedure yielded, after filtration over a plug of silica (pentane), 2.04 g (100% over 2 steps) of the title compound as a colorless oil.

2-Methyl-1-phenylbut-2-en-1-ol (151-a)



151-a

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.28 (m, 4H, H^{Ar}), 7.26-7.19 (m, 1H, H^{Ar}), 5.77 (s, 1H, H^1), 5.43 (qq, *J* = 6.9, 0.7 Hz, 1H, H^3), 2.67 (s broad, 1H, OH), 1.79 (dq, *J* = 1.5, 6.9 Hz, 3H,

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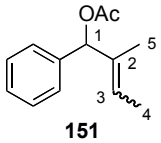
H^4), 1.56 (quint, J = 1.5 Hz, 3H, H^5). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 142.9 (C, C^{Ar}), 137.5 (C, C^2), 128.3 (CH, C^{Ar}), 126.9 (CH, C^{Ar}), 125.6 (CH, C^{Ar}), 122.3 (CH, C^3), 70.4 (CH, C^1), 17.5 (CH_3, Me), 13.5 (CH_3, Me).

2-Methyl-1-phenylbut-2-enyl acetate (151)



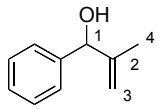
151

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.25 (m, 5H, H^{Ar}), 6.78 (s, 1H, H^1), 5.50 (q, J = 6.9 Hz, 1H, H^3), 2.17 (s, 3H, OAc), 1.87-1.83 (m, 3H, Me), 1.60-1.57 (m, 3H, Me). [***distinctive signals for the other isomer***: δ 6.21 (s, 1H, H^1), 5.64 (q, J = 6.9 Hz, 1H, H^3), 2.13 (s, 3H, OAc), 1.67-1.64 (m, 3H, Me), 1.53-1.51 (m, 3H, Me)] **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.3 (C, C=O), 139.3 (C, C^{Ar}), 133.8 (C, C^2), 128.5 (CH, C^{Ar}), 127.6 (CH, C^{Ar}), 125.9 (CH, C^{Ar}), 124.5 (CH, C^3), 73.0 (CH, C^1), 21.4 (CH_3, OAc), 18.3 (CH_3, Me), 13.8 (CH_3, Me). **Calcd. HMRS** for $C_{13}H_{16}O_2Na$ (M+Na): 227.1048. Found: 227.1045.

2-Methyl-1-phenylallyl acetate (152)

The general procedure (starting with 5 mmol of the corresponding aldehyde) yielded, after filtration over a plug of silica (pentane), 0.92 g (98% over 2 steps) of the title compound as a yellow oil.

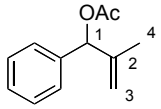
2-Methyl-1-phenylprop-2-en-1-ol (152-a)



152-a

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.29 (m, 4H, H^{Ar}), 7.26-7.23 (m, 1H, H^{Ar}), 5.17-5.16 (m, 1H, $1H^3$), 5.07 (s, 1H, H^1), 4.93-4.92 (m, 1H, $1H^3$), 2.55 (s broad, 1H, OH), 1.58 (s, 3H, H^4). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 147.0 (C, C^2), 142.2 (C, C^{Ar}), 128.5 (CH, C^{Ar}), 127.7 (CH, C^{Ar}), 126.6 (CH, C^{Ar}), 111.2 (CH_2, C^3), 77.9 (CH, C^1), 18.4 (CH_3, C^4).

2-Methyl-1-phenylallyl acetate (152)



152

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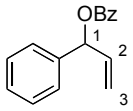
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.28 (m, 5H, H^{Ar}), 6.17 (s, 1H, H^1), 5.12-5.10 (m, 1H, $1H^3$), 4.98-4.96 (m, 1H, $1H^3$), 2.11 (s, 3H, OAc), 1.64-1.63 (m, 3H, H^4). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.0 (C, C=O), 143.2 (C, C^2), 138.5 (C, C^{Ar}), 128.5 (CH, C^{Ar}), 128.2 (CH, C^{Ar}), 127.2 (CH, C^{Ar}), 112.5 (CH_2, C^2), 78.5 (CH, C^1), 21.3 (CH_3, OAc), 19.0 (CH_3, C^4). **Calcd. HMRS** for $C_{12}H_{14}O_2Na$ (M+Na): 213.0891. Found: 213.0887.

