UNIVERSITAT DE BARCELONA

# Palladium, ruthenium and iron in intramolecular transition metal-catalyzed carbene functionalization reactions of amino-tethered α–diazoesters

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Programa de Doctorado: Química Orgánica

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Memoria presentada por Arianna Amenta

para optar al título de Doctor por la Universidad de Barcelona

Director de la Tesis: Doctorando:

Dr. Daniel Solé Arjó Arianna Amenta

Arianna Amenta

Barcelona, 2020

En primer lugar quisiera agradecer a mi director de tesis, el Dr. Daniel Solé, por haberme dado la oportunidad de realizar esta tesis doctoral bajo su dirección. Su apoyo y confianza en mi trabajo y sus conocimientos han sido un aporte invaluable.

Agradezco también al Dr. Israel Fernández de la Universidad Complutense de Madrid su colaboración en la realización de los cálculos computacionales que se recogen en este trabajo.

Gracias a todos los compañeros del laboratorio de Química Orgánica de la Facultad de Farmacia: ¡nada hubiera sido lo mismo sin vosotros!

Gracias a Cri, Moni, Uri y Salvo: mi segunda familia.

Grazie alla mia famiglia per avermi costantemente supportata ed aiutata nel corso di questi anni ed a Mirko, per tutto quello che giá sai.

El presente trabajo ha sido financiado por la "Dirección General de Investigación" (Proyectos CTQ2015-64937-R y RT2018-093946-B-I00).

Los cálculos computacionales han sido realizados por el Dr. Israel Fernández del Departamento de Química Orgánica I, Facultad de Ciencias Químicas de la Universidad Complutense de Madrid.

# PUBLICATIONS

This doctoral thesis has resulted in the following publications:

- Transition Metal-Catalysed Intramolecular Carbenoid C-H Insertion for Pyrrolidine Formation by Decomposition of α-Diazoesters. Solé, D.; Amenta, A.; Mariani, F.; Bennasar, M.-L; Fernández, I. *Adv. Synth. Catal.* **2017**, *359*, 3654-3664.

- Grubbs catalysts in intramolecular carbene C($sp^3$)-H insertion reactions from α-diazoesters. Solé, D.; Amenta, A.; Bennasar, M.-L; Fernández, I. *Chem. Comm.* **2019**, *55*, 1160-1163.

- Palladium- and Ruthenium-Catalyzed Intramolecular Carbene $C_{Ar}$-H Functionalization of γ-Amino-α-diazoesters for the Synthesis of Tetrahydroquinolines. Solé, D.; Amenta, A.; Bennasar, M.-L; Fernández, I. *Chem. Eur. J.* **2019**, *25*, 10239-10245.

# SUMMARY

Transition metal-catalyzed intramolecular C–H insertions of diazo compounds represent one of the most elegant and versatile methods in organic synthesis for the construction of carbocyclic and heterocyclic frameworks. In these reactions a C–C bond is formed with high atom economy, with $N_2$ gas being the only subproduct.

In the last years, in the context of a research program aimed at developing efficient methodologies for the synthesis of nitrogen heterocycles, our research group has been studying the transition metal-catalyzed decomposition of amino-tethered α-diazo carbonyl compounds. Specifically, we have reported that palladium catalysts are able to promote the intramolecular carbene C–H insertions to produce pyrrolidines from α-diazoesters, and oxindoles as well as β-lactams from α-diazo-α-(methoxycarbonyl)acetamides.

As a continuation of these studies, in this Thesis we first explored the use of Pd, Rh(II) and Ru(II)-based catalysts for the intramolecular carbene C($sp^3$)–H insertion of γ-amino-α-diazoesters leading to pyrrolidines. Our comparative study allowed us to identify differences in the reactivities and selectivities between the different transition metals. The results obtained in these annulation reactions show that, although the chemoselectivity of the process is highly substrate-dependent, it can be controlled by adequate catalyst selection.

Taking this work as a reference, we then investigated the use of some structurally diverse Ru(II)-complexes to promote the C($sp^3$)–H insertion of γ-amino-α-diazoesters to form pyrrolidines. In this context, we have described the first examples of an unprecedented non-metathetic chemistry of Grubbs complexes, which were applied to achieve this target. Moreover, in our preliminary attempts to develop an enantioselective version of this carbene C($sp^3$)–H insertion reaction, we focused our attention on the use of different chiral Ru(II)-catalysts.

We also investigated the synthesis of tetrahydroquinolines by transition metal-catalyzed intramolecular aromatic $C_{Ar}(sp^2)$-H functionalization of γ-anilino α-diazoesters. Both palladium(0)- and Grubbs catalysts were explored for this purpose.

Finally, we broadened our investigation on the transition metal-catalyzed decomposition of amino-tethered diazoesters by exploring the reactions of δ-amino and β-amino α-diazoesters. Some diverse palladium and ruthenium complexes as well as different iron salts were studied.

# RESUMEN

Las reacciones de inserción intramolecular de diazocompuestos en enlaces C–H catalizadas por metales de transición se han convertido en una metodología extraordinariamente versátil para la construcción de sistemas carbocíclicos y heterocíclicos. En estas reacciones, la formación del enlace C–C tiene lugar con una economía atómica considerable ya que se genera $N_2$ gas como único subproducto.

Durante los últimos años, como parte de un ambicioso proyecto de investigación enfocado al desarrollo de metodologías más eficientes para la síntesis de heterociclos nitrogenados, en nuestro grupo de investigación se ha estudiado la inserción de carbenos metálicos derivados de compuestos α-diazocarbonilicos en enlaces C–H. En este contexto, se ha demostrado que los catalizadores de paladio pueden promover la inserción intramolecular de carbenos generados a partir de diferentes compuestos α-diazocarbonilicos. En concreto, se ha descrito su utilización en la síntesis de pirrolidinas a partir de α-diazoésteres, y de oxindoles y β-lactamas a partir de α-diazo-α-(metoxycarbonil)acetamidas.

Como continuación de estos estudios y con el objetivo de desarrollar una metodología más eficiente para la síntesis de pirrolidinas, en la primera parte de la presente tesis doctoral nos propusimos explorar la viabilidad de diversos complejos de Pd, Rh(II) y Ru(II)como catalizadores en la reacción de inserción en enlaces C($sp^3$)–H a partir de γ-amino-α-diazoésteres. Este estudio comparativo ha permitido identificar las diferencias de reactividad y selectividad entre los distintos metales de transición. Los resultados obtenidos han puesto de manifiesto que la quimioselectividad de la reacción, aunque es altamente dependiente de la estructura del substrato, puede controlarse mediante una adecuada selección del catalizador.

Seguidamente, decidimos explorar la utilización de otros complejos de Ru(II), escogidos en base a su considerable diversidad estructural, como catalizadores de la inserción en enlaces C($sp^3$)–H a partir de γ-amino-α-diazoésteres. En este contexto, hemos

demostrado que los complejos de Grubbs también pueden emplearse para promover la inserción de carbenos en enlaces C($sp^3$)–H para preparar pirrolidinas. Este trabajo constituye el primer ejemplo de la utilización de este tipo de catalizadores en reacciones de inserción, una transformación química muy distinta de su aplicación clásica en las reacciones de metátesis.

En este mismo contexto, hemos realizado también un estudio preliminar encaminado al desarrollo de una versión enantioselectiva de la reacción de inserción, utilizando distintos catalizadores de Ru(II) quirales.

Por otro lado, hemos desarrollado un procedimiento para la síntesis de tetrahidroquinolinas mediante la inserción intramolecular de carbenos generados a partir de γ-anilino-α-diazoésteres en enlaces C($sp^2$)–H aromáticos. Para esta reacción se han explorado tanto los catalizadores de Pd(0) como los complejos de Grubbs.

Finalmente, hemos ampliado nuestra investigación acerca de la utilización de distintos metales de transición para promover la descomposición de compuestos α-diazocarbonilicos con el estudio de la reacción a partir de δ-amino- y β-amino-α-diazoésteres. Para ello hemos explorado la utilización de distintos complejos de paladio y rutenio, así como de sales de hierro.

# ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| acac | acetylacetonate |
| AcO | acetate |
| Ar | aryl |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| bpy | 2,2'-bipyridyl |
| $^{t}$Bu | *tert*-butyl |
| ca. | circa (approximately) |
| cat. | catalyst |
| Cbz | benzyloxycarbonyl |
| CHIRAPHOS | 2,3-bis(diphenylphosphino)butane |
| Cy | cyclohexyl |
| dba | dibenzylideneacetone |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCE | 1,2-dichloroethane |
| DCM | dichloromethane |
| DFT | density functional theory |
| DIBAL-H | diisobutylaluminum hydride |
| DIMAP | 4-(*N,N*-dimethylamino)pyridine |
| DIPAMP | 1,2-bis[(2-methoxyphenyl)(phenylphosphino)]ethane |
| DMF | dimethylformamide |
| DPEA | diisopropylethylamine |

| | |
|---|---|
| DPEN | diphenylethylenediamine |
| dppe | 1,2-bis(diphenylphosphino)ethane |
| dppf | 1,1’-bis(diphenylphosphino)ferrocene |
| dppp | 1,3-bis(diphenylphosphino)propane |
| dr | diastereomer ratio |
| EDG | electron donating group |
| ee | enantiomeric excess |
| eq | equivalent |
| Et | ethyl |
| EWG | electron withdrawing group |
| HPLC | hightperfomance liquid chromatography |
| HRMS | hight resolution mass spectrum |
| IMes | 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene |
| INT | intermediate |
| *i*-Pr | isopropyl |
| IR | infrared spectroscopy |
| LiHMDS | lithium bis(trimethylsilyl)amide |
| M | molar |
| Me | methyl |
| Me-DUPHOS | 1,2-bis(2,5-dimethylphospholano)benzene |
| Mes | mesityl (2,4,6-trimethylphenyl) |
| MONOPHOS | (3,5-Dioxa-4-phosphacyclohepta[2,1-a:3,4-a’]dinaphthalen-4-yl)dimethylamine |
| MsCl | mesyl chloride |
| $NaBAR_F$ | sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate |
| ND | not determined |

| | |
|---|---|
| NHC | N-heterocyclic carbene |
| NMR | nuclear magnetic resonance |
| NQ | 1,4-naphthoquinone |
| p-ABSA | 4-acetamidobenzenesulfonyl azide |
| Pc | phthalocyanine |
| Ph | phenyl |
| SEGPHOS | 4,4’-bi-1,3-benzodioxole-5,5’-diylbis(diphenylphosphine) |
| selectofluor | 1-(Chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) |
| TBABr | tetrabutylammonium bromide |
| TFA | trifluoroacetate |
| TfO | trifluoromethanesulfonate |
| THF | tetrahydrofurane |
| TLC | thin-layer chromatography |
| TM | transition metal |
| TMEDA | N,N,N’,N’-tetramethylethylenediamine |
| TMS | tetramethylsilane |
| 9-trp | 9-triptycenecarboxylate |
| TS | transition state |
| Ts | tosyl (*p*-toluenesulphonyl) |
| TTP | tetraphenylporphyrin |
| UV | Ultraviolet |
| Xantphos | 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene |

# TABLE OF CONTENTS

# Chapter 1

## General Introduction

The development of practical and green methods for C–C bond formation by the selective functionalization of unactivated C–H bonds is an area of great interest and has been extensively studied over the last years.[1] Two fundamentally different strategies for C–H functionalization have been developed (Figure 1.1). The more traditional C–H activation approach proceeds through the insertion of a metal into a C–H bond, followed by a reaction to introduce the new organic substituent (type A reaction).[2] In search of selective reactions in this area, organometallic chemists have focused considerable attention on developing C–H functionalization methodologies whereby a neighboring group directs the initial selective metalation of a C–H bond.

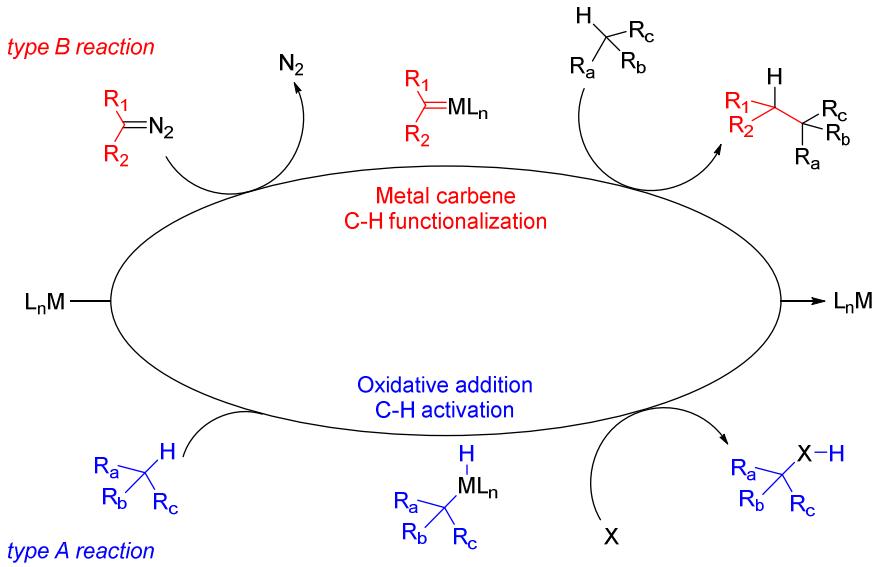



**Figure 1.1.** Metal carbene C–H functionalization versus "traditional" C–H activation.

An attractive alternative approach to these classical methodologies involves the insertion of metal-bound species, such as a metal carbene generated from a diazo compound, into an unactivated C–H bond (type B reaction).[3] Since it was first reported

[1] (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960.

[2] (a) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

[3] (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (b) Davies, H. M. L.; Denton, J. R. *Chem. Soc. Rev.* **2009**, *38*, 3061. (c) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704. (d)

as an unusual reaction more than sixty years ago,[4] diazoalkane-derived carbene insertion into C–H bonds has attracted considerable interest because of their C–C bond-forming potential.

Diazo compounds act as precursors of carbenes, neutral species that possess a divalent carbon. Carbenes can be generated from diazoalkanes thermally and photochemically or, as first demonstrated by Greuter in 1958,[5] by the action of a transition metal catalyst (Figure 1.2).

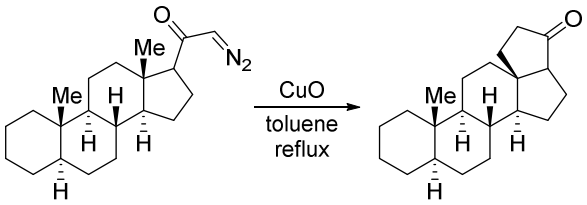



**Figure 1.2**.

Although thermally or photochemically generated carbenes can partake in a number of reactions, these processes tend to be unselective, difficult to control, and consequently of little synthetic value.

On the other hand, complexation of the diazo compound with a transition metal leads to the formation of a metal carbene, which retains the synthetic versatility of free carbenes, while also exhibiting enhanced chemo-, regio- and stereoselectivity. As C–H insertion reactions from diazo compounds require carbene transfer, the catalysts employed are necessarily those affording carbene stability. Accordingly, transition metals that form metal carbenes are optimum for this transfer, although excessive stability can preclude insertion, as occurs with Fischer carbenes.[6] Conversely, other carbenes, like those of some of the coinage metals, are frequently so reactive as to be

Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981. (e) Burtoloso, A. C. B.; Dias, R. M. P.; Bernardim, B. *Acc. Chem. Res.* **2015**, *48*, 921. (f) Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. *Chem. Commun.* **2015**, *51*, 7986.

[4] Doering, W, v. E.; Buttery, R. G.; Laughlin, R. G.; Chaudhuri, N. *J. Am. Chem. Soc.* **1956**, *78*, 3224.

[5] Greuter, F.; Kalvoda, J.; Jeger, O. *Proc. Chem. Soc.* **1958**, 349.

[6] Tonzetich, Z. J. Nucleophilic carbenes of the chromium triad. In *Contemporary Carbene Chemistry*; Wiley: Hoboken, NJ, USA, 2013, pp 452-490.

unselective. Despite this, silver[7] (Figure 1.3) and gold[8,9] catalysts (Figure 1.4) have been successfully used in some C–H insertion reactions.