1-Phenylallyl benzoate (153)



153

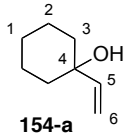
The general procedure (starting with 5 mmol of the corresponding alcohol **57-a**) yielded, after flash chromatography on silica gel (hexane/Et_2O, 95/5), 0.92 g (77%) of the title compound as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12-8.08 (m, 2H, H^{Ar}), 7.56-7.26 (m, 8H, H^{Ar}), 6.52 (d, *J* = 6.0 Hz, 1H, H^1), 6.12 (ddd, *J* = 17.2, 10.4, 6.0 Hz, 1H, H^2), 5.39 (dt, *J* = 17.2, 1.3 Hz, 1H, $1H^3$), 5.28 (dt, *J* = 10.4, 1.3 Hz, 1H, $1H^3$). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.6 (C, C=O), 139.1 (C, C^{Ar}), 136.4 (CH, C^2), 133.2 (CH, C^{Ar}), 130.4 (C, C^{Ar}), 129.8 (CH, C^{Ar}), 128.7 (CH, C^{Ar}), 128.5 (CH, C^{Ar}), 128.3 (CH, C^{Ar}), 127.3 (CH, C^{Ar}), 117.2 (CH_2, C^3), 76.8 (CH, C^1). **Calcd. HMRS** for $C_{16}H_{14}O_2Na$ (M+Na): 261.0891. Found: 261.0884.

1-Vinylcyclohexyl acetate (154)

The general procedure yielded, after flash chromatography on silica gel (gradient hexane/Et_2O, from 98/2 to 70/30), 0.96 g (57% over 2 steps) of the title compound as a colorless oil.

1-Vinylcyclohexanol (154-a)



154-a

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.96 (dd, *J* = 17.3, 10.8 Hz, 1H, H^5), 5.23 (dd, *J* = 17.4, 1.4 Hz, 1H, $1H^6$), 5.01 (dd, *J* = 10.8, 1.4 Hz, 1H, $1H^6$), 2.20 (s broad, 1H, OH), 1.70-1.62 (m, 2H, $2H^3$), 1.56-1.46 (m, 8H, $2H^3$ + $1H^5$ + H^1 + H^2). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 146.2 (CH, C^5), 111.4 (CH_2, C^6), 71.6 (C, C^4), 37.6 (CH_2, C^3), 25.6 (CH_2, C^1), 22.1 (CH_2, C^2).

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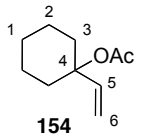
1-Vinylcyclohexyl acetate (154)



154

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.10 (dd, *J* = 17.8, 11.1 Hz, 1H, H^5), 5.16 (d, *J* = 17.8 Hz, 1H, $1H^6$), 5.12 (d, *J* = 11.1 Hz, 1H, $1H^6$), 2.19-2.16 (m, 2H, $2H^3$), 2.02 (s, 3H, OAc), 1.61-1.50 (m, 6H, $2H^3$ + H^2), 1.33-1.22 (m, 2H, H^1). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 170.1 (C, C=O), 142.1 (CH, C^5), 113.7 (CH_2, C^6), 81.9 (C, C^4), 35.0 (CH_2, C^3), 25.5 (CH_2, C^1), 22.2 (CH_3, OAc), 22.0 (CH_2, C^2). **Calcd. HMRS** for $C_{10}H_{16}O_2Na$ (M+Na): 191.1048. Found: 191.1056.

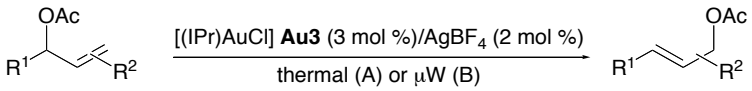
2. Optimization of the catalytic system

General Procedure

To a solution of [(NHC)AuCl] (0.004 mmol, 2 mol %) in solvent "S" (2.5 mL) in a microwave-designed vial, AgX (0.004 mmol, 2 mol %) was added. The solution instantly became cloudy and the reaction mixture was stirred for 1 min before a solution (2.5 mL) of allylic acetate (0.2 mmol, 1.0 equiv) in solvent "S" was added. The vial was then placed in a scientific microwave reactor and the reaction mixture stirred for 12 min at 80ºC and allowed to cool down to room temperature. The resulting mixture was dissolved in pentane, filtered through Celite and concentrated. ^{1}H NMR analysis relies on characteristic vinylic signals.

3. Au-Catalyzed rearrangement of allylic acetates

General procedure



Conventional heating (A). To a DCE solution (15 mL) of [(IPr)AuCl] **Au3** (18 mg, 0.03 mmol, 3 mol %) in an oven-dried round-bottom flask equipped with a condenser, $AgBF_4$ (3.9 mg, 0.02 mmol, 2 mol %) was added. The solution instantly became cloudy and the reaction mixture was stirred for 1 min before a DCE solution (5 mL) of allylic acetate (1 mmol, 1.0 equiv) was added. The flask was then placed in an oil bath at 85ºC, the reaction mixture stirred for 12 h and allowed to cool down to room temperature. The resulting

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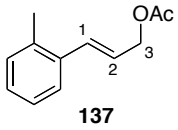
mixture was dissolved in pentane, filtered through Celite and concentrated. The crude product was purified by flash chromatography on silica gel.

Microwave heating (B). To a DCE solution (15 mL) of [(IPr)AuCl] **Au3** (18 mg, 0.03 mmol, 3 mol %) in a microwave-designed vial, $AgBF_4$ (3.9 mg, 0.02 mmol, 2 mol %) was added. The solution instantly became cloudy and the reaction mixture was stirred for 1 min before a DCE solution (5 mL) of allylic acetate (1 mmol, 1.0 equiv) was added. The vial was then closed and placed in a microwave reactor and heated at 80ºC for 12 min. The resulting mixture was dissolved in pentane, filtered through Celite and concentrated. The crude product was purified by flash chromatography on silica gel when necessary.

*Characterization of rearranged allylic acetates **58**, **137-141**, **147-148**, and **155-160***

The synthesis and characterization of rearranged allylic acetate **58** is described in Chapter II, section **V.E.1**.

(*E*)-3-*o*-Tolylallyl acetate (137)



137

A) The general procedure, using allylic acetate **132** under conventional heating, yielded, after flash chromatography on silica gel (gradient hexane/Et_2O, from 90/10 to 80/20), 175 mg (92%) of the title compound as a colorless oil.

B) The general procedure, using allylic acetate **132** under microwave heating, yielded, after flash chromatography on silica gel (gradient hexane/Et_2O, from 90/10 to 80/20), 171 mg (90%) of the title compound as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.41 (m, 1H, H^{Ar}), 7.17-7.12 (m, 3H, H^{Ar}), 6.87 (d, *J* = 15.7 Hz, 1H, H^1), 6.16 (dt, *J* = 15.7, 6.5 Hz, 1H, H^2), 4.74 (dd, *J* = 6.5, 1.3 Hz, 2H, H^3), 2.34 (s, 3H, Me or OAc), 2.09 (s, 3H, Me or OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.9 (C, C=O), 135.8 (C, C^{Ar}), 135.5 (C, C^{Ar}), 132.3 (CH, C^1), 130.5 (CH, C^{Ar}), 128.1 (CH, C^{Ar}), 126.3 (CH, C^{Ar}), 126.0 (CH, C^{Ar}), 124.7 (CH, C^2), 65.5 (CH_2, C^3), 21.2 (CH_3, OAc), 19.9 (CH_3, Me). **Calcd. HMRS** for $C_{12}H_{14}O_2Na$ (M+Na): 213.0891. Found: 213.0899.

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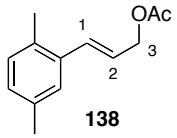
(*E*)-3-(2,5-Dimethylphenyl)allyl acetate (138)

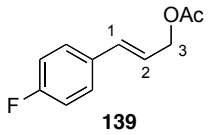


138

B) The above general procedure, using allylic acetate **133** under microwave heating, yielded, after flash chromatography on silica gel (gradient hexane/Et_2O, from 95/5 to 80/20), 172 mg (87%) of the title compound as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (s, 1H, H^{Ar}), 7.02 (d, *J* = 8.0 Hz, 1H, H^{Ar}), 6.97 (dd, *J* = 8.0, 1.6 Hz, 1H, H^{Ar}), 6.84 (d, *J* = 15.6 Hz, 1H, H^1), 6.16 (dt, *J* = 15.6, 6.4 Hz, 1H, H^2), 4.73 (dd, *J* = 6.4, 1.2 Hz, 3H, H^4), 2.30 (s, 6H, 2Me) 2.09 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 171.1 (C, C=O), 135.7 (C, C^{Ar}), 135.2 (C, C^{Ar}), 132.8 (C, C^{Ar}), 132.5 (CH, C^1), 130.5 (CH, C^{Ar}), 128.9 (CH, C^{Ar}), 126.6 (CH, C^{Ar}), 124.4 (CH, C^2), 65.6 (CH_2, C^3), 21.23 (CH_3, Me or OAc), 21.17 (CH_3, OAc or Me), 19.4 (CH_3, Me). **Calcd. HMRS** for $C_{13}H_{16}O_2Na$ (M+Na): 227.1048. Found: 227.1042.

(*E*)-3-(4-Fluorophenyl)allyl acetate (139)



139

A) The general procedure, using allylic acetate **134** under conventional heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 184 mg (95%) of the title compound as a colorless oil.

B) The general procedure, using allylic acetate **134** under microwave heating, yielded, after filtration over a plug of silica (pentane), 184 mg (95%) of the title compound as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.32 (m, 2H, H^{Ar}), 7.04-6.98 (m, 2H, H^{Ar}), 6.61 (d, *J* = 15.9 Hz, 1H, H^1), 6.20 (dt, *J* = 15.9, 6.5 Hz, 1H, H^2), 4.71 (dd, *J* = 6.5, 1.2 Hz, 2H, H^3), 2.10 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 171.0 (C, C=O), 162.8 (d, *J* = 246.5 Hz, C, C^{Ar}), 133.3 (CH, C^2), 132.6 (d, *J* = 3.7 Hz, C, C^{Ar}), 128.4 (d, *J* = 8.0 Hz, CH, C^{Ar}), 123.2 (d, *J* = 2.2 Hz, CH, C^1), 115.7 (d, *J* = 21.0 Hz, CH, C^{Ar}), 65.2 (CH, C^1), 21.2 (CH_3, OAc). **Calcd. HMRS** for $C_{11}H_{11}FO_2Na$ (M+Na): 217.0641. Found: 217.0644.