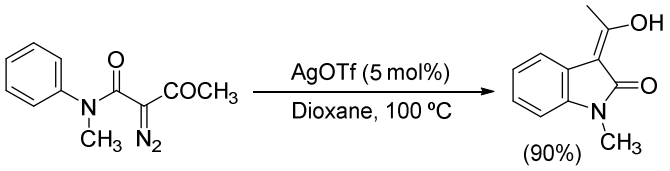



**Figure 1.3.**

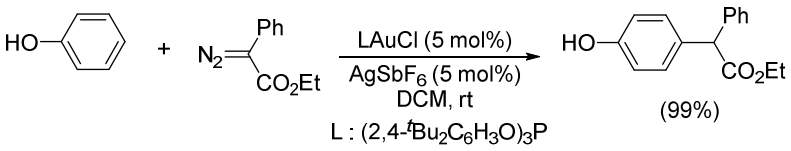



**Figure 1.4.**

Among the transition-metal catalysts effective for cyclopropanation with diazo compounds,[10] only copper, rhodium, ruthenium and palladium stand out as having high potential for selective reactions, and of these only copper and rhodium have shown generality for C–H insertion. Cobalt-based carbenes have also been applied to catalyze selective carbene transfer reactions, such as cyclopropanation, cyclopropenation, carbonylation and olefination reactions,[11] but their use in C–H insertion reactions has been negligible[12] probably because of the single-electron reaction mechanism involved in these processes.

[7] See, for example: Wang, H.-L.; Li, Z.; Wang, G.-W.; Yang, S.-D. *Chem. Commun.*, **2011**, *47*, 11336.
[8] (a) 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. (b) Yu, Z.; Ma, B.; Chen, M.; Wu, H.-H.; Liu, L.; Zhang, J. *J. Am. Chem. Soc.* **2014**, *136*, 6904. (c) Fructos, M. R.; Besora, M.; Braga, A. A. C.; Díaz-Requejo, M. M.; Maseras, F.; Pérez, P. J. *Organometallics* **2017**, *36*, 172.
[9] (a) Liu, L.; Zhang, J. *Chem. Soc. Rev.,* **2016**, *45*, 506. (b) Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Commun.* **2016**, *52*, 7326.
[10] Doyle, M. P.;McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley-Interscience: New York, 1998.
[11] Cui, X.; Zhang, X. P. Cobalt-mediated carbene transfer reactions. In *Contemporary Carbene Chemistry*; Wiley: Hoboken, NJ, USA, 2013, pp 491-525.
[12] See, for example: (a) Karns, A. S.; Goswami, M.; de Bruin, B. *Chem. Eur. J.* **2018**, *24*, 5253. (b) Lankelma, M.; Olivares, A. M.; de Bruin, B. *Chem. Eur. J.* **2019**, *25*, 5658.

Although copper (Figure 1.5) and copper compounds (Figure 1.6) were initially employed for C–H insertion reactions,[13] few reported examples exhibit generality or synthetic utility beyond intramolecular reactions in geometrically rigid systems. The explanation is that copper catalysts tend to be highly electrophilic and so typically generate carbenes that are too reactive to undergo selective C–H insertion reactions.

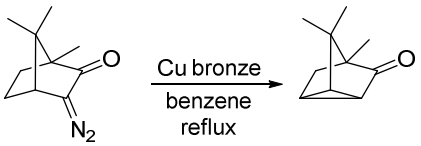



**Figure 1.5.**

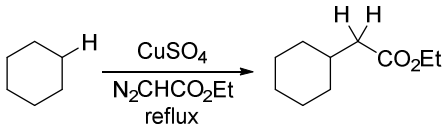



**Figure 1.6.**

However, virtually all the early work on transition metal-catalyzed carbene C–H insertion relied on copper complexes as catalysts, and before the advent of dirhodium tetraacetate, copper catalysis dominated the literature.[14] Only a few examples of silver-promoted C–H insertion, mainly observed in the context of Wolff rearrangement of diazo ketones, challenged the predominance of copper.[15] The discovery in the early 1980s that dirhodium(II) tetracarboxylates are highly effective catalysts for diazo compound decomposition transformed C–H insertion reactions into viable synthetic tools. Since the pioneering work of Noels and coworkers in the intermolecular version of the reaction (Figure 1.7),[16] research in this area has experienced tremendous growth, especially with the development of chiral dirhodium catalysts capable of highly

[13] (a) Yates, P.; Danishefsky, S. *J. Am. Chem. Soc.* **1962**, *84*, 879. (b) Scott, L. T.; DeCicco, G. J. *J. Am. Chem. Soc.* **1974**, *96*, 322.
[14] (a) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379. (b) Zhao, X.; Zhang, Y.; Wang, J. *Chem. Commun.* **2012**, *48*, 10162.
[15] (a) Tresca, J. P.; Fourrey, J. L.; Polonsky, J.; Wenkert, E. *Tetrahedron Lett.* **1973**, *14*, 895. (b)Wolff, S.; Agosta, W. C. *J. Org. Chem.* **1973**, *38*, 1964.
[16] (a) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssié, P. *J. Chem. Soc., Chem. Commun.* **1981**, 688. (b) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssié, P. *Bull. Soc. Chim. Belg.* **1984**, 93, 945.

enantioselective transformations.[17] As a consequence, dirhodium(II) compounds have long been the most utilized and versatile catalysts for C–H insertion reactions.[18,19]

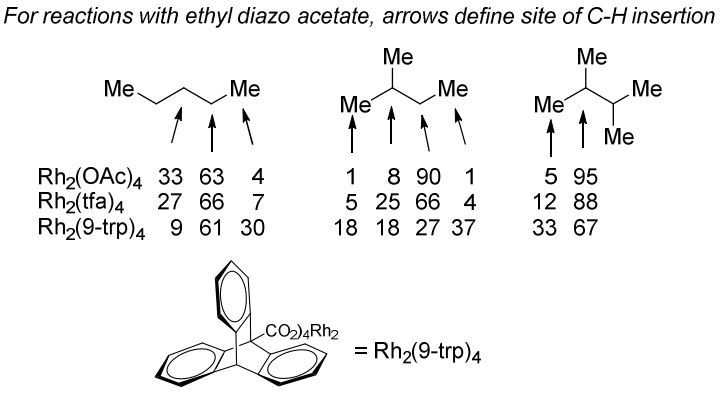



**Figure 1.7.** Reaction of alkanes with ethyl diazoacetate using Rh(II)-catalysts.

Recognizing that the intramolecular insertion reactions were more likely to succeed than intermolecular processes, very early on Wenkert[20] and Taber[21] began a series of investigations with diazo carbonyl compounds that also confirmed the advantages of dirhodium tetracarboxylates as catalysts in the annulation reactions. Their seminal work allowed a basic understanding of the extraordinary preference for the formation of five-membered rings, as well as the regiochemical preference for intramolecular insertion into a tertiary over a secondary C–H bond. The site-selectivity achieved in these intramolecular metal-carbene reactions is usually due to the preferential formation of five-membered rings driven by entropic factors, although the formation of four- and six-membered rings is also relatively common.

Besides the transition metal, the reactivity of metal carbenes is also defined by the substituents adjacent to the carbene center, leading to their classification in three

[17] (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Zheng, C.; You, S.-L. *RSC Adv.* **2014**, *4*, 6173.
[18] Davies, H. M. L.; Parr, B. T. Rhodium carbenes. In *Contemporary Carbene Chemistry*; Wiley: Hoboken, NJ, USA, 2013, pp 363-403.
[19] Yakura, T.; Nambu, H. *Tetrahedron Lett.* **2018**, *59*, 188.
[20] Wenkert, E.; Davies, L. L.; Mylari, B. L.; Solomon, M. F.; Da Silva, R. R.; Shulman, S.; Warnet, R. J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1982**, *47*, 3242.
[21] Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808.

main groups: acceptor/acceptor-, acceptor-, and donor/acceptor-carbenes (Figure 1.8). The acceptor/acceptor- and acceptor-carbenes are highly reactive species because the acceptor groups do not stabilize the highly electrophilic carbene center. The vast majority of synthetically useful C–H functionalizations with these two types of metal carbenes have been intramolecular processes.

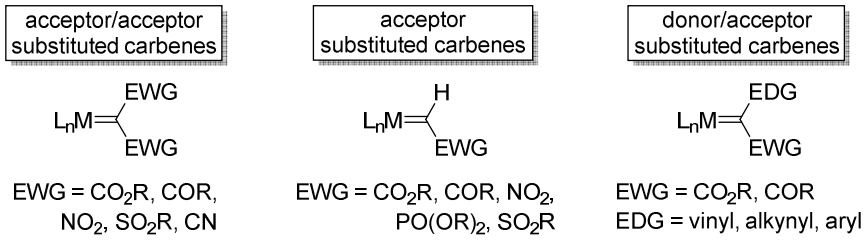



**Figure 1.8.** Classification of metal-carbene intermediates.

In contrast, the introduction of a donor group stabilizes the electron-deficient metal carbene and attenuates its reactivity by reducing its electrophilicity. A variety of aryl and vinyl groups have been employed as the donor substituent in donor/acceptor-carbenes, which has allowed their intermolecular C–H insertion to evolve from a synthetically limited reaction to a broadly useful transformation.[3b-c]

The "purely donor" rhodium carbenes are relatively rare in the literature, largely owing to the hazards associated with the synthesis of the required unstabilized diazo precursors. However, as demonstrated by Cossy *et al.*, despite reduced electrophilicity, these carbenes can also undergo intramolecular C–H insertion reactions.[22]

Diazo alkanes, bearing neither donor nor acceptor substituents on the diazo carbon, are also generally unstable and difficult to handle. This has significantly limited their application in C–H insertion reactions. In this context, it should be noted that the use of *N*-tosylhydrazones as generally reliable precursors for the *in situ* generation of nonstabilized diazo compounds through the Bamford-Stevens reaction has allowed the development of useful transition-metal carbene reactions. The utility of *N*-tosylhydrazone salts for the generation of metal carbene complexes in catalytic

[22] Archambeau, A.; Miege, F.; Meyer, C.; Cossy, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 11540.

processes was first demonstrated by Aggarwal *et al.*[23] and has been successfully exploited in a number of processes, including olefination, epoxidation, cyclopropanation, and C–H and N–H insertion reactions.[24]

Parallel to the methodological studies directed at establishing the scope and generality of the transition metal-catalyzed C–H insertion reactions, intensive research has also been carried out to determine the reaction mechanisms, especially with dirhodium(II) and copper catalysts.

The transition metal-catalyzed carbene insertion from diazo derivatives consists of three fundamental steps: the metal-catalyzed nitrogen extrusion to give the metal carbene, C–H activation and C–C bond formation. From the mechanistic point of view, it is necessary to differentiate between the C($sp^3$)–H insertion and the aromatic C–H insertion.

The C($sp^3$)–H insertion is by far the most explored process from the mechanistic point of view. For tertiary and secondary C–H bond insertions catalyzed by rhodium complexes, the first step (the formation of the metal carbene) is rate-determining, and it is assumed that the other two steps (C–H activation and C–C bond formation) usually take place as a single reaction (Figure 1.9).

The reaction is initiated by the nucleophilic attack of the diazo compound to the transition-metal catalyst to generate a metal carbenoid. This intermediate loses $N_2$ to give the transient metal carbene, which is electrophilic in nature and immediately reacts with surrounding nucleophiles in the reaction mixture to release the insertion product as well as the active catalyst.

[23] Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 10926.
[24] (a) Barluenga, J.; Valdés, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 7486. (b) Shao, Z.; Zhang, H. *Chem. Soc. Rev.,* **2012**, *41*, 560. (c) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236.

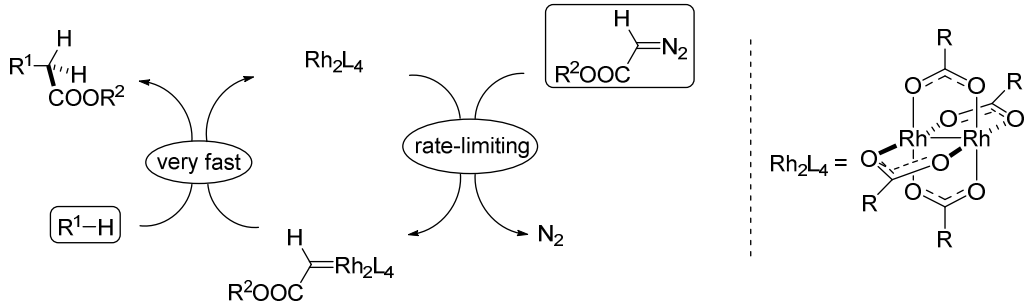



**Figure 1.9.** Schematic Representation of the Catalytic Cycle of the Rhodium Tetracarboxylate-Catalyzed C–H Bond Activation/C–C Bond-Forming Reaction of an α-Diazoacetate with an Alkane.

The reactivities of diazo compounds toward Lewis acids in diazo decomposition reactions follow the order of basicity of the diazo compound and are generally in the order:

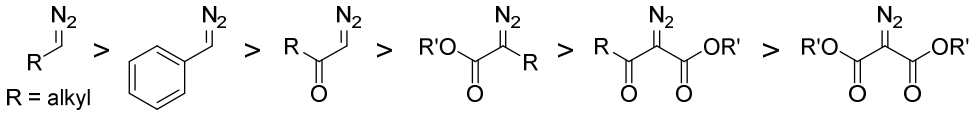



**Figure 1.10.**

Among α-diazoesters, reactivity follows the order:

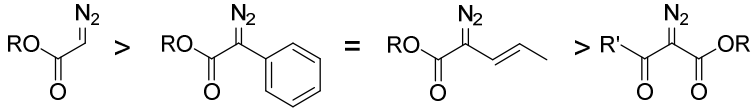


**Figure 1.11.**

In accordance with the mechanistic proposal originally advanced by Doyle,[25] it is commonly accepted that the rhodium-catalyzed insertion reaction involves a dirhodium(II)-carbene complex, from which the C–H activation and C–C bond formation take place in a concerted but asynchronous process, with the hydrogen transfer preceding C–C bond formation.

[25] Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.

A density functional theory (DFT) calculation by Nakamura and coworkers[26] using rhodium formate as a model catalyst confirmed Doyle's mechanistic proposal and showed that the C–H insertion occurs in a single step through a three-centered transition state with a low activation barrier. Neither of the rhodium atoms interacts directly with the C–H bond undergoing insertion. Interestingly, although only one of the two rhodium atoms constitutes the binding site for the carbene, the other one serves as a ligand to the carbene-bound rhodium, thereby enhancing the electrophilicity of the bound carbene and facilitating the cleavage of the rhodium-carbon bond (Figure 1.12).

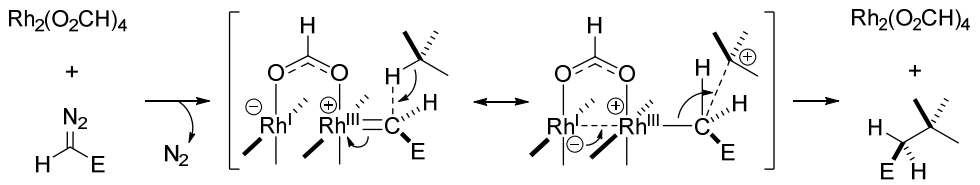



**Figure 1.12.** Transition state model of C–H bond activation with dirhodium-carbene complexes.

As a consequence of this mechanism, the insertion site-selectivity in dirhodium(II)-catalyzed reactions is controlled by a combination of steric and electronic factors within the substrate. From an electronic perspective, the ability to stabilize the build-up of positive charge is favored; hence preferential insertion into tertiary over secondary C–H bonds, and secondary over primary would be observed. However, as the dirhodium(II) catalysts are sterically hindered, from the steric point of view, the insertion into primary C–H bonds would be enhanced.

Prior to the density functional theory computational study by Nakamura, alternative proposals to explain the rhodium-catalyzed reactions included hydrogen transfer from the C($sp^3$)–H bond to the metal at the metal carbene, synchronous with C–C bond formation, followed by a reductive elimination.[27]

The transition metal-catalyzed reactions of diazo compounds with aromatic substrates leading to aromatic substitution products have been inaccurately referred to

[26] Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181.
[27] Taber, D. F.; You, K. K.; Reingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547.

as aromatic C–H insertions.[28] These types of reactions, which can proceed both in an inter- and intramolecular fashion, are a powerful synthetic tool by which C–C bonds can be formed between two $sp^2$-hybridized carbons under relatively mild conditions. They have also been traditionally carried out in the presence of either dirhodium(II) or copper catalysts.