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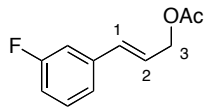
(*E*)-3-(3-Fluorophenyl)allyl acetate (140)



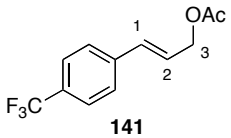
140

A) The general procedure, using allylic acetate **135** under conventional heating, yielded, after flash chromatography on silica gel (hexane/Et_2O, 90/10), 146 mg (75%) of the title compound as a colorless oil.

B) The general procedure, using allylic acetate **135** under microwave heating, yielded, after flash chromatography on silica gel (hexane/Et_2O, 90/10), 157 mg (81%) of the title compound as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.25 (m, 1H, H^{Ar}), 7.14 (d, *J* = 8.0 Hz, 1H, H^{Ar}), 7.09 (dt, *J* = 10.0, 2.0 Hz, 1H, H^{Ar}), 6.95 (td, *J* = 8.4, 2.4 Hz, 1H, H^{Ar}), 6.62 (d, *J* = 16.0 Hz, 1H, H^1), 6.29 (dt, *J* = 16.0, 6.4 Hz, 1H, H^2), 4.73 (dd, *J* = 6.4, 1.2 Hz, 2H, H^3), 2.11 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 171.0 (C, C=O), 163.3 (d, *J* = 244.9 Hz, C, C^{Ar}), 138.7 (C, C^{Ar}), 133.0 (d, *J* = 2.9 Hz, CH, C^1), 130.3 (d, *J* = 8.8 Hz, CH, C^{Ar}), 124.9 (CH, C^{Ar}), 122.7 (d, *J* = 2.9 Hz, CH, C^2), 115.1 (d, *J* = 21.1 Hz, CH, C^{Ar}), 113.2 (d, *J* = 21.8 Hz, CH, C^{Ar}), 64.9 (CH_2, C^3) 21.2 (CH_3, OAc). **Calcd. HMRS** for $C_{11}H_{11}FO_2Na$ (M+Na): 217.0641. Found: 217.0646.

(*E*)-3-(4-(Trifluoromethyl)phenyl)allyl acetate (141)



141

B) The general procedure, using allylic acetate **136** under microwave heating, yielded, after filtration over a plug of silica (pentane), 230 mg (94%) [*E*:*Z*, 93:7] of the title compound as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8.4 Hz, 2H, H^{Ar}), 7.48 (d, *J* = 8.4 Hz, 2H, H^{Ar}), 6.68 (d, *J* = 16.0 Hz, 1H, H^1), 6.38 (dt, *J* = 16.0, 6.2 Hz, 1H, H^2), 4.75 (dd, *J* = 6.2, 1.4 Hz, 2H, H^3), 2.12 (s, 3H, OAc); [***distinctive signals for the (Z)-isomer***: δ 6.46 (dt, *J* = 16.1, 5.9 Hz, 1H, H^2), 4.81 (dd, *J* = 6.2, 1.3 Hz, 2H, H^3)]. **^{13}C NMR (75 MHz, $CDCl_3$):** δ 171.0 (C, C=O), 139.9 (q, *J* = 1.5 Hz, C, C^{Ar}), 132.5 (CH, C^1), 130.1 (q, *J* = 32.0 Hz, C, CF_3), 127.0 (CH, C^{Ar}), 126.2 (CH, C^2), 125.8 (q, *J* = 3.7 Hz, CH, C^{Ar}), 123.0 (C, C^{Ar}), 64.8 (CH_2, C^3) 21.2 (CH_3, OAc). **Calcd. HMRS** for $C_{12}H_{11}F_3O_2Na$ (M+Na): 267.0609. Found: 267.0610.

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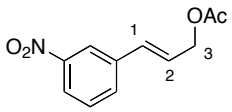
(*E*)-3-(3-Nitrophenyl)allyl acetate (147)

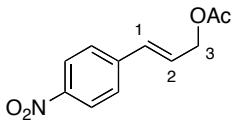


147

B) The above general procedure, using allylic acetate **145** under microwave heating, yielded, after flash chromatography on silica gel (pentane/Et_2O, 95/5), 117 mg (53%) [*E*:*Z*, 70:30] of the title compound as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25-8.23 (m, 1H, H^{Ar}), 8.10 (dd, *J* = 8.2, 2.2 Hz, 1H, H^{Ar}), 7.69 (d, *J* = 7.6 Hz, 1H, H^{Ar}), 7.50 (t, *J* = 7.8 Hz, 1H, H^{Ar}), 6.70 (d, *J* = 16.0 Hz, 1H, H^1), 6.43 (dt, *J* = 16.0, 6.0 Hz, 1H, H^2), 4.77 (dd, *J* = 6.0, 1.4 Hz, 2H, H^3), 2.13 (s, 3H, OAc); [***distinctive signals for the (Z)-isomer***: δ 8.18 (d, *J* = 8.0 Hz, 1H, H^{Ar}), 7.56 (t, *J* = 8.0 Hz, 1H, H^{Ar}), 5.20 (s, 2H, H^3), 2.15 (s, 3H, OAc)]. **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.7 (C, C=O), 148.6 (C, C–NO_2), 138.0 (C, C^{Ar}), 132.4 (CH, C^{Ar}), 131.2 (CH, C^{Ar}), 129.59 (CH, C^1), 123.1 (CH, C^{Ar}), 122.6 (CH, C^{Ar}), 121.2 (CH, C^2), 64.3 (CH_2, C^3), 20.9 (CH_3, OAc); [***distinctive signals for the (Z)-isomer***: δ 170.6 (C, C=O), 148.7 (C, C–NO_2), 138.1 (C, C^{Ar}), 133.9 (CH, C^{Ar}), 129.57 (CH, C^1), 122.8 (CH, C^{Ar}), 65.0 (CH_2, C^3)]. **Calcd. HMRS** for $C_{11}H_{11}NO_4Na$ (M+Na): 221.0688. Found: 221.0690.

(*E*)-3-(4-Nitrophenyl)allyl acetate (148)



148

A) The general procedure, using allylic acetate **146** under conventional heating, yielded, after flash chromatography on silica gel (gradient hexane/Et_2O, from 90/10 to 80/20), 212 mg (96%) [*E*:*Z*, 92:8] of the title compound as a colorless oil.

B) The general procedure, using allylic acetate **146** under microwave heating, yielded, after flash chromatography on silica gel (gradient hexane/Et_2O, from 90/10 to 80/20), 217 mg (98%) [*E*:*Z*, 95:5] of the title compound as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.8 Hz, 2H, H^{Ar}), 7.52 (d, *J* = 8.8 Hz, 2H, H^{Ar}), 6.71 (d, *J* = 16.0 Hz, 1H, H^1), 6.46 (dt, *J* = 16.0, 6.0 Hz, 1H, H^2), 4.78 (dd, *J* = 6.0, 1.6 Hz, 2H, H^3), 2.13 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.9 (C, C=O), 147.5 (C, C^{Ar}), 142.8 (C, C^{Ar}), 131.5 (CH, C^1), 128.5 (C, C^{Ar}), 127.3 (C, C^{Ar}), 124.2 (CH, C^2), 64.5 (CH, C^3), 21.1 (CH_3, OAc). **Calcd. HMRS** for $C_{11}H_{11}NO_4Na$ (M+Na): 221.0688. Found: 221.0681.

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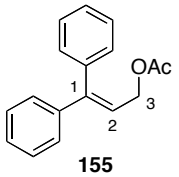
3,3-Diphenyl allyl acetate (155)

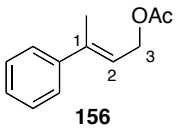


155

B) The general procedure, using allylic acetate **149** under microwave heating, yielded, after flash chromatography on silica gel (gradient hexane/Et_2O, from 90/10 to 80/20), 222 mg (88%) of the title compound as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.34 (m, 3H, H^{Ar}), 7.30-7.24 (m, 5H, H^{Ar}), 7.19-7.17 (m, 2H, H^{Ar}), 6.18 (t, *J* = 7.2 Hz, 1H, H^2), 4.64 (d, *J* = 7.2 Hz, 2H, H^3), 2.07 (s, 3H, OAc). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 171.1 (C, C=O), 146.6 (C, C^1), 141.7 (C, C^{Ar}), 138.9 (C, C^{Ar}), 129.9 (CH, C^{Ar}), 128.5 (CH, C^{Ar}), 128.4 (CH, C^{Ar}), 128.1 (CH, C^{Ar}), 128.0 (CH, C^{Ar}), 127.9 (CH, C^{Ar}), 122.6 (CH, C^2), 62.9 (CH, C^3), 21.2 (CH_3, OAc). **Calcd. HMRS** for $C_{17}H_{16}O_2Na$ (M+Na): 275.1048. Found: 275.1040.