The early examples of this reaction were intramolecular in scope, but intermolecular aromatic functionalization with diazo compounds has received increased attention in recent years. Thus, in 2010 Tayama *et al.* reported the intermolecular aromatic substitution of *N*,*N*-disubstituted anilines with diazo esters using copper(II) triflate as the catalyst (Figure 1.13).[29]

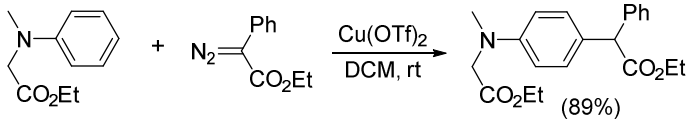



**Figure 1.13.**

The $C_{Ar}sp^2$–H functionalization reactions differ mechanistically from the aliphatic version and they generally proceed through the formation of a zwitterionic intermediate from the electrophilic addition of the metal carbene to the aromatic ring and a subsequent rapid proton transfer.[30] In one example, for the intramolecular dirhodium(II)-catalyzed insertion of a carbene generated by *N*-aryl diazoamide, Doyle *et al.* proposed the initial formation of a zwitterionic intermediate (Figure 1.14). This intermediate is electronically favorable, because the positive charge of the zwitterionic species is stabilized by the formation of an iminium conjugated system. In addition, the negative charge is stabilized by the carbenoid moiety.[31]

[28] Li, Y.-P.; Li, Z.-Q.; Zhu, S.-F. *Tetrahedron Lett*. **2018**, *59*, 2307.
[29] Tayama, E.; Yanaki, T.; Iwamoto, H.; Hasegawa, E. *Eur. J. Org. Chem.* **2010**, 6719.
[30] (a) Jia, S.; Xing, D.; Zhang, D.; Hu, W. *Angew. Chem. Int. Ed.* **2014**, *53*, 13098. (b) Zheng, C.; You, S.-L.; *RSC Adv.* **2014**, *4*, 6173.
[31] Doyle, M. P.; Shanklin, M. S.; Pho, H. Q.; Mahapatro, S. N. *J. Org. Chem.* **1988**, *53*, 1017.

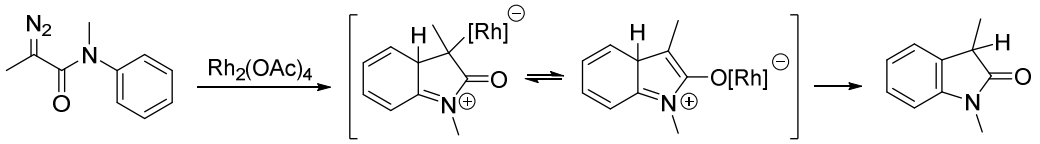


**Figure 1.14.**

More recently, trapping of the transient zwitterionic intermediates generated in this type of reactions has allowed the development of highly efficient domino processes (Figure 1.15).[32]

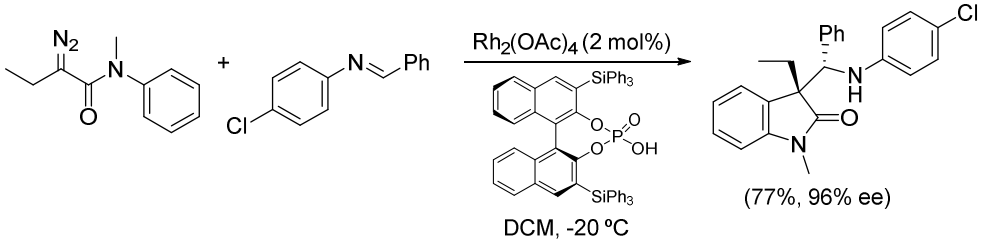



**Figure 1.15.**

Although the use of dirhodium(II) and copper catalysts has traditionally monopolized the research on carbene C–H insertion, in recent years different transition metals have emerged as useful alternatives.

Because of their stability, ruthenium catalysts have been generally considered too unreactive for C–H insertion.[33] However, in the last years several types of ruthenium complexes have emerged as potential alternatives to the well-established rhodium catalysts for carbene C–H insertion of diazo compounds. Thus, Che's group first identified ruthenium(II) porphyrins as effective catalysts for this type of reaction, starting from *N*-tosylhydrazones to prepare 2,3-dihydrobenzofurans, indolines and β-

[32] See for example: (a) Qiu, H.; Li, M.; Jiang, L.-Q.; Lv, F.-P.; Zan, L.; Zhai, C.-W.; Doyle, M. P.; Hu, W.-H. *Nature Chem.* **2012**, *4*, 733. (b) Jia, S.; Xing, D.; Zhang, D.; Hu, W. *Angew. Chem. Int. Ed.* **2014**, *53*, 13098. (c) Chen, L.-H.; Ma, Y.-T.; Yang, F.; Huang, X.-Y.; Chen, S.-W.; Ji, K.; Chen, Z.-S. *Adv. Synth. Catal.* **2019**, *361*, 1307.

[33] Diver, S. T.; French, J. M. Ruthenium carbenes. In *Contemporary Carbene Chemistry*; Wiley: Hoboken, NJ, USA, 2013, pp 404-451.

lactams (Figure 1.16).[34] More recently, they have applied the reaction for the synthesis of tetrahydrofurans and pyrrolidines (Figure 1.17).[35]

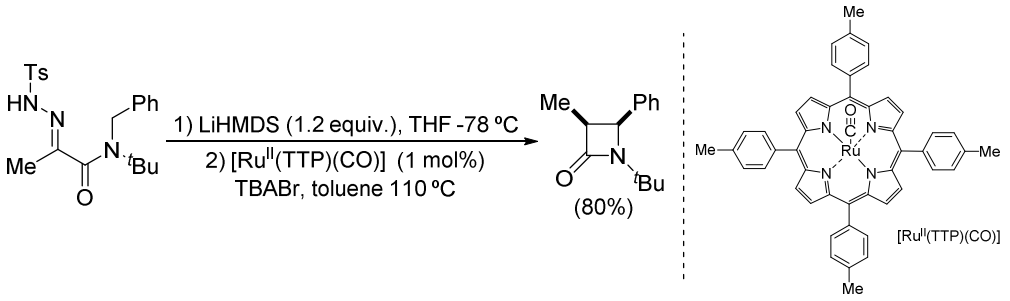



**Figure 1.16.**

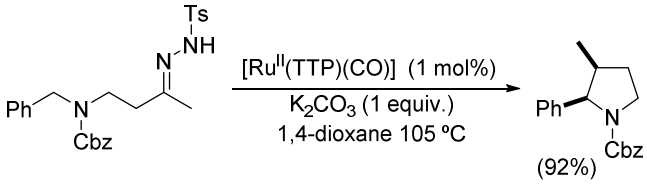



**Figure 1.17.**

They also reported that $[RuCl_2(p\text{-cymene})]_2$ effectively catalyzes the formation of lactams from diazomalonic ester amides and 2-diazo-3-oxocarboxamides (Figure 1.18),[36] and that soluble polystyrene-supported Ru(II) catalysts can be used to promote carbene insertion into C–H and N–H bonds starting from diazo carbonyl compounds.[37]

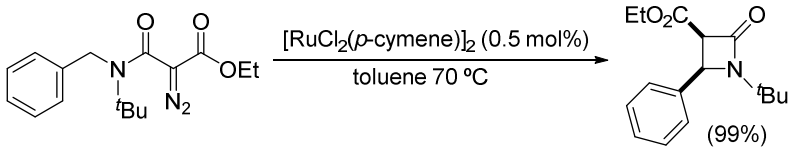



**Figure 1.18.**

[34] Cheung, W.-H.; Zheng, S.-L.; Yu, W.-Y.; Zhou, G.-C.; Che, C.-M. *Org. Lett.* **2003**, *5*, 2535.
[35] Reddy, A. R.; Zhou, C.-Y.; Guo, Z.; Wei, J.; Che, C.-M. *Angew. Chem. Int. Ed.* **2014**, *53*, 14175.
[36] Choi, M. K.-W.; Yu, W.-Y.; Che, C.-M. *Org. Lett.* **2005**, *7*, 1081.
[37] Choi, M. K.-W.; Yu, W.-Y.; So, M.-H.; Zhou, C.-Y.; Deng, Q.-H.; Che, C.-M. *Chem. Asian J.* **2008**, *3*, 1256.

The $[RuCl_2(p\text{-cymene})]_2$ catalyst has been used by different groups to promote intramolecular carbene arene C–H bond functionalization toward a variety of functionalized oxindoles (Figures 1.19 and 1.20).[38,39]

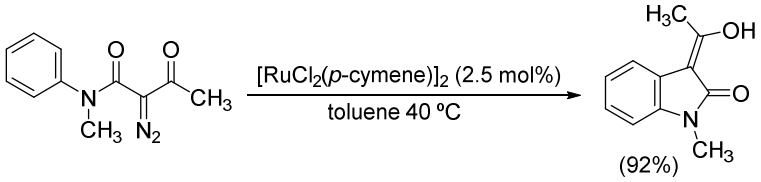



**Figure 1.19.**

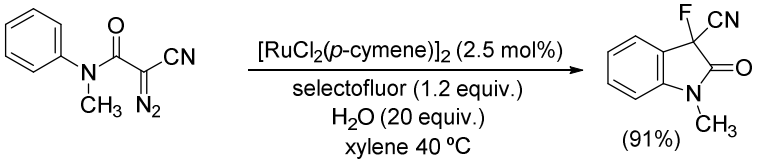



**Figure 1.20.**

Especially interesting is the combination of ruthenium-catalyzed C–H functionalization with palladium-catalyzed asymmetric allylic alkylation, which allowed the synthesis of enantiopure 3-allyl-3-aryl oxindole derivatives (Figure 1.21).[40]

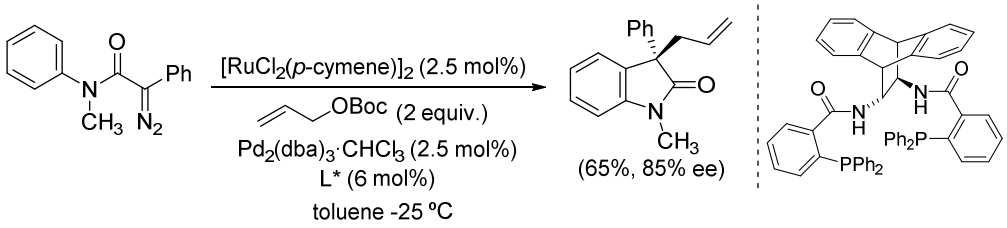



**Figure 1.21.**

Maas *et al.* have explored the use of dinuclear Ru(I,I) complexes for the intramolecular carbene C–H insertion of 2-diazoacetoacetamides to prepare γ- and β-

[38] Chan, W.-W.; Kwong, T.-L.; Yu, W.-Y. *Org. Biomol. Chem.,* **2012**, *10*, 3749.
[39] Liu, N.; Tian, Q.-P.; Yang, Q.; Yang, S.-D. *Synlett* **2016**, *27*, 2621.
[40] Yamamoto, K.; Qureshi, Z.; Tsoung, J.; Pisella, G.; Lautens, M. *Org. Lett.* **2016**, *18*, 4954.

lactams (Figure 1.22). Interestingly, even the ruthenium(0) cluster $Ru_3(CO)_{12}$ proved to be an effective catalyst for the insertion of these compounds.[41]

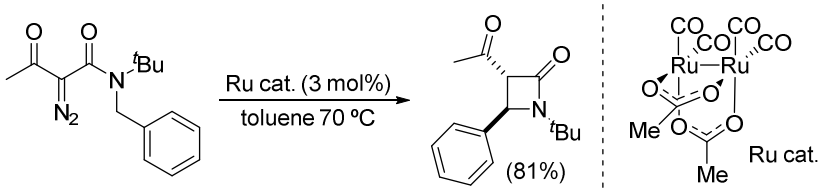



**Figure 1.22.**

Very recently, Chanthamath and Iwasa described the regio- and enantioselective intramolecular carbene insertion of α-diazoacetamides into primary C–H bonds using a Ru(II)-Pheox catalyst (Figure 1.23).[42]

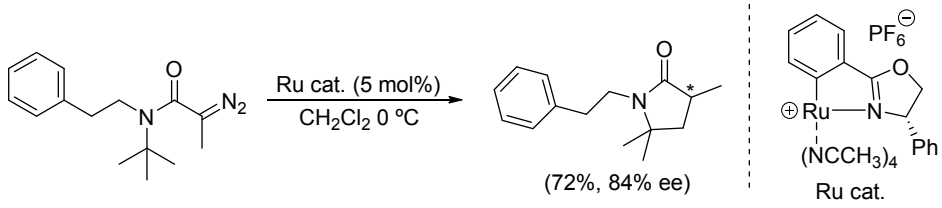



**Figure 1.23.**

In the search of low cost and more environmentally benign catalysts, some other metals have been explored to promote carbene transfer reactions from diazo compounds. Thus, Zhou *et al.* reported in 2011 the iron-catalyzed $C(sp^2)$–H functionalization of indoles with α-aryl-α-diazoesters (Figure 1.24).[43]

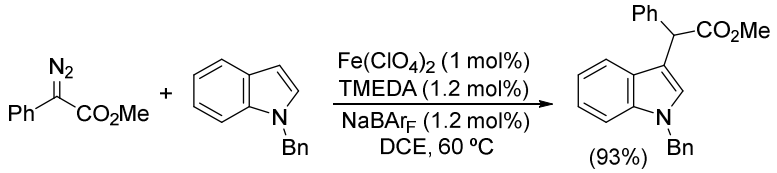



**Figure 1.24.**

[41] (a) Grohmann, M.; Maas, G. *Tetrahedron* **2007**, *63*, 12172. (b) Grohmann, M.; Buck, S.; Schäffler, L.; Maas, G. *Adv. Synth. Catal.* **2006**, *348*, 2203.
[42] Nakagawa, Y.; Chanthamath, S.; Liang, Y.; Shibatomi, K.; Iwasa, S. *J. Org. Chem.* **2019**, *84*, 2607.
[43] Cai, Y.; Zhu, S.-F.; Wang, G.-P.; Zhou, Q.-L. *Adv. Synth. Catal.* **2011**, *353*, 2939.

Pérez and Costas and coworkers also demonstrated the utility of either iron or manganese catalysts for the selective functionalization of arene C($sp^2$)–H bonds by intermolecular carbene insertion.[44] Later on, White *et al.* described the intramolecular catalytic C($sp^3$)–H bond insertion via an iron carbene intermediate using iron phthalocyanine complexes as the catalyst (Figure 1.25).[45]

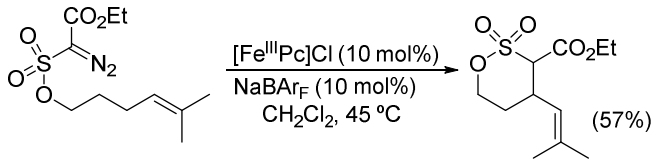



**Figure 1.25.**

Iron catalysts have also been used to promote intermolecular carbene transfer from α-diazoesters to different X–H bonds.[46,47]

Recently, de Bruin *et al.* reported the cobalt(II)-porphyrin-catalyzed synthesis of indolines[12a] (Figure 1.26) and piperidines[12b] (Figure 1.27) from *N*-tosylhydrazones.

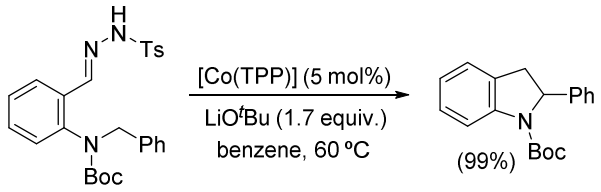



**Figure 1.26.**

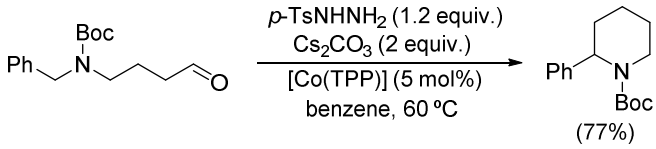



**Figure 1.27.**

[44] Conde, A.; Sabenya, G.; Rodríguez, M.; Postils, V.; Luis, J. M.; Díaz-Requejo, M. M.; Costas, M.; Pérez, P. J. *Angew. Chem. Int. Ed.* **2016**, *55*, 6530.
[45] Griffin, J. R.; Wendell, C. I.; Garwin, J. A.; White, M. C. *J. Am. Chem. Soc.* **2017**, *139*, 13624.
[46] Keipour, H.; Ollevier, T. *Org. Lett.* **2017**, *19*, 5736.
[47] Röske, A.; Alt, I.; Plietker, B. *ChemCatChem* **2019**, *11*, 5260.

These reactions proceed via a radical mechanism and involve hydrogen atom transfer to transient cobalt(III)-carbene intermediates.

Interestingly, palladium, though one of the most commonly employed metals in homogeneous catalysis, has been scarcely applied to promote this type of carbene insertion reactions. Thus, although the effectiveness of palladium complexes in catalyzing intramolecular carbene reactions from α-diazo carbonyl compounds was demonstrated some time ago by Taber *et al.* (Figure 1.28),[48] their use has long been restricted to a couple of examples of α-diazo-β-ketoester insertion into $C_{Ar}sp^2$–H bonds (Figure 1.29).[49]

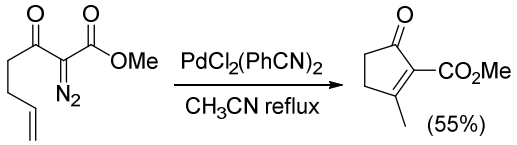
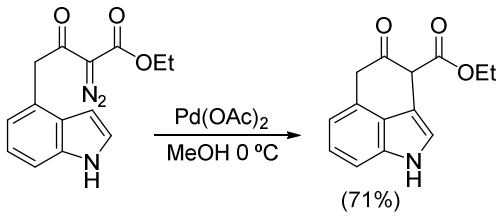



**Figure 1.28.**




**(Figure 1.29).**

This neglect is highly surprising in view of the great success of palladium catalysis in cross-coupling reactions of diazo compounds with either organic halides, pseudohalides or arylboronic acids,[50] and the widespread synthetic application of

[48] Taber, D. F.; Amedio Jr., J. C.; Sherill, R. G. *J. Org. Chem.* **1986**, *51*, 3382.
[49] (a) Matsumoto, M.; Watanabe, N.; Kobayashi, H. *Heterocycles*, **1987**, *26*, 1479. (b) Rosenberg, M. L.; Aasheim, J. H. F.; Trebbin, M.; Uggerud, E.; Hansen, T. *Tetrahedron Lett.* **2009**, *50*, 6506.
[50] For reviews, see: (a) Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2011**, 1015. (b) Barluenga, J.; Valdés, C.; *Angew. Chem. Int. Ed.* **2011**, *50*, 7486. (c) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2012**, *41*, 560. (d) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236.

palladium(II) acetate-catalyzed cyclopropanation of olefins with diazomethane.[51] Moreover, it should be noted that palladium carbenes have been repeatedly proposed as intermediates in a number of transformations.[52]

Very recently, Jiang and Hu and coworkers reported the enantioselective palladium(II)-catalyzed three-component coupling of pyrroles, α-diazoesters and imines (Figure 1.30),[53] and Zhou *et al.* described the enantioselective palladium-catalyzed C–H functionalization of indoles with α-diazoesters to give indol-3-acetate derivatives (Figure 1.31).[54]

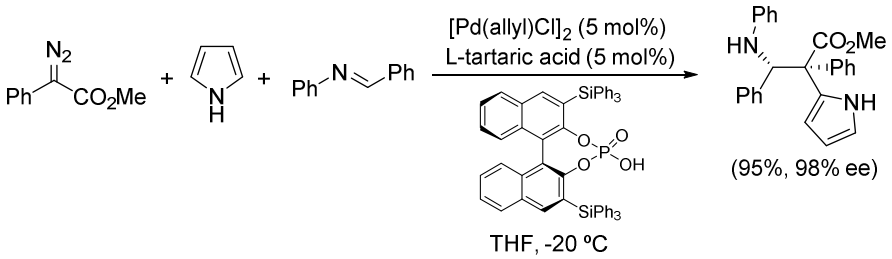



**Figure 1.30.**

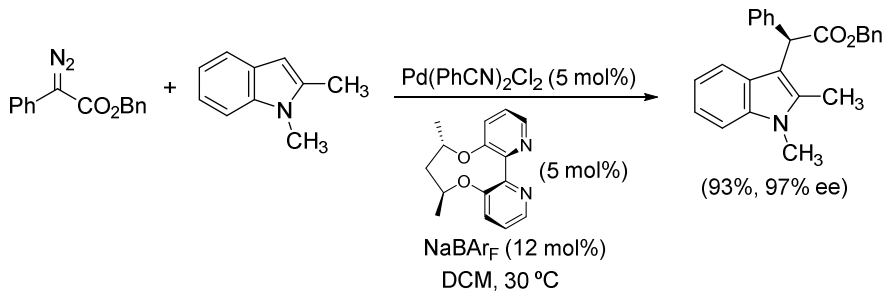



**Figure 1.31.**

In the last years, as part of a program on the synthesis of nitrogen heterocycles, our research group has been exploring different ways to increase the versatility of palladium catalysis in C–C bond-forming reactions, for example, by controlling the

[51] Reiser, O. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. Ed.; Wiley-Interscience: New York, 2002, Vol. 1, pp 1561-1577.
[52] See Goll, J. M.; Fillion, E. *Organometallics* **2008**, *27*, 3622, and references therein.
[53] Zhang, D.; Qiu, H.; Jiang, L.; Lv, F.; Ma, C.; Hu, W. *Angew. Chem. Int. Ed.* **2013**, *52*, 13356.
[54] Gao, X.; Wu, B.; Huang, W.-X.; Chen, M.-W.; Zhou, Y.-G. *Angew. Chem. Int. Ed.* **2015**, *54*, 11956.

ambiphilic character of organopalladium intermediates in intramolecular coupling reactions with carbonyl derivatives,[55] and by developing domino processes centered in palladium-catalyzed arylation reactions.[56]

Continuing this search for methodologies to enhance the synthetic potential of organopalladium chemistry, our group has also investigated the versatility of palladium as a catalyst for the carbene C–H insertion. In this context, the group first reported that either palladium(0)- or palladium(II)-catalysts are able to promote $Csp^3$–H insertion of carbenes derived from α-diazoesters to form pyrrolidines through intramolecular $Csp^3$–$Csp^3$ bond formation (Figure 1.32).[57] This reaction represents the first example of palladium-catalyzed carbene insertion into C($sp^3$)–H bonds.

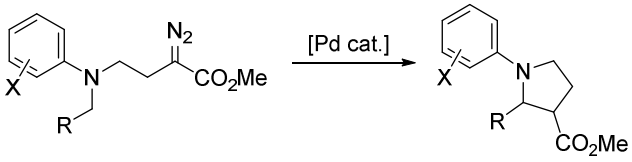



**Figure 1.32.**

It was subsequently demonstrated that the carbene $C_{Ar}sp^2$–H functionalization of α-diazo-α-(methoxycarbonyl)acetanilides to give oxindoles can also be promoted by using $Pd_2(dba)_3$ as the catalyst. This allowed the group to develop a one-pot methodology to prepare 3-(chloroethyl)oxindoles by means of a sequential C–H insertion/alkylation process (Figure 1.33).[58]

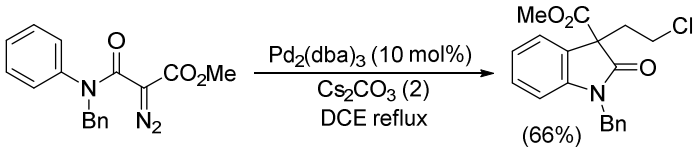



**Figure 1.33.**

[55] Solé, D.; Fernández, I. *Acc. Chem. Res.* **2014**, *47*, 168.
[56] (a) Solé, D.; Pérez-Janer, F.; Mancuso, R. *Chem. Eur. J.* **2015**, *21*, 4580. (b) Solé, D.; Pérez-Janer, F.; Zulaica, E.; Guastavino, J.F.; Fernández, I. *ACS Catal.* **2016**, *6*, 1691. (c) Solé, D.; Pérez-Janer, F.; García-Rodeja, Y.; Fernández, I. *Eur. J. Org. Chem.* **2017**, 799.
[57] Solé, D.; Mariani, F.; Bennasar, M.-L.; Fernández, I. *Angew. Chem. Int. Ed.* **2016**, *55*, 6467.
[58] Solé, D.; Pérez-Janer, F.; Fernández, I. *Chem. Commun.* **2017**, *53*, 3110.

More recently, our group also described the synthesis of β-lactams by Pd(II)-catalyzed carbene $Csp^3$–H insertion of α-diazo-α-(methoxycarbonyl)acetamides (Figure 1.34).[59] It was shown that Pd(0) catalysts can also be used to promote $Csp^3$–H insertion leading to β-lactams.[60] However, the Pd(II)-complexes proved to be more versatile for β-lactam elaboration since the use of Pd(0)-catalysts resulted in the formation of significant amounts of Buchner products and, in some cases, of the corresponding γ-lactams.

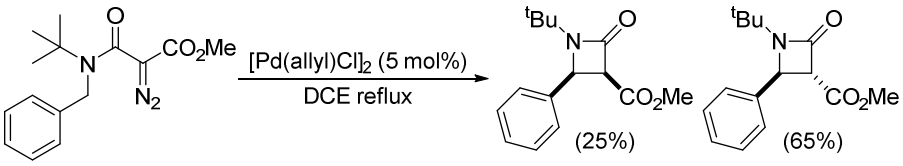



**Figure 1.34.**

[59] Solé, D.; Pérez-Janer, F.; Bennasar, M.-L.; Fernández, I. *Eur. J. Org. Chem.* **2018**, 4446.
[60] Solé, D.; Pérez-Janer, F.; Amenta, A.; Bennasar, M.-L.; Fernández, I. *Molecules* **2019**, *24*, 3551.

# Chapter 2

## Objectives

Considering the precedents described in the General Introduction and pursuing the interest of our research group in developing more efficient methodologies for the synthesis of nitrogen heterocycles, in this PhD Thesis it was decided to expand our previous studies on the use of different transition metal catalysts as alternatives to the widely used dirhodium(II) complexes for carbene C–H insertion of α-diazocarbonyl compounds.

In this context, the general objective of the Thesis was to study how the transition metal moiety influences the intramolecular carbene C–H insertion reactions of amino-tethered α-diazoesters.

In this investigation, we first compared the efficiency of several Pd, Rh(II) and Ru(II) catalysts to promote the C–H insertion of γ-amino-α-diazoesters to give pyrrolidines (Figure 2.1). With this study, we sought to identify differences in the reactivities and selectivities between the different transition-metal catalysts, in the search for a more effective synthetic methodology. This research is described in *Chapter 3*.

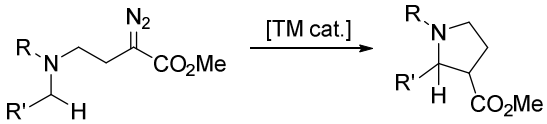



**Figure 2.1.**

Secondly, we explored the ability of a range of structurally diverse Ru(II) catalysts to promote carbene C–H insertion reactions of γ-amino-α-diazoesters (Figure 2.2). Thus, in *Chapter 4* we disclose our studies on the use of Grubbs catalysts to promote carbene $Csp^3$–H insertion of α-diazoesters to prepare pyrrolidines, as well as our preliminary work on the use of different chiral Ru(II) catalysts to develop an enantioselective carbene C–H insertion reaction.

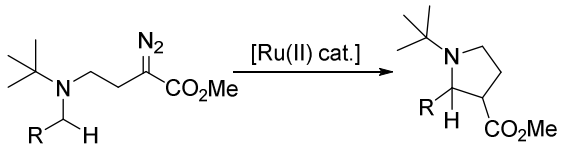



**Figure 2.2.**

We also investigated the use of both Pd(0) and Grubbs catalysts to promote the intramolecular aromatic C–H functionalization of γ-(arylamino)-α-diazoesters leading to tetrahydroquinolines (Figure 2.3). The results obtained are described in *Chapter 5*.

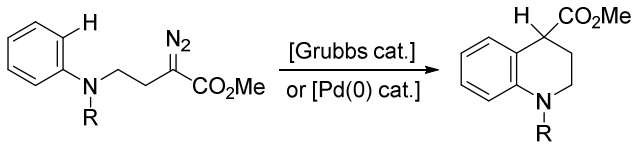



**Figure 2.3.**

Finally, we extended our investigation of amino-tethered α-diazocarbonyl compounds to the transition metal-catalyzed decomposition of δ-amino- and β-amino-α-diazoesters (Figure 2.4). These studies are described in *Chapter 6*.

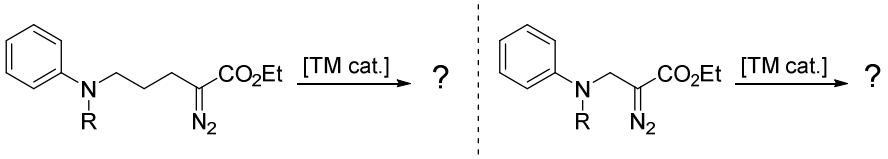



**Figure 2.4.**

## Chapter 3

# Transition Metal-Catalyzed Intramolecular Carbene C–H Insertion for Pyrrolidine Formation by Decomposition of α-Diazoesters

The intramolecular transition metal-catalyzed carbene C–H insertion by decomposition of α-diazocarbonyl compounds constitutes a powerful methodology for C–C bond formation and has been extensively used for the synthesis of carbocyclic and heterocyclic frameworks.[3] For a given substrate, several C–H insertion pathways may be available, the chemoselectivity, regioselectivity and stereoselectivity being dependent on the nature of both the substrate and the catalyst.[17a,61] Many transition metal complexes have proven to be effective catalysts to generate reactive metal carbenes starting from α-diazocarbonyl compounds.[8,9,43,44,62] Among them, rhodium(II),[18] copper,[14] and more recently ruthenium(II) catalysts[34-42] have been particularly useful for the development of highly selective carbene C–H insertion methodologies via a variety of reaction modes. Surprisingly, palladium, one of the most commonly employed metals in homogeneous catalysis, has been scarcely applied to this type of processes.[48-49]

In this context, our research group reported in 2016 that palladium catalysts are able to promote the intramolecular carbene C–H insertion of γ-(arylamino)-α-diazoesters to produce pyrrolidines through C($sp^3$)–C($sp^3$) bond formation (Figure 3.1).[57]

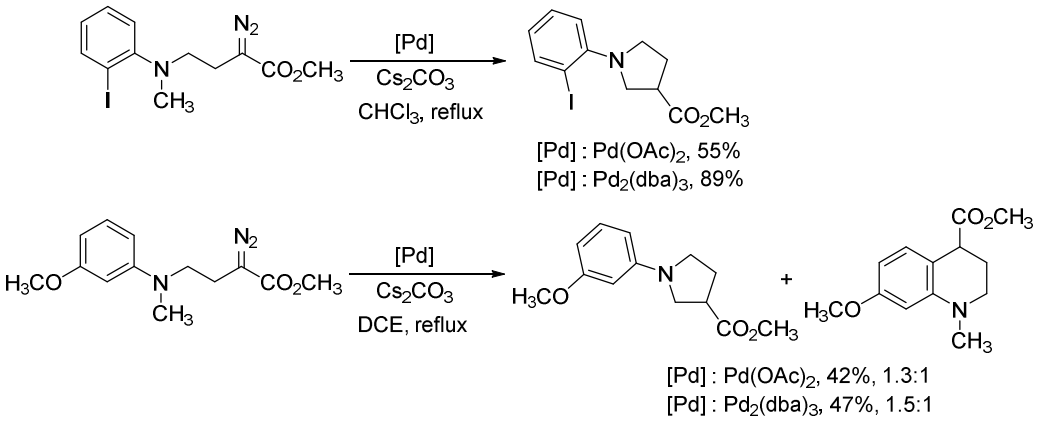



**Figure 3.1.**

[61] (a) Merlic, C. A.; Zechman, A. L. *Synthesis* **2003**, 1137. (b) Gois, P. M. P.; Afonso, C. A. M.; *Eur. J. Org. Chem.* **2004**, 3773. (c) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857. (d) Ring, A.; Ford, A.; Maguire, A. R. *Tetrahedron Lett.* **2016**, *57*, 5399.

[62] (a) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 775. (b) Liu, X.-G.; Zhang, S.-S.; Wu, J.-Q.; Li, Q.; Wang, H. *Tetrahedron Lett.* **2015**, *56*, 4093. (c) Zhao, D.; Kim, J. H.; Stegemann, L.; Strassert, C. A.; Glorius, F. *Angew. Chem. Int. Ed.* **2015**, *54*, 4508.

It was found that the outcome of this reaction was highly substrate-dependent. Thus, while *ortho*-substituted anilines chemoselectively underwent C($sp^3$)–H insertion to give the corresponding pyrrolidines, competition between C($sp^3$)–H and $C_{Ar}$($sp^2$)–H insertion was observed in the reactions involving *meta*- and *para*-substituted anilines.