(*E*)-3-Phenylbut-2-enyl acetate (156)



156

B) The general procedure, using allylic acetate **150** under microwave heating, yielded, after flash chromatography on silica gel (gradient hexane/Et_2O, from 90/10 to 80/20), 148 mg (78%) [*E*:*Z*, 75:25] of the title compound as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14-7.39 (m, 5H, H^{Ar}), 5.90 (t, *J* = 5.3 Hz, 1H, H^2), 4.78 (d, *J* = 5.3 Hz, 2H, H^3), 2.12 (d, *J* = 1.2 Hz, 3H, Me), 2.09 (s, 3H, OAc); [***distinctive signals for the (Z)-isomer***: δ 5.66 (t, *J* = 5.4 Hz, 1H, H^2), 4.50 (d, *J* = 5.4 Hz, 2H, H^3), 2.10 (d, *J* = 1.4 Hz, 3H, Me), 2.05 (s, 3H, OAc)]. **^{13}C NMR (75 MHz, $CDCl_3$):** δ 171.3 (C, C=O), 143.0 (C, C^{Ar}), 140.4 (C, C^1), 128.49 (CH, C^{Ar}), 127.7 (CH, C^{Ar}), 126.0 (CH, C^{Ar}), 121.6 (CH, C^2), 61.9 (CH_2, C^3), 21.23 (CH_3, OAc), 16.4 (CH_3, Me); [***distinctive signals for the (Z)-isomer***: δ 171.2 (C, C=O), 142.7 (C, C^{Ar}), 128.46 (CH, C^{Ar}), 127.9 (CH, C^{Ar}), 127.6 (CH, C^{Ar}), 121.2 (CH, C^2), 62.6 (CH_2, C^3), 25.6 (CH_3, Me), 21.24 (CH_3, OAc)]. **Calcd. HMRS** for $C_{12}H_{14}O_2Na$ (M+Na): 213.0891. Found: 213.0897.

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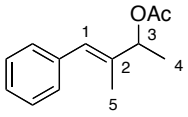
(*E*)-3-Methyl-4-phenylbut-3-en-2-yl acetate (157)

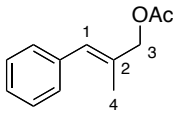


157

B) The general procedure, using allylic acetate **151** under microwave heating, yielded, after flash chromatography on silica gel (gradient hexane/Et_2O, from 90/10 to 80/20), 155 mg (76%) [*E*:*Z*, 85:15] of the title compound as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.31 (m, 2H, H^{Ar}), 7.27-7.18 (m, 3H, H^{Ar}), 6.51 (s, 1H, H^1), 5.42 (q, *J* = 6.4 Hz, 1H, H^3), 2.08 (s, 3H, OAc), 1.88 (s, 3H, H^5), 1.40 (d, *J* = 6.4 Hz, 3H, H^4); [***distinctive signals for the (Z)-isomer***: δ 6.39 (s, 1H, H^1), 5.81 (q, *J* = 6.4 Hz, 1H, H^3), 2.01 (s, 3H, OAc), 1.89 (s, 3H, H^5), 1.38 (d, *J* = 6.4 Hz, 3H, H^4)]. **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.5 (C, C=O), 137.5 (C, C^{Ar}), 129.2 (CH, C^{Ar}), 128.3 (CH, C^{Ar}), 126.8 (CH, C^{Ar}), 126.6 (CH, C^1), 75.6 (CH, C^3), 21.6 (CH_3, OAc), 19.5 (CH_3, C^4), 14.0 (CH_3, C^5). **Calcd. HMRS** for $C_{13}H_{16}O_2Na$ (M+Na): 227.1048. Found: 227.1044.

(*E*)-3-Methyl-3-phenylallyl acetate (158)



158

B) The general procedure, using allylic acetate **152** under microwave heating, yielded, after flash chromatography on silica gel (gradient hexane/Et_2O, from 90/10 to 80/20), 177 mg (93%) [*E*:*Z*, 85:15] of the title compound as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.30 (m, 2H, H^{Ar}), 7.29-7.21 (m, 3H, H^{Ar}), 6.53 (s, 1H, H^1), 5.42 (s, 2H, H^3), 2.12 (s, 3H, OAc), 1.90 (d, *J* = 1.6 Hz, 3H, H^4); [***distinctive signals for the (Z)-isomer***: δ 6.55 (s, 1H, H^1), 5.81 (s, 2H, H^3), 2.09 (s, 3H, OAc), 1.94 (d, *J* = 1.6 Hz, 3H, H^4)]. **^{13}C NMR (75 MHz, $CDCl_3$):** δ 171.1 (C, C=O), 137.3 (C, C^{Ar}), 133.0 (C, C^2), 129.1 (CH, C^{Ar}), 128.4 (CH, C^{Ar}), 127.0 (CH, C^1), 70.4 (CH_2, C^3), 21.2 (CH_3, OAc), 15.8 (CH_3, C^4); [***distinctive signals for the (Z)-isomer***: δ 130.7 (C, C^2), 128.8 (CH, C^{Ar}), 128.5 (CH, C^{Ar})]. **Calcd. HMRS** for $C_{12}H_{14}O_2Na$ (M+Na): 213.0891. Found: 213.0888.