Using these studies as a basis, we sought to develop a more efficient methodology for the synthesis of pyrrolidines and decided to revisit the transition metal-catalyzed carbene insertion of γ-amino-α-diazoesters. The objective of this study was to establish how the reaction of γ-amino-α-diazoesters is affected by the transition metal moiety, using Pd(0), Rh(II) as well as Ru(II) catalysts. In this investigation, we sought to identify differences in the reactivities and selectivities between these transition metals to ultimately achieve catalyst-controlled insertion reactions. In this context, it should be noted that most of the extensive research on the transition metal-catalyzed carbene C–H insertion has focused on studying different diazo compounds or a range of ligands, but without varying the nature of the transition metal.[63]

We commenced our investigation by looking more closely at the palladium-catalyzed carbene insertion of α-diazoester **3.1** (Figure 3.2).

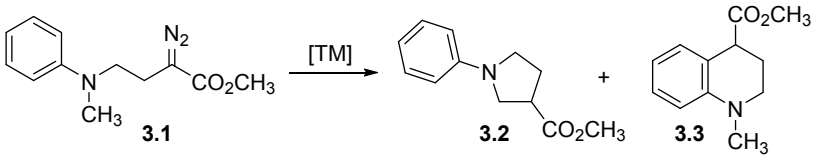



**Figure 3.2.**

During our previous optimization studies with α-diazoester **3.1**, it was found that the carbene C–H insertion can be promoted by both Pd(0) and Pd(II) catalysts. These reactions afforded mixtures of pyrrolidine **3.2** and tetrahydroquinoline **3.3**, arising from the activation of the C($sp^3$)–H and $C_{Ar}$($sp^2$)–H bonds, respectively. The best

[63] For selected examples on catalyst-controlled selectivities using a broader set of catalysts, see: (a) Ma, B.; Chen, F.-L.; Xu, X.-Y.; Zhang, Y.-N.; Hu, L.-H. *Adv. Synth. Catal.* **2014**, *356*, 416. (b) Deng, Y.; Jing, C.; Arman, H.; Doyle, M. P. *Organometallics* **2016**, *35*, 3413.

chemoselectivity (i.e. a **3.2**:**3.3** ratio of ≈2.7:1) was obtained when using a combination of $Pd_2(dba)_3$ with a bidentate phosphine (dppp, dppf or xantphos) as the catalyst.[57]

DFT calculations performed by our group suggested that these insertion reactions do not involve a concerted asynchronous process (as in Rh(II)-catalyzed insertions) but metalation-deprotonation reactions. Figure 3.3 shows the corresponding computed reaction profiles for the insertion reactions of α-diazoester **3.1** in the presence of either $Pd_2(dba)_3$/dppp or $Pd(OAc)_2/Cs_2CO_3$ as the catalysts.[57]

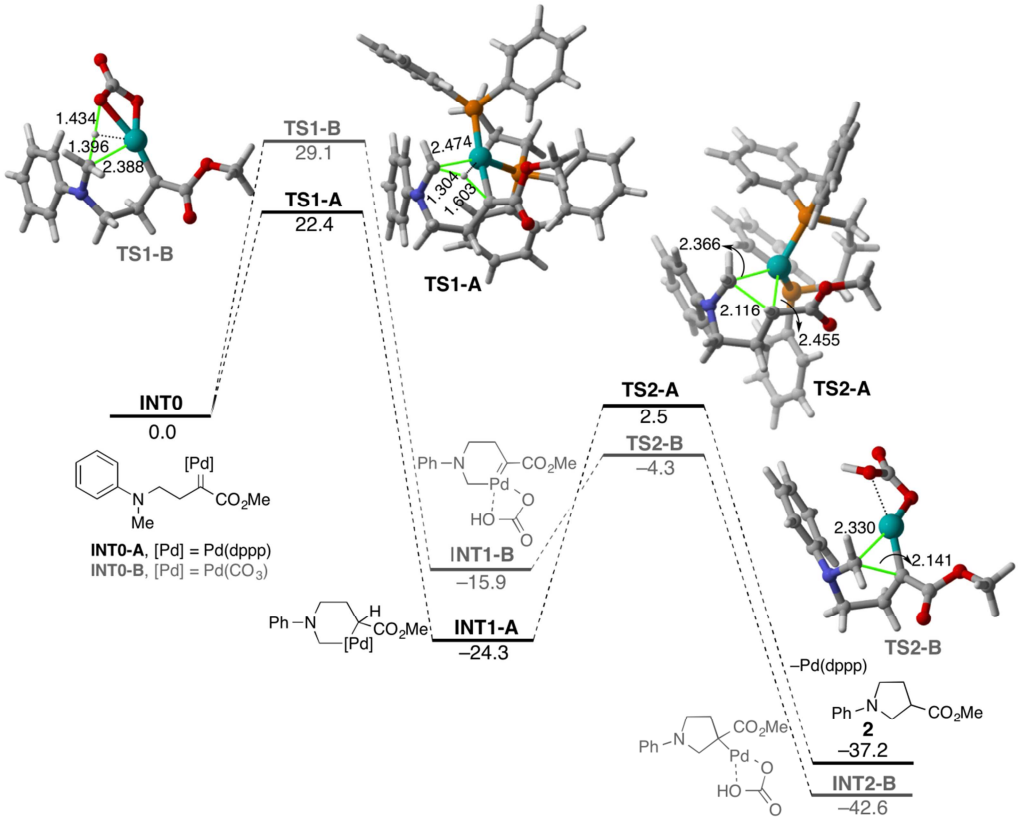



**Figure 3.3.** Computed reaction profiles for the formation of pyrrolidine **3.2**. Relative free energies ($\Delta G_{298}$, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data were computed at the PCM($CHCl_3$)-M06L/def2-TZVP//RI-BP86-D3/def2-SVP level. Atom colors: N = blue, O = red, C = gray, P = orange, Pd = turquoise.

Thus, the Pd(0)-dppp catalyzed C($sp^3$)–H insertion of aniline **3.1** would proceed via a genuine stepwise reaction mechanism involving: (i) the formation of an initial

pallada(0)carbene complex, (ii) a Pd-mediated 1,5-hydrogen migration from the N-$CH_3$ moiety to the carbene atom, which results in the formal oxidation of the transition metal, and (iii) the final reductive elimination leading to the observed pyrrolidine **3.2** with concomitant release of the active Pd(0)-dppp catalyst.

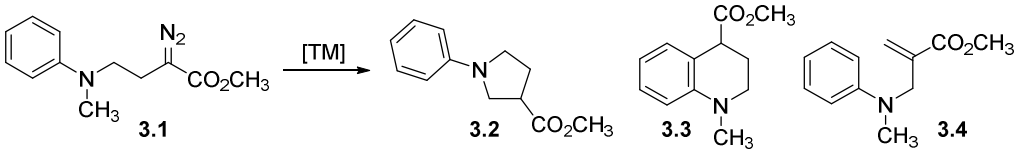
On the other hand, in the Pd(II)-pathway, the initially formed pallada(II)carbene complex would undergo the concerted hydrogen migration from the N–$CH_3$ moiety to the carbonate ligand and Pd–C bond formation. This transformation is analogous to related concerted metalation-deprotonation (CMD) C–H activations which are assisted by acetate or carbonate. Subsequent migratory insertion of the carbene carbon atom into the Pd–C bond would lead to the formation of a Pd(II)-enolate complex. Final protonolysis of the Pd–C bond would afford pyrrolidine **3.2** and release the Pd(II) catalyst.

With this information in hand, we continued or studies to gain more insight into the Pd(0)-catalyzed carbene insertion of α-diazoester **3.1**. Table 3.1 gathers the results of the new optimization studies with **3.1** (entries 6-17, Table 3.1), and for the sake of comparison it also includes some results of our previous study (entries 1-5, Table 3.1).

Although the initial Pd(0)-catalyzed reactions had been performed in the presence of $Cs_2CO_3$, our initial DFT computational studies suggested that when using Pd(0), the C–H insertion reaction can take place without this base. This was experimentally confirmed by treatment of **3.1** with a catalytic amount of $Pd_2(dba)_3$ in the absence of $Cs_2CO_3$, which afforded a similar result to that previously obtained in the presence of the base (compare entries 2 and 6, Table 3.1).

Other palladium catalysts lacking phosphine ligands were also explored in order to increase the selectivity of the insertion reaction. Unfortunately, when using $[(IMes)Pd(NQ)]_2$ as the catalyst a 1:1 mixture of **3.2** and **3.3** was obtained (entry 7, Table 3.1), while $[Pd(allyl)Cl]_2$ led to a mixture of **3.2**, **3.3**, and rearranged alkene **3.4** (entry 8, Table 3.1). The formation of such alkenes in the transition metal-catalyzed reactions of α-alkylsubstituted α-diazoesters is a well-known process.[63a]

**Table 3.1.** Transition metal-catalyzed cyclization of α-diazoester **3.1**.




| | [TM cat.] (mol%) ligand (mol%) | Base[a] | Solvent | Temp. | Time | Product ratio | Yield (%)[b],[c] |
|---|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (10) | $Cs_2CO_3$ (2) | $CHCl_3$ | reflux | 48 h | **3.2/3.3** (2:1)[d] | **3.2/3.3** (2:1, 45%) |
| 2 | $Pd_2(dba)_3$ (2.5) | $Cs_2CO_3$ (2) | DCE | 80 °C | 24 h | **3.2/3.3** (2.2:1)[d] | |
| 3 | $Pd_2(dba)_3$ (2.5) dppp (5) | $Cs_2CO_3$ (2) | DCE | 80 °C | 24 h | **3.2/3.3** (2.6:1)[e] | **3.2/3.3** (2.6:1, 57%) |
| 4 | $Pd_2(dba)_3$ (2.5) dppf (5) | $Cs_2CO_3$ (2) | DCE | 80 °C | 22 h | **3.2/3.3** (2.7:1)[e] | **3.2/3.3** (2.7:1, 51%) |
| 5 | $Pd_2(dba)_3$ (2.5) xantphos (5) | $Cs_2CO_3$ (2) | DCE | 80 °C | 24 h | **3.2/3.3** (2.8:1)[e] | **3.2/3.3** (2.8:1, 55%) |
| 6 | $Pd_2(dba)_3$ (2.5) | ----- | DCE | 80 °C | 24 h | **3.2/3.3** (2.1:1)[d] | **3.2/3.3** (2.1:1, 55%) |
| 7 | $[(IMes)Pd(NQ)]_2$ (2.5) | ---- | $CHCl_3$ | reflux | 24 h | **3.2/3.3** (1:1)[d] | **3.2/3.3** (1:1, 60%) |
| 8 | $[Pd(allyl)Cl]_2$ (5) | ---- | $CHCl_3$ | reflux | 24 h | **3.2/3.3/3.4** (1.5:1:1.2)[d] | |
| 9 | $Pd(OAc)_2$ (100) | $Cs_2CO_3$ (2) | $CHCl_3$ | r.t. | 100 h | **3.2/3.3** (3.5:1)[d] | **3.2/3.3** (3.5:1, 51%) |
| 10 | $Pd_2(dba)_3$ (35) dppf (70) | $Cs_2CO_3$ (2) | DCE | r.t. | 120 h | **3.2/3.3** (5:1)[d] | **3.2/3.3** (5:1, 63%) |
| 11 | $Pd(TFA)_2$ (20) | ----- | $CHCl_3$ | r.t. | 24 h | **3.2/3.3/3.4** (2.5:1:2.5)[d] | |
| 12 | $[Rh(OAc)_2]_2$ (4) | ----- | $CH_2Cl_2$ | r.t. | 24 h | **3.2/3.3** (2.4:1)[d] | **3.2/3.3** (2.4:1, 75%) |
| 13 | $[Rh(TFA)_2]_2$ (4) | ----- | $CH_2Cl_2$ | r.t. | 6 h | **3.2/3.3/3.4** (3:1:5)[d] | **3.2** (25%), **3.4** (41%) |
| 14 | $[Rh(Ph_3CCO_2)_2]_2$ (3) | ----- | $CH_2Cl_2$ | r.t. | 5 h | **3.2/3.3** (9:1)[d] | **3.2/3.3** (9:1, 94%) |
| 15 | $[Rh(Ph_3CCO_2)_2]_2$ (2) | ----- | $CH_2Cl_2$ | -10 °C | 5 h | **3.2/3.3** (9:1)[d] | **3.2/3.3** (9:1, 95%) |
| 16 | $[Rh(Ph_3CCO_2)_2]_2$ (2) | ----- | $CH_2Cl_2$ | -78 °C | 5 h | **3.2/3.3** (9:1)[d] | **3.2/3.3** (9:1, 89%) |
| 17 | $[Ru(p\text{-cymene})Cl_2]_2$ (3) | ----- | toluene | 40 °C | 24 h | **3.2**[f] | **3.2** (49%) |

[a] Equivalents in parentheses. [b] Yields refer to products isolated by chromatography. [c] For product mixtures the yield refers to the combined yield. [d] Product ratio measured by $^1H$ NMR. [e] Product ratio measured by GC. [f] Traces of **3.3** were also observed in the crude reaction mixture. $Pd_2(dba)_3$: Tris(dibenzylideneacetone)dipalladium(0). dppp: 1,3-Bis(diphenylphosphino)propane. dppf: 1,1'-Bis(diphenylphosphino)ferrocene. Xantphos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene. $[(IMes)Pd(NQ)]_2$ = 1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (1,4-naphthoquinone)palladium(0) dimer.

We also found that the reaction can proceed at room temperature, although longer reaction times and higher catalyst loading are required (entries 9-10, Table 3.1). Thus, treatment of **3.1** with an equimolar amount of $Pd(OAc)_2$ in $CHCl_3$ at room temperature gave a 3.5:1 mixture of pyrrolidine **3.2** and tetrahydroquinoline **3.3** (entry 9, Table 3.1), whereas using $Pd_2(dba)_3$ (35 mol%) and dppf (70 mol%) in DCE provided a 5:1 mixture of **3.2** and **3.3** (entry 10, Table 3.1). Interestingly, the chemoselectivity of both reactions was quite different from that obtained when using the same catalytic systems at higher temperatures (compare entries 1 and 4 with entries 9 and 10 in Table 3.1, respectively). On the other hand, treatment of **3.1** with a catalytic amount of

$Pd(TFA)_2$ at room temperature afforded a mixture of **3.2**, **3.3**, and alkene **3.4** (entry 11, Table 3.1).

At this point, some commercially available dirhodium(II) dicarboxylate catalysts as well as $[Ru(p\text{-cymene})Cl_2]_2$ were also explored to promote the carbene insertion of α-diazoester **3.1**. The use of $Rh_2(OAc)_4$ afforded a mixture of pyrrolidine **3.2** and tetrahydroquinoline **3.3** (2.4:1 ratio), which were isolated in 75% combined yield (entry 12, Table 3.1). Changing the catalyst from $Rh_2(OAc)_4$ to $Rh_2(TFA)_4$ resulted in the formation of alkene **3.4** as the major product (entry 13, Table 3.1), while $[Rh(Ph_3CCO_2)_2]_2$ gave a 9:1 mixture of **3.2** and **3.3** in a combined 94% reaction yield (entry 14, Table 3.1). A similar chemoselectivity was observed when the reaction was performed at lower temperatures (entries 15-16, Table 3.1). The best selectivity in the C–H insertion of α-diazoester **3.1** was obtained when using $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst, although the yield dropped to 49% (entry 17, Table 3.1).

The results in Table 3.1 therefore indicate that the carbene C–H insertion of α-diazoester **3.1** can be promoted by either Pd(0) or Pd(II), as well as by Rh(II) and Ru(II)-based catalysts, the $C(sp^3)$–H rather than $C_{Ar}(sp^2)$–H insertion being favored in all cases. The studies with α-diazoester **3.1** also showed that the more efficient and selective catalysts for the the $C(sp^3)$–H insertion are $Pd_2(dba)_3$, $[Rh(Ph_3CCO_2)_2]_2$ and $[Ru(p\text{-cymene})Cl_2]_2$. It should also be noted that although many reactions of functionalized diazo compounds have been described, the use of α-alkylsubstituted α-diazo carbonyl compounds has been more restricted. This is primarily due to the propensity of the corresponding transient carbenes to undergo β-hydride migration, an olefin-forming pathway that typically precludes both inter- and intramolecular reactivity.[64] Interestingly, the β-hydride migration was not observed in any of the reactions shown in Table 3.1.

In order to seek more information about the catalyst-controlled selectivity in the carbene C–H insertion of γ-amino α-diazoesters, we decided to explore the different

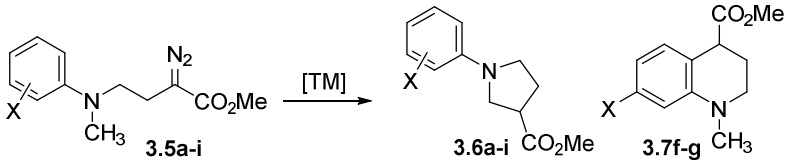
[64] DeAngelis, A.; Panish, R.; Fox, J. M. *Acc. Chem. Res.* **2016**, *49*, 115.

transition metals to promote the reaction starting from a variety of substrates. Firstly, we investigated how the introduction of substituents at the aniline ring affects the selectivity of the process. Table 3.2 gathers the reactions of substrates bearing different substituents at the aryl ring in the presence of $[(IMes)Pd(NQ)]_2$, $[Rh(Ph_3CCO_2)_2]_2$ or $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst. As before, for the sake of comparison, the results previously obtained with $Pd_2(dba)_3$ are also included.[57]

As can be seen in Table 3.2, the effect of the substituent on the course of the process varied according to its position on the aniline ring as well as the nature of the transition metal catalyst employed. Thus, the *ortho*-substituted anilines chemoselectively underwent $C(sp^3)$–H insertion to give the corresponding pyrrolidines regardless of the transition metal catalyst or the nature of the substituent (entries 1-20, Table 3.2). For these substrates, the Pd(0)-catalysts were at least as efficient as $[Rh(Ph_3CCO_2)_2]_2$, whereas $[Ru(p\text{-cymene})Cl_2]_2$ invariably provided the worst yields. When using either $[(IMes)Pd(NQ)]_2$ or the Rh(II)-catalyst to promote the reaction of the highly crowded *ortho*-methyl substituted aniline **3.5e**, significant amounts of the rearranged alkene **3.4'** (Figure 3.4) were also isolated (entries 18-19, Table 3.2). It is worth noting that no product resulting from the potentially competitive palladium-catalyzed reaction of the aryl halide with the α-diazoester moiety[50] was observed in any of the palladium-catalyzed reactions of **3.5a** and **3.5b** (entries 1, 2, 5 and 6, Table 3.2). This could allow further synthetic transformation by transition metal-catalyzed coupling reactions from these substrates.

On the other hand, competition between $C(sp^3)$–H and $C_{Ar}(sp^2)$–H insertion was evident in the reactions involving *meta*- and *para*-substituted anilines when using $Pd_2(dba)_3$ as the catalyst, despite the $C(sp^3)$–H insertion still being the preferred reaction pathway (entries 21, 25, 28 and 31, Table 3.2). The use of $[(IMes)Pd(NQ)]_2$ as the catalyst to promote the reaction of **3.5f** resulted in a complex mixture, in which only trace amounts of the insertion products were observed (entry 22, Table 3.2).

**Table 3.2.** Transition metal-catalyzed reactions of α-diazoesters **3.5a-i**.




| Entry | 3.5 (X) | [TM cat.] (mol%)/ligand (mol%) | Solvent | Temp. | Product Yield [%][a] |
|---|---|---|---|---|---|
| 1 | **3.5a** (2-I) | $Pd_2(dba)_3$ (2.5)[b] | $CHCl_3$ | reflux | **3.6a** (89) |
| 2 | **3.5a** (2-I) | $[(IMes)Pd(NQ)]_2$ (2.5)[c] | $CHCl_3$ | reflux | **3.6a** (85) |
| 3 | **3.5a** (2-I) | $[Rh(Ph_3CCO_2)_2]_2$ (2)[d] | $CH_2Cl_2$ | r.t. | **3.6a** (70) |
| 4 | **3.5a** (2-I) | $[Ru(p\text{-cymene})Cl_2]_2$ (3)[e] | toluene | 40 °C | **3.6a** (66)[f] |
| 5 | **3.5b** (2-Br) | $Pd_2(dba)_3$ (2.5)[b] | $CHCl_3$ | reflux | **3.6b** (66) |
| 6 | **3.5b** (2-Br) | $[(IMes)Pd(NQ)]_2$ (2.5)[c] | $CHCl_3$ | reflux | **3.6b** (70) |
| 7 | **3.5b** (2-Br) | $[Rh(Ph_3CCO_2)_2]_2$ (2)[d] | $CH_2Cl_2$ | r.t. | **3.6b** (82) |
| 8 | **3.5b** (2-Br) | $[Ru(p\text{-cymene})Cl_2]_2$ (3)[e] | toluene | 40 °C | **3.6b** (61) |
| 9 | **3.5c** (2-Cl) | $Pd_2(dba)_3$ (2.5)/dppf (5)[b] | DCE | 80 °C | **3.6c** (69) |
| 10 | **3.5c** (2-Cl) | $[(IMes)Pd(NQ)]_2$ (2.5)[c] | $CHCl_3$ | reflux | **3.6c** (85) |
| 11 | **3.5c** (2-Cl) | $[Rh(Ph_3CCO_2)_2]_2$ (2)[d] | $CH_2Cl_2$ | r.t. | **3.6c** (88) |
| 12 | **3.5c** (2-Cl) | $[Ru(p\text{-cymene})Cl_2]_2$ (3)[e] | toluene | 40 °C | **3.6c** (57)[g] |
| 13 | **3.5d** (2-F) | $Pd_2(dba)_3$ (2.5)[b] | DCE | 80 °C | **3.6d** (62) |
| 14 | **3.5d** (2-F) | $[(IMes)Pd(NQ)]_2$ (2.5)[c] | $CHCl_3$ | reflux | **3.6d** (71) |
| 15 | **3.5d** (2-F) | $[Rh(Ph_3CCO_2)_2]_2$ (2)[d] | $CH_2Cl_2$ | r.t. | **3.6d** (87) |
| 16 | **3.5d** (2-F) | $[Ru(p\text{-cymene})Cl_2]_2$ (3)[e] | toluene | 40 °C | **3.6d** (56) |
| 17 | **3.5e** (2-Me) | $Pd_2(dba)_3$ (2.5)[b] | DCE | 80 °C | **3.6e** (58) |
| 18 | **3.5e** (2-Me) | $[(IMes)Pd(NQ)]_2$ (2.5)[c] | $CHCl_3$ | reflux | **3.6e** (68), **3.4'** (10) |
| 19 | **3.5e** (2-Me) | $[Rh(Ph_3CCO_2)_2]_2$ (2)[d] | $CH_2Cl_2$ | r.t. | **3.6e** (56), **3.4'** (27) |
| 20 | **3.5e** (2-Me) | $[Ru(p\text{-cymene})Cl_2]_2$ (3)[e] | toluene | 40 °C | **3.6e** (46) |
| 21 | **3.5f** (3-Cl) | $Pd_2(dba)_3$ (2.5)[b] | DCE | 80 °C | **3.6f**/**3.7f** (2.7:1, 45) |
| 22 | **3.5f** (3-Cl) | $[(IMes)Pd(NQ)]_2$ (4)[c] | $CHCl_3$ | reflux | **CM**[h] |
| 23 | **3.5f** (3-Cl) | $[Rh(Ph_3CCO_2)_2]_2$ (2)[d] | $CH_2Cl_2$ | r.t. | **3.6f** (92) |
| 24 | **3.5f** (3-Cl) | $[Ru(p\text{-cymene})Cl_2]_2$ (3)[e] | toluene | 40 °C | **3.6f** (33)[i] |
| 25 | **3.5g** (3-MeO) | $Pd_2(dba)_3$ (2.5)[b] | DCE | 80 °C | **3.6g**/**3.7g** (1.5:1, 47) |
| 26 | **3.5g** (3-MeO) | $[Rh(Ph_3CCO_2)_2]_2$ (2)[d] | $CH_2Cl_2$ | r.t. | **3.6g** (81) |
| 27 | **3.5g** (3-MeO) | $[Ru(p\text{-cymene})Cl_2]_2$ (3)[e] | toluene | 40 °C | **3.6g** (55) |
| 28 | **3.5h** (4-Cl) | $Pd_2(dba)_3$ (2.5)/dppf (5)[b] | DCE | 80 °C | **3.6h** (35)[j] |
| 29 | **3.5h** (4-Cl) | $[Rh(Ph_3CCO_2)_2]_2$ (3)[d] | $CH_2Cl_2$ | r.t. | **3.6h** (78) |
| 30 | **3.5h** (4-Cl) | $[Ru(p\text{-cymene})Cl_2]_2$ (3)[e] | toluene | 40 °C | **3.6h** (34)[k] |
| 31 | **3.5i** (4-MeO) | $Pd_2(dba)_3$ (2.5)[b] | $CHCl_3$ | reflux | **3.6i** (38)[l] |
| 32 | **3.5i** (4-MeO) | $[Rh(Ph_3CCO_2)_2]_2$ (3)[d] | $CH_2Cl_2$ | r.t. | **3.6i** (74) |
| 33 | **3.5i** (4-MeO) | $[Ru(p\text{-cymene})Cl_2]_2$ (3)[e] | toluene | 40 °C | **3.6i** (85) |

[a] Yields refer to products isolated by chromatography and for entries in which a product mixture was obtained, the yield refers to the combined yield. [b] Reaction conditions: Catalyst/ligand (see table) and $Cs_2CO_3$ (2 equiv.) in $CHCl_3$ or DCE at the indicated temperature for 24 h. [c] Reaction conditions: Catalyst (see table) in $CHCl_3$ at reflux for 24 h. [d] Reaction conditions: $[Rh(Ph_3CCO_2)_2]_2$ (see table) in $CH_2Cl_2$ at r.t. for 5 h. [e] Reaction conditions: $[Ru(p\text{-cymene})Cl_2]_2$ (see table) in toluene at 40 °C (bath temperature) for 24 h. [f] **3.8a** (≈10%) was also obtained. [g] **3.8c** (≈5%) was also obtained. [h] Complex mixture in which trace amounts of **3.6f** and **3.7f** were observed. [i] Small amounts of **3.8f** were also observed in the reaction mixture. [j] $^1$H NMR analysis of the reaction mixture showed a ≈4:1 $C(sp^3)$–H/$C_{Ar}(sp^2)$–H activation ratio. [k] **3.8h** (15%) was also obtained. [l] $^1$H NMR analysis of the reaction mixture showed a ≈5:1 $C(sp^3)$–H/$C_{Ar}(sp^2)$–H activation ratio.

Similar results were obtained when this catalyst was used with **3.5g-i**. In contrast, in the presence of either the Rh(II)- or Ru(II)-based catalysts, these anilines led to the

corresponding pyrrolidines with complete chemoselectivity but with different yields. Thus, whereas all the pyrrolidines were obtained in good yields when using $[Rh(Ph_3CCO_2)_2]_2$, in the presence of the Ru(II)-catalyst, the yields for the substrates bearing a Cl-substituent were far worse than for those with a MeO group. Interestingly, in some of the reactions using $[Ru(p\text{-cymene})Cl_2]_2$ (entries 4, 12, 24 and 30, Table 3.2) minor amounts of the secondary aniline (i.e. **3.8a**,**c**,**f**,**h**, Figure 3.4), resulting from the demethylation and protonation of the starting diazoester were also observed (*vide infra*).

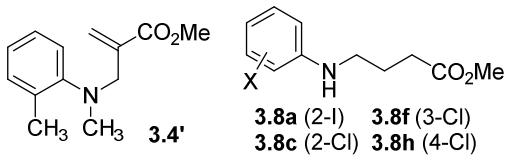
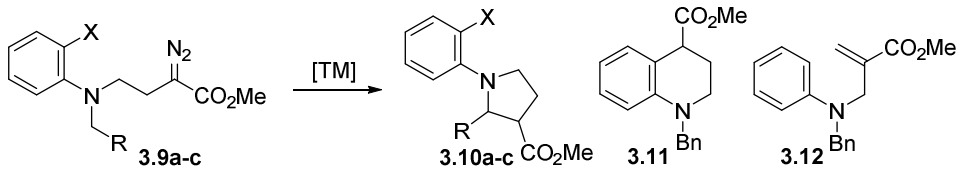



**Figure 3.4.**

The palladium-catalyzed C–H insertion reaction was not limited to *N*-methylanilines but also proved suitable for secondary $C(sp^3)$–H bonds. Table 3.3 gathers the results obtained in the reactions with the anilines bearing diverse *N*-methylene moieties when using different palladium catalysts as well as $[Rh(Ph_3CCO_2)_2]_2$ and $[Ru(p\text{-cymene})Cl_2]_2$. Thus, *N*-benzyl-2-iodoaniline **3.9a** chemoselectively afforded pyrrolidine **3.10a** (5.5:1 *cis*/*trans* ratio) in 66% yield when the reaction was performed in the presence of $Pd_2(dba)_3$ (entry 1, Table 3.3). Changing the catalyst to $[(IMes)Pd(NQ)]_2$ gave a similar reaction (entry 2, Table 3.3). $[Rh(Ph_3CCO_2)_2]_2$ (entry 3, Table 3.3) and $[Ru(p\text{-cymene})Cl_2]_2$ (entry 4, Table 3.3) also promoted the $C(sp^3)$–H insertion to give ≈3.3:1 mixtures of the *cis*/*trans* isomers, the Rh(II)-catalyst affording the higher yield.

Treatment of *N*-allyl-2-iodoaniline **3.9b** with catalytic amounts of either $Pd_2(dba)_3$ (entry 5, Table 3.3) or $[(IMes)Pd(NQ)]_2$ (entry 6, Table 3.3) in $CHCl_3$ at reflux afforded pyrrolidine **3.10b** (≈1.7:1 *cis*/*trans* ratio) in acceptable yields. The use of $[Rh(Ph_3CCO_2)_2]_2$ increased the yield up to 80% (entry 7, Table 3.3). When the reaction was promoted by $[Ru(p\text{-cymene})Cl_2]_2$ a slight change in the *cis*/*trans* selectivity and a decrease in the cyclization yield was observed (entry 8, Table 3.3).

**Table 3.3.** Transition metal-catalyzed reactions of α-diazoesters **3.9a-c**.




| Entry | 3.9 | [TM cat.] (mol%)/ligand (mol%)[a] | Solvent | Temp. | Product Yield [%][b] |
|---|---|---|---|---|---|
| 1 | **3.9a** (X:I, R:$C_6H_5$) | $Pd_2(dba)_3$ (2.5) | $CHCl_3$ | reflux | **3.10a** (66, *cis*/*trans* 5.5:1) |
| 2 | **3.9a** (X:I, R:$C_6H_5$) | $[(IMes)Pd(NQ)]_2$ (2.5) | $CHCl_3$ | reflux | **3.10a** (70, *cis*/*trans* 5.5:1) |
| 3 | **3.9a** (X:I, R:$C_6H_5$) | $[Rh(Ph_3CCO_2)_2]_2$ (2) | $CH_2Cl_2$ | r.t. | **3.10a** (75, *cis*/*trans* 3.3:1) |
| 4 | **3.9a** (X:I, R:$C_6H_5$) | $[Ru(p\text{-cymene})Cl_2]_2$ (3) | toluene | 40 °C | **3.10a** (60, *cis*/*trans* 3.4:1) |
| 5 | **3.9b** (X:I, R:$CH=CH_2$) | $Pd_2(dba)_3$ (2.5) | $CHCl_3$ | reflux | **3.10b** (58, *cis*/*trans* 1.7:1) |
| 6 | **3.9b** (X:I, R:$CH=CH_2$) | $[(IMes)Pd(NQ)]_2$ (2.5) | $CHCl_3$ | reflux | **3.10b** (68, *cis*/*trans* 1.8:1) |
| 7 | **3.9b** (X:I, R:$CH=CH_2$) | $[Rh(Ph_3CCO_2)_2]_2$ (2) | $CH_2Cl_2$ | r.t. | **3.10b** (80, *cis*/*trans* 1.6:1) |
| 8 | **3.9b** (X:I, R:$CH=CH_2$) | $[Ru(p\text{-cymene})Cl_2]_2$ (3) | toluene | 40 °C | **3.10b** (43, *cis*/*trans* 1:1.2) |
| 9 | **3.9c** (X:H, R:$C_6H_5$) | $Pd_2(dba)_3$ (2.5) | $CHCl_3$ | reflux | ***cis*-3.10c** (28),[c] **3.11** (17) |
| 10 | **3.9c** (X:H, R:$C_6H_5$) | $Pd_2(dba)_3$ (2.5)/dppf (5) | DCE | 80 °C | ***cis*-3.10c** (19),[c] **3.11** (19) |
| 11 | **3.9c** (X:H, R:$C_6H_5$) | $Pd(PPh_3)_4$ (5) | DCE | 80 °C | ***cis*-3.10c** (10),[c] **3.11** (25) |
| 12 | **3.9c** (X:H, R:$C_6H_5$) | $[(IMes)Pd(NQ)]_2$ (2.5) | $CHCl_3$ | reflux | ***cis*-3.10c/3.11** (1:1.9, 75) |
| 13 | **3.9c** (X:H, R:$C_6H_5$) | $[Pd(allyl)Cl]_2$ (5) | $CHCl_3$ | reflux | ***cis*-3.10c/3.11/3.12** (1:1.4:1.1)[d] |
| 14 | **3.9c** (X:H, R:$C_6H_5$) | $[Rh(Ph_3CCO_2)_2]_2$ (2) | $CH_2Cl_2$ | r.t. | ***cis*-3.10c/3.11** (1:1.6, 73)[e] |
| 15 | **3.9c** (X:H, R:$C_6H_5$) | $[Ru(p\text{-cymene})Cl_2]_2$ (3) | toluene | 40 °C | ***cis*-3.10c** (47), ***trans*-3.10c** (44) |

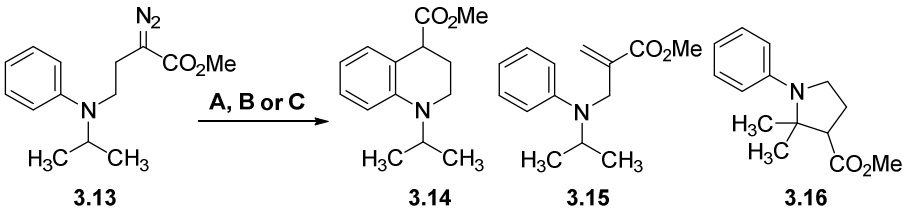
[a] See Table 3.2 for reaction conditions. [b] Yields refer to products isolated by chromatography and for entries in which a product mixture was obtained, the yield refers to the combined yield. [c] ***trans*-3.10c** (<5%) was also observed in the crude reaction mixture. [d] Product ratio measured by $^1$H NMR, yield not quantified. [e] **3.12** (<10%) was also observed in the crude reaction mixture.