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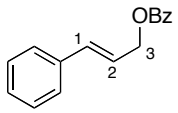
Cinnamyl benzoate (159)

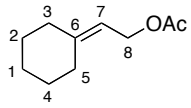


159

B) The general procedure, using allylic benzoate **153** under microwave heating, yielded, after flash chromatography on silica gel (gradient hexane/Et_2O, from 90/10 to 80/20), 214 mg (90%) of the title compound as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.2 Hz, 2H, H^{Ar}), 7.54 (t, *J* = 7.0 Hz, 1H, H^{Ar}), 7.45-7.40 (m, 4H, H^{Ar}), 7.32 (t, *J* = 7.3 Hz, 2H, H^{Ar}), 7.27-7.23 (m, 1H, H^{Ar}), 6.73 (d, *J* = 15.9 Hz, 1H, H^1), 6.40 (dt, *J* = 15.9, 6.4 Hz, 1H, H^2), 4.97 (d, *J* = 6.4 Hz, 2H, H^3). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 166.3 (C, C=O), 136.2 (C, C^{Ar}), 134.2 (CH, C^{Ar}), 132.9 (CH, C^1), 130.2 (C, C^{Ar}), 129.6 (CH, C^{Ar}), 128.6 (CH, C^{Ar}), 128.3 (CH, C^{Ar}), 128.0 (CH, C^{Ar}), 126.6 (CH, C^{Ar}), 123.2 (CH, C^2), 65.5 (CH_2, C^3). **Calcd. HMRS** for $C_{16}H_{14}O_2Na$ (M+Na): 261.0891. Found: 261.0895.

2-Cyclohexylideneethyl acetate (160)



160

A) The general procedure, using allylic acetate **154** under conventional heating, yielded, after flash chromatography on silica gel (gradient hexane/Et_2O, from 90/10 to 80/20), 163 mg (97%) of the title compound as a colorless oil.

B) The general procedure, using allylic acetate **154** under microwave heating, yielded, after flash chromatography on silica gel (gradient hexane/Et_2O, from 90/10 to 80/20), 165 mg (98%) of the title compound as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.29 (td, *J* = 7.3, 1.1 Hz, 1H, H^7), 4.58 (d, *J* = 7.3 Hz, 2H, H^8), 2.20 (s broad, 2H, CH_2–C=), 2.13 (s broad, 2H, CH_2–C=), 2.05 (s, 3H, OAc), 1.56 (s broad, 6H, H^1 + H^2 + H^4). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 171.3 (C, C=O), 147.1 (C, C^6), 115.3 (CH, C^7), 60.9 (CH_2, C^8), 37.2 (CH_2, C^3), 29.2 (CH_2, C^5), 28.5 (CH_2), 27.9 (CH_2), 26.8 (CH_2), 21.3 (CH_3, OAc). **Calcd. HMRS** for $C_{10}H_{16}O_2Na$ (M+Na): 191.1048. Found: 191.1040.

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CONCLUSION

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CONCLUSION

The principal objective of this work was to study the effect of N-heterocyclic carbenes (NHC) as supporting ligands in metal-based homogeneous catalysis. To this end, three main directions were selected, each of them based on a distinct chemical element. Hence, Palladium, Gallium, and Gold have been the focus of this Ph.D. work. Palladium was notably chosen as a development axis of previous studies carried out in the laboratory. On the other hand, Gallium was primarily interesting as a coordination chemistry project, while Gold was elected for the development of novel organic transformations.

Palladium

The roots of [(NHC)Pd(R-allyl)Cl] complexes are to be found in their common precursor possessing an unsubstituted η^3-π-allyl moiety, [(NHC)Pd(allyl)Cl]. Relying on previous observations from our laboratory, we hypothesized that, by substituting the allyl moiety, an unbalance would be generated in the Pd–allyl interaction, leading to a more facile activation step. Comparative trials in the Suzuki-Miyaura and the Buchwald-Hartwig reactions validated an easier activation step, especially at room temperature, for the substituted allyl compounds. Hence, [(SIPr)Pd(cinnamyl)Cl] **Pd4** was notably shown to perform aryl amination reactions of a wide range of amines with aryl chlorides at room temperature in minutes, and with as low as 10 ppm of catalyst at 80ºC.

Considering the extremely high catalytic activity observed in Suzuki-Miyaura and Buchwald-Hartwig coupling reactions, further developments will aim at testing the activity of this catalytic system in a variety of other cross-coupling reactions in order to broaden its applications.