It should be pointed out that, similar to the reactions involving 2-iodoaniline **3.5a** and 2-bromoaniline **3.5b**, no product resulting from the competitive palladium-catalyzed reaction of the aryl iodide with the α-diazoester moiety was observed in any of the considered palladium-catalyzed reactions of 2-iodoanilines **3.9a-b** (entries 1, 2, 5 and 6, Table 3.3). On the other hand, and more importantly, no competition between the allylic insertion and cyclopropanation[51] was apparent in either of the transition metal-catalyzed reactions of *N*-allylaniline **3.9b** (entries 5-8, Table 3.3).

The reaction of *N*-benzylaniline **3.9c**, which has no substituent at the aniline ring, was also explored. Similar to the reactions involving *N*-methylaniline **3.1**, the C($sp^3$)–H and $C_{Ar}$($sp^2$)–H insertions competed when using the Pd- or the Rh(II)-based catalysts (entries 9-14, Table 3.3). Thus, for example, treatment of **3.9c** with catalytic amounts of either $[(IMes)Pd(NQ)]_2$ (entry 12, Table 3.3) or $[Rh(Ph_3CCO_2)_2]_2$ (entry 14, Table 3.3) resulted in the formation of mixtures of pyrrolidine ***cis*-3.10c** and tetrahydroquinoline

**3.11** with similar C–H activation selectivities and in a yield of up to 75%. In contrast, in the presence of $[Ru(p\text{-cymene})Cl_2]_2$, the insertion proceeded selectively at the $C(sp^3)$–H bond (entry 15, Table 3.3). While ***cis*-3.10c** was selectively produced with the Pd- or Rh(II)-based catalysts, no stereoselectivity was observed in the $C(sp^3)$–H insertion when using the Ru(II)-catalyst.

At this point, we wondered if it would be possible to promote C–H insertion into tertiary $C(sp^3)$–H bonds. To this end, the reaction of *N-iso*propylaniline **3.13** was explored (Figure 3.5). Interestingly, insertion into the $C_{Ar}(sp^2)$–H bond was favored in the transition metal-catalyzed reactions of **3.13** when using either palladium- or rhodium-catalysts. Thus, the use of $Pd_2(dba)_3$ as the catalyst led to the major formation of tetrahydroquinoline **3.14**, which was isolated in 80% yield, together with alkene **3.15** (9%).




**A:** $Pd_2(dba)_3$ (2.5 mol%), $CHCl_3$, reflux, 24 h, **3.14** (80%), **3.15** (9%)
**B:** $[(IMes)Pd(NQ)]_2$ (2.5 mol%), $CHCl_3$, reflux, 24 h, **3.14** (75%)
**C:** $[Rh(Ph_3CCO_2)_2]_2$ (2 mol%), $CH_2Cl_2$, r.t., 5 h, **3.14** (42%), **3.15** (29%), **3.16** (6%)

**Figure 3.5.**

Changing the catalyst to $[(IMes)Pd(NQ)]_2$ resulted in the chemoselective formation of **3.14** (75%). In contrast, the use of $[Rh(Ph_3CCO_2)_2]_2$ afforded a mixture of tetrahydroquinoline **3.14** (42%), alkene **3.15** (29%), and pyrrolidine **3.16** (6%). Unfortunately, no reaction was observed when **3.13** was treated with $[Ru(p\text{-cymene})Cl_2]_2$, the starting material being recovered unchanged.

At this point, some comments on the transition metal-catalyzed C–H insertion reactions of aniline-type substrates are warranted. As in similar Rh(II)-mediated transformations, the site selectivity of the metal carbene insertions is probably

governed by a combination of electronic, steric as well as conformational factors.[65] Thus, in freely rotating systems, like those considered in this work, the 1,5 C($sp^3$)–H insertion is overwhelmingly predominant due to the entropically favorable six-membered transition states (*see below*). However, the sterically encumbered *N-iso*propyl aniline overturns this preference in favor of the formation of the six-membered ring by insertion into the $C_{Ar}(sp^2)$–H bond.

The initial computational studies performed by our group suggested that when using Pd(0)-dppp as the catalyst, the C($sp^3$)–H insertion proceeds via a genuine stepwise reaction mechanism (Figure 3.3).[57] In order to obtain more information on the reaction mechanism of the Pd(0)-catalyzed insertion reaction, in collaboration with Prof. Israel Fernández from the "Universidad Complutense de Madrid" we checked the generality of this unprecedented Pd(0)-mediated mechanism using the model $Pd(PMe_3)_2$ and Pd(NHC) (NHC = 1,3-bis(phenyl)-imidazol-2-ylidene) catalysts (Figure 3.6). From the data in Figure 3.6, it becomes clear that the C($sp^3$)–H insertion reaction proceeds through an identical mechanism to that reported previously for the Pd(0)-dppp catalytic system. In the particular case of the Pd(NHC)-catalyst, our calculations indicate that the initial 1,5-H migration is thermodynamically favored ($\Delta\Delta G_R$ = –5.0 kcal/mol) and the subsequent reductive elimination becomes kinetically easier ($\Delta\Delta G^{\neq}$ = 10.7 kcal/mol) than the process involving $PMe_3$ as the ligand in the coordination sphere of palladium.

We also computationally explored the reaction profile involving α-diazoester **3.1** and the model $Ru(C_6H_6)Cl_2$ catalyst. Figure 3.7 shows the corresponding computed reaction profile of the process involving **INT0-Ru**, the initial ruthena(II)-carbene complex formed upon reaction of the active catalytic species $Ru(C_6H_6)Cl_2$ with **3.1**. For the sake of comparison, the previously commented Pd(0)-catalyzed reaction profile is also represented. As in the Pd(0)-catalyzed process, the analogous carbene C-H insertion involving the Ru(II)-catalyst ($Ru(C_6H_6)Cl_2$ in the calculations) proceeds stepwise.

[65] See: Shi, W.; Zhang, B.; Zhang, J.; Liu, B.; Zhang, S.; Wang, J. *Org. Lett.* **2005**, *7*, 3103; and references therein.

However, from a mechanistic point of view, the Ru(II)-mediated transformation is completely different.

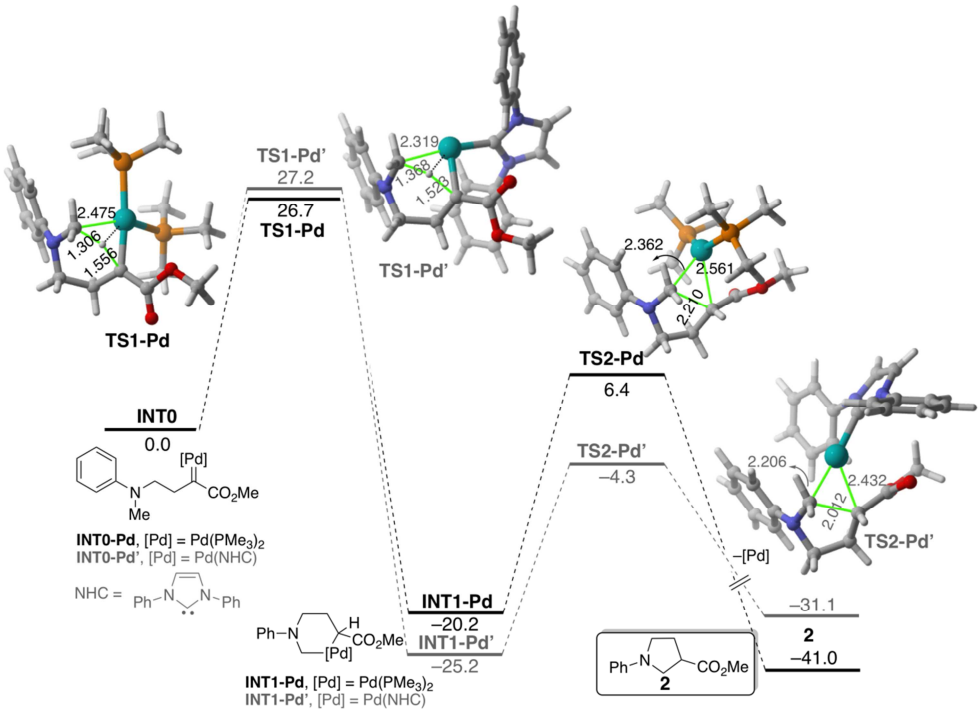



**Figure 3.6.** Computed reaction profiles for the palladium(0)-catalyzed formation of pyrrolidine **3.2**. Relative free energies ($\Delta G_{298}$, at 298 K) and bond distances are given in kcal/mol and angstroms (Å), respectively. All data were computed at the PCM($CHCl_3$)-M06L/def2-TZVPP//PCM($CHCl_3$)-B3LYP-D3/def2-SVP level. Atom colors: N = blue, O = red, C = gray, P = orange, Pd = turquoise.

According to our calculations, the initial ruthena(II)carbene **INT0-Ru** evolves to the zwitterionic complex **INT1-Ru** through the transition state **TS1-Ru** with a rather low activation barrier of 4.9 kcal/mol in an exergonic transformation ($\Delta G_R$ = –4.7 kcal/mol). Although this step can also be viewed as a 1,5-H migration, thus resembling the Pd(0)-mediated process, it is not directly assisted by the transition metal, and therefore, no oxidation of the ruthenium center occurs. As a result, the zwitterionic intermediate **INT1-Ru**, which is stabilized by conjugation from the lone-pair of the aniline nitrogen atom, is produced. This finding sheds light on the crucial role of the heteroatom directly attached to the involved $Csp^3$ atom in the Ru(II)-promoted process, as will be discussed

below. Finally, **INT1-Ru** is easily transformed into the observed pyrrolidine **3.2** via **TS2-Ru** (activation barrier of only 5.6 kcal/mol) in a strongly exergonic transformation ($\Delta G_R$ = –30.8 kcal/mol) that also releases the active catalytic species. As depicted in Figure 3.7, the latter saddle point is associated with the simultaneous C–Ru bond rupture and C–C bond formation. Therefore, this transformation can be considered as an intramolecular Ru(II)-promoted Mannich type reaction. The intermediacy of a zwitterionic intermediate in the Ru(II)-catalyzed reactions is experimentally supported by the formation of minor amounts of the secondary anilines **3.8a**,**c**,**f**,**h** in the insertion reactions of α-diazoesters **3.5a**,**c**,**f**,**h** (entries 4, 12, 24 and 30, Table 3.2). These anilines would be formed by the competitive hydrolysis of the iminium moiety and simultaneous protonolysis of the Ru(II)-enolate function of the zwitterionic species.

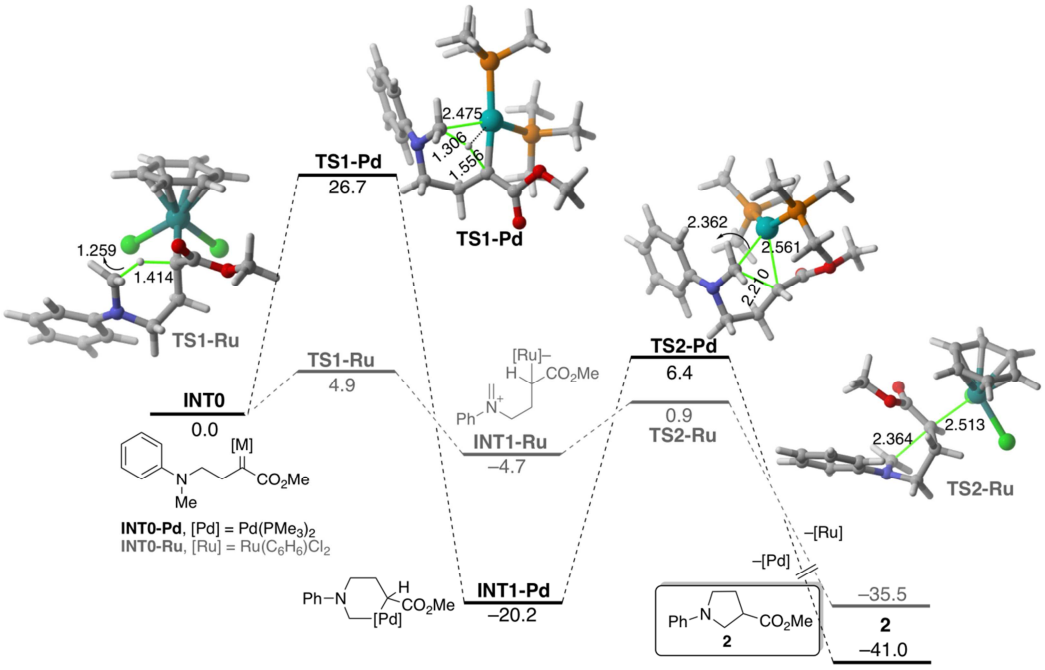
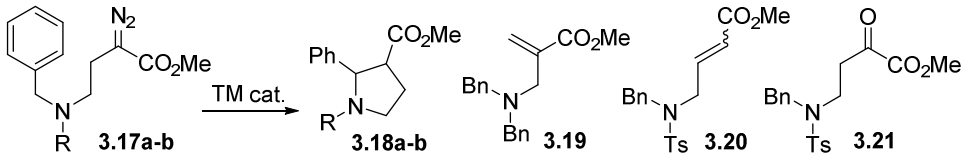



**Figure 3.7.** Computed reaction profiles for the formation of pyrrolidine **3.2**. Relative free energies ($\Delta G_{298}$, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data were computed at the PCM($CHCl_3$)-M06L/def2-TZVPP//PCM($CHCl_3$)-B3LYP-D3/def2-SVP level. Atom colors: N = blue, O = red, C = gray, P = orange, Pd and Ru = turquoise.

Interestingly, both Pd(0)- and Ru(II)-mediated mechanisms are fundamentally different from that accepted for related Rh(II)-catalyzed (and also Cu-catalyzed) C–H insertions, which are assumed to proceed in a concerted but asynchronous manner that directly releases the insertion product and the metal catalyst in a single reaction step.

Once the influence of the transition metal catalyst on the reactions of γ-(arylamino) α-diazoesters was experimentally and computationally revealed, we decided to investigate the carbene C($sp^3$)–H insertion reactions of some non-aniline substrates (Table 3.4).