The synthesis of [(NHC)Pd(acac)Cl] arose from the desire of developing a practical catalytic tool for chemists in a wide sense. These studies led to the synthesis of [(IPr)Pd(acac)Cl] **Pd6** from two commercially available starting materials, employing a synthetic route that requires no precaution and a simple filtration as purification step. The resulting pre-catalyst was further showed to be highly efficient in aryl amination and α-

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ketone arylation reactions, allowing for the coupling of unactivated chlorides and heteroaromatic halides. Following the idea we applied to the "allyl family", we further derivatized the acac moiety with different types of substitution. Examination of the catalytic activity of these [(IPr)Pd(R-acac)Cl] complexes allowed for the proposal of an activation pathway. Along the way, inert atmosphere MALDI-TOF MS studies, in addition to supporting some hypotheses regarding the activation mode of these pre-catalysts, furnished clear evidence for the existence of the highly unsaturated 12-electron species [(IPr)Pd^0] as true catalyst in these reactions.

As with the modified Pd–allyl complexes, the activity of the Pd–acac compounds family will be tested in other cross-coupling reactions. Futher developments will also target modified acac ligands in order to control the activation rate of these pre-catalysts; a malonate-like ligand "acacOR" and an unsymmetrical "acactBuMe" are among the structures of interest.

Gallium

We have described the very straightforward synthesis of three air- and moisture-stable NHC-containing Ga^{III} complexes. These [(NHC)$GaCl_3$] adducts were fully characterized and the first X-ray structures of [(NHC)$GaCl_3$] adducts could notably be obtained. The presence of a NHC, possessing indifferently aryl or alkyl groups, clearly has a stabilizing effect on $GaCl_3$.

The catalytic activity of these complexes was tested in two different organic transformations. While they failed to efficiently catalyze the reaction of cycloisomerization of enyne, examination of an allylic rearrangement reaction proved more successful. Interestingly, the latter transformation was found to be efficiently catalyzed by [(IPrMe)$GaCl_3$] whereas [(IPr)$GaCl_3$] and [(IMes)$GaCl_3$] led only to oligomerization of the substrate. This last result indicates that these group 13 adducts can indeed lead to catalytic applications and that the nature of the NHC bound to the gallium center is key for fine-tuning their activity.

Further developments of this project would include the screening of their catalytic activity, notably in reactions where an electrophilic Lewis acid is required. As the nature of the NHC on the gallium center already appeared to be a key parameter, the synthesis of an extended series of [(NHC)$GaCl_3$] complexes would also desirable.

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Gold

[(NHC)AuCl] complexes have been shown to be excellent pre-catalysts for the activation of alkynes, allenes, and alkenes. We have notably been able to perform a number of transformations, including unprecedented ones, allowing for the formation of structurally diversified products, such as fused bicyclohexenes, indenes, conjugated carbonyl derivatives, and allylic esters.

In collaboration with theoretical chemists, we have proposed that the cationic [(NHC)Au] fragment could also "activate" a molecule of water and "deliver" it to an alkyne moiety. In an attempt to take advantage of this unprecedented reactivity, we plan on investigating the activity of [(NHC)AuCl] complexes in the alkyne hydration reaction. Furthermore, considering that Au^{I} and Pd^{0} are isoelectronic, it will be tempting to examine the possible activity of NHC–Au^{I} catalysts in cross-coupling reactions, notably in the Suzuki-Miyaura reaction for which preliminary results from the Corma research group appear promising.

Overall, and regardless of the metal employed, it was clearly shown that N-heterocyclic carbenes are highly stabilizing ligands. All NHC-containing complexes prepared and used during this work were benchtop-stable for months. It is clear that the high electron-donating nature of the NHC associated with their steric hindrance create a protective environment for the metal center, therefore leading to highly stable species.

This enhanced stability of the pre-catalytic species is an advantage in terms of storage and handling but demand for an activation step in order to perform catalysis. Therefore, subsequently to the synthesis of novel pre-catalysts, this work focused on the optimization of catalytic systems that would permit highly efficient catalysis. Mild reaction conditions, rapidity, and low catalyst loadings were, among others, regarded as key aspects of an *efficient* catalysis.

Following the optimization studies, the next step of this work has been to challenge the catalytic systems developed. This meant bringing a system to its limits in terms of catalyst loadings, substrate tolerance and transformation performed.

Finally, and especially when a new type of reactivity was uncovered, we have attempted to gather experimental evidence allowing us to propose a mechanistic rationale

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accounting for a given transformation. We have also enjoyed collaborations with theoretical chemists that have clearly been a strong incentive to continue further some of the research presented here.

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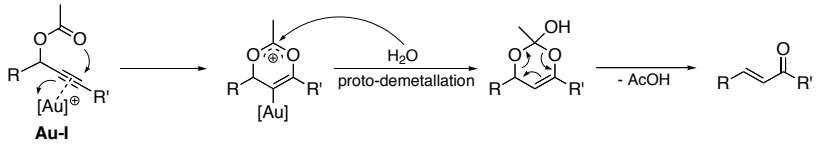

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