**Table 3.4.** Transition metal-catalyzed reactions of α-diazoesters **3.17a-b**.




| Entry | 3.17 | [TM cat.] (mol%)/ligand (mol%)[a] | Solvent | Temp. | Product Yield [%][b] |
|---|---|---|---|---|---|
| 1 | **3.17a** (R:Bn) | $Pd_2(dba)_3$ (2.5) | $CHCl_3$ | reflux | **3.18a** (35, *cis*/*trans* 1:1)<br>**3.19** (22) |
| 2 | **3.17a** (R:Bn) | $Pd_2(dba)_3$ (2.5)/dppf (5) | DCE | 80 °C | **3.18a** (35, *cis*/*trans* 1:1)<br>**3.19** (20) |
| 3 | **3.17a** (R:Bn) | $[(IMes)Pd(NQ)]_2$ (2.5) | $CHCl_3$ | reflux | **3.18a** (60, *cis*/*trans* 2:1)[c] |
| 4 | **3.17a** (R:Bn) | $[Rh(Ph_3CCO_2)_2]_2$ (2) | $CH_2Cl_2$ | r.t. | **3.18a** (40, *cis*/*trans* 1.1:1)<br>**3.19** (54) |
| 5 | **3.17a** (R:Bn) | $[Ru(p\text{-cymene})Cl_2]_2$ (3) | toluene | 40 °C | **3.18a** (90, *cis*/*trans* 2.8:1) |
| 6 | **3.17b** (R:Ts) | $Pd_2(dba)_3$ (2.5) | $CHCl_3$ | reflux | **3.20** (80, *Z*/*E* 1:1) |
| 7 | **3.17b** (R:Ts) | $[(IMes)Pd(NQ)]_2$ (2.5) | $CHCl_3$ | reflux | **3.20** (61, *Z*/*E* 1:1.8) |
| 8 | **3.17b** (R:Ts) | $[Rh(Ph_3CCO_2)_2]_2$ (2) | $CH_2Cl_2$ | r.t. | ***cis*-3.18b** (66) |
| 9 | **3.17b** (R:Ts) | $[Ru(p\text{-cymene})Cl_2]_2$ (3) | toluene | 40 °C | **3.21** (38) |

[a] See Table 3.2 for reaction conditions. [b] Yields refer to products isolated by chromatography and for entries in which a product mixture was obtained, the yield refers to the combined yield. [c] Trace amounts of **3.19** were also observed in the crude reaction mixture.

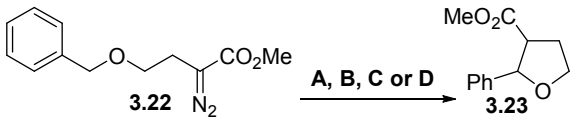
When the decomposition of *N*,*N*-dibenzyl-α-diazoester **3.17a** was promoted by $Pd_2(dba)_3$ either with (entry 1, Table 3.4) or without the phosphine ligand (entry 2, Table 3.4), pyrrolidine **3.18a** (1:1 *cis*/*trans* ratio), resulting from the C($sp^3$)–H insertion, was isolated in 35% yield, together with the rearranged alkene **3.19**. Changing the catalyst to $[(IMes)Pd(NQ)]_2$ increased the yield of **3.18a** up to 60%, the *cis* isomer being predominant (entry 3, Table 3.4). In the presence of $[Rh(Ph_3CCO_2)_2]_2$, alkene **3.19** was

the main product (entry 4, Table 3.4), while [Ru(*p*-cymene)$Cl_2$]$_2$ led to pyrrolidine **3.18a** (2.8:1 *cis*/*trans* ratio) in high yield (entry 5, Table 3.4).

On the other hand, *N*-benzylsulfonamide **3.17b** showed a notably different behavior depending on the transition metal catalyst employed. Thus, the use of Pd(0)-catalysts (entries 6-7, Table 3.4) resulted in the exclusive formation of alkene **3.20**, due to the 1,2-H migration of the metal carbene intermediate,[64] while in the presence of the Ru(II)-catalyst a complex reaction mixture was obtained, from which only ketone **3.21** was isolated (entry 9, Table 3.4). The lack of the C–H insertion product in the latter case may be ascribed to the delocalization of the nitrogen lone-pair into the sulfonyl group, which would hamper the stabilization required in the corresponding zwitterionic intermediate (*vide supra*).

In contrast, treatment of **3.17b** with the Rh(II)-catalyst afforded pyrrolidine ***cis*-3.18b** as the only reaction product, which was isolated in 66% yield (entry 8, Table 3.4). This is also consistent with the different mechanism proposed for the Rh(II)-catalyzed C–H insertions.

The reaction of α-diazoester **3.22**, which bears a benzyloxy group instead of the *N*-substituted moiety, was then explored (Figure 3.8). The $Pd_2(dba)_3$-catalyzed decomposition of **3.22** afforded tetrahydrofuran **3.23** (1:1.8 *cis*/*trans* ratio) in 38% yield. Significant amounts of the alkene (*Z*/*E* mixture) resulting from the 1,2-H migration of the metal carbene intermediate were also observed in the crude reaction mixture.

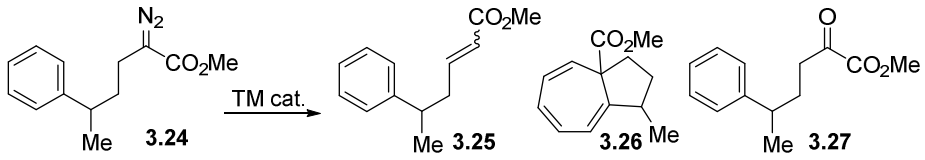



**A:** $Pd_2(dba)_3$ (2.5 mol%), $CHCl_3$, reflux, 24 h, **3.23** (38%, 1:1.8 *cis*/*trans*)
**B:** [(IMes)Pd(NQ)]$_2$ (2.5 mol%), $CHCl_3$, reflux, 24 h, **3.23** (50%, 1.3:1 *cis*/*trans*)
**C:** [$Rh(Ph_3CCO_2)_2$]$_2$ (2 mol%), $CH_2Cl_2$, r.t., 5 h, **3.23** (90%, 7:1 *cis*/*trans*)
**D:** [Ru(*p*-cymene)$Cl_2$]$_2$ (3 mol%), toluene, 40 ºC, 5 h, **3.23** (79%, 1:1 *cis*/*trans*)

**Figure 3.8.**

The use of $[(IMes)Pd(NQ)]_2$ as the catalyst slightly changed the stereoselectivity of the annulation to give a 1.3:1 mixture of ***cis*-3.23** and ***trans*-3.23** in a 50% combined yield. Better results were obtained when using either $[Rh(Ph_3CCO_2)_2]_2$ or $[Ru(p\text{-cymene})Cl_2]_2$. However, while the Ru(II)-catalyst led to a 1:1 mixture of ***cis*-3.23** and ***trans*-3.23** (79% combined yield), the use of the Rh(II)-catalyst[66] resulted in the stereoselective formation of ***cis*-3.23** (7:1 *cis*/*trans* ratio, 90% combined yield).

The experimental results obtained in the above studies and our DFT calculations seem to indicate that the success of the $C(sp^3)$–H insertion relies in the presence of a heteroatom at the $\gamma$ position of the $\alpha$-diazoester. In order to further confirm the need for a heteroatom directly attached to the $C(sp^3)$–H moiety involved in the carbene C–H insertion, we decided to study the reaction of $\alpha$-diazoester **3.24** (Figure 3.9).




**A:** $Pd_2(dba)_3$ (2.5 mol%), $CHCl_3$, reflux, 24 h, **3.25** (75%, 1:1 *Z*/*E*)
**B:** $[(IMes)Pd(NQ)]_2$ (2.5 mol%), $CHCl_3$, reflux, 24 h, **3.25** (72%, 1:1 *Z*/*E*)
**C:** $[Rh(Ph_3CCO_2)_2]_2$ (2 mol%), $CH_2Cl_2$, r.t., 5 h, ***Z*-3.25** (59%), **3.26** (15%)
**D:** $[Ru(p\text{-cymene})Cl_2]_2$ (3 mol%), toluene, 40 ºC, 5 h, ***Z*-3.25** (53%), **3.27** (17%)

**Figure 3.9.**

Not surprisingly, no C–H insertion product was isolated in any of the transition metal-catalyzed reactions with this substrate. Instead, a 1:1 mixture of ***Z*-3.25** and ***E*-3.25** was obtained when using either $Pd_2(dba)_3$ (75% combined yield) or $[(IMes)Pd(NQ)]_2$ (72% yield). Similarly, in the presence of $[Rh(Ph_3CCO_2)_2]_2$, ***Z*-3.25** (59%) was isolated together with a minor product (15%) identified as cycloheptatriene **3.26**, which arises from an intramolecular Buchner reaction.[67] Finally, the $[Ru(p\text{-cymene})Cl_2]_2$-catalyzed

[66] For selected examples on the use Rh(II)-catalysts for the synthesis of tetrahydrofuranes, see: (a) Taber, D. F.; Song, Y. *J. Org. Chem.* **1996**, *61*, 6706. (b) Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887.
[67] See, for example: Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Roos, G. H. P. *J. Chem. Soc., Chem. Commun.* **1990**, 361.

decomposition of **3.24** led to the stereoselective formation of ***Z*-3.25** (53%) together with ketone **3.27** (17%).

The transformations summarized in Table 3.4 and Figures 3.8 and 3.9 confirm that in the intramolecular reaction of α-diazoesters, regardless of the transition-metal catalytic system [Pd(0), Rh(II) or Ru(II)], the presence of a heteroatom (N or O) in the tether is essential for the successful carbene C($sp^3$)–H insertion. Regarding the nitrogen moiety, both the Pd(0)- and Ru(II)-catalysts need the presence of an amine nitrogen, while the Rh(II)-catalyst also tolerates a sulfonamide function. For the Ru(II)-promoted insertion reactions, these results are in good agreement with those expected from the computed reaction profile depicted in Figure 3.7.

In order to understand the influence of the heteroatom on the above palladium(0)-catalyzed insertion reactions, some new DFT calculations were carried out. To unravel the role of the heteroatom, we compared the palladium(0)-catalyzed insertion reaction profiles involving aniline **3.1** and compound **3.24**, which begin with palladacarbenes **INT0-Pd** and **INT0-Pd''**, respectively (Figure 3.10). From our calculations, it becomes clear that the first step of the transformation, which involves the metal-mediated 1,5-H migration, is similar for both systems, as it occurs with nearly identical activation barriers. This might be somewhat surprising if we consider the well-known higher C–H bond dissociation energy of the parent H–$CH_3$ bond (431 kJ/mol) with respect to H–$CH_2NH_2$ (397 kJ/mol).[68] However, due to the delocalization of the nitrogen lone-pair into the phenyl group in **3.1**, the C–H bond strength in intermediates **INT0-Pd** and **INT0-Pd''** is quite similar, as indicated by the computed corresponding Wiberg Bond Indices (0.95 and 0.94, respectively). Therefore, no significant differences in the barriers of these processes should be expected. Nevertheless, this 1,5-H migration is clearly thermodynamically favored for the reaction involving aniline **3.1** ($\Delta G_R$ = 3.1 kcal/mol). More importantly, the activation barrier associated with the subsequent reductive elimination process is clearly much higher for the species lacking the heteroatom ($\Delta\Delta G^{\neq}$ = 6.6 kcal/mol). Indeed, the high barrier computed for the process involving **TS2-Pd''**

[68] Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res*. **2003**, *36*, 255.

($\Delta G^{\neq}$ = 30.1 kcal/mol) indicates that this final step is severely hampered, which matches the experimental findings.

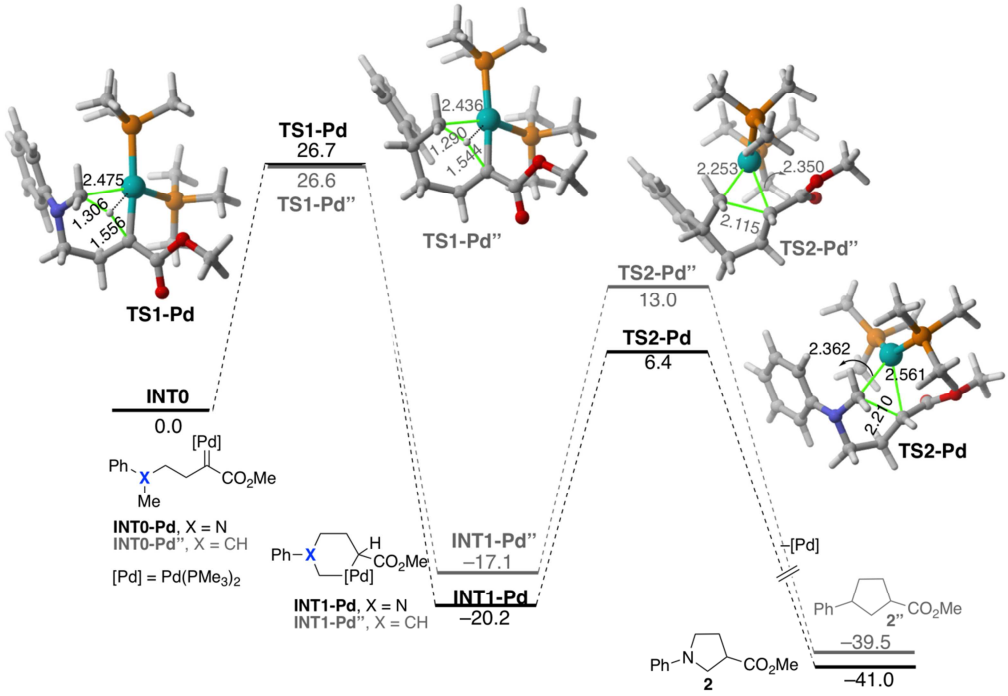



**Figure 3.10.** Computed reaction profiles for the formation of pyrrolidine **3.2** and cyclopentane **3.2"**. Relative free energies ($\Delta G_{298}$, at 298 K) and bond distances are given in kcal/mol and angstroms (Å), respectively. All data were computed at the PCM($CHCl_3$)-M06L/def2-TZVPP//PCM($CHCl_3$)-B3LYP-D3/def2-SVP level. Atom colors: N = blue, O = red, C = gray, P = orange, Pd = turquoise.

In summary, in this work we have explored the use of Pd(0)-, Rh(II)- as well as Ru(II)-catalysts for the transition metal-catalyzed intramolecular carbene C($sp^3$)–H insertion of γ-amino-α-diazoesters leading to pyrrolidines. The results obtained in the annulation reactions show that the transition metal catalyst of choice for the process was highly substrate-dependent. On the whole, although $[Rh(Ph_3CCO_2)_2]_2$ proved to be the most versatile catalyst, it did not always give the highest yield and selectivity.

In the reactions of *N*-alkylaniline substrates, the insertion occurred selectively on primary and secondary C($sp^3$)–H bonds rather than $C_{Ar}$($sp^2$)–H bonds, regardless of the transition-metal catalytic system. In general, the Rh(II)- and Ru(II)-based catalysts

provided better chemoselectivity than the Pd(0)-catalysts. However, with *ortho*-substituted anilines, the Pd(0)-catalysts were at least as efficient as $[Rh(Ph_3CCO_2)_2]_2$, the $C(sp^3)$–H insertion being the only reaction observed. The generality and functional group tolerance of the insertion reaction for the synthesis of *N*-arylpyrrrolidines is well illustrated by the fact that both electron-donating and electron-withdrawing groups were perfectly accommodated on the aromatic ring.

The $C(sp^3)$–H insertion was not limited to anilines but also proved to be suitable for alkylamine-type substrates. $[Ru(p\text{-cymene})Cl_2]_2$ was more efficient than the Pd- and Rh-based catalysts in the insertion reaction of the *N*,*N*-dibenzyl-α-diazoester, whereas only $[Rh(Ph_3CCO_2)_2]_2$ was able to promote the insertion of the *N*-benzylsulfonamide derivative.

The mechanism involved in the C–H insertion process strongly depends on the nature of the transition metal. Whereas Rh(II)-catalysts are reported to directly release the insertion product and the metal catalyst in a single reaction step, both Pd(0)- and Ru(II)-catalysts involve genuine stepwise reaction mechanisms. Nevertheless, the corresponding transformations are essentially different because the initially formed metallacarbene complex follows a distinct reaction pathway to produce the observed products, i.e. a metal-mediated 1,5-H migration followed by reductive elimination is suggested for the Pd(0)-catalyzed process, while a Ru(II)-promoted Mannich type reaction is proposed for the Ru(II)-mediated reaction.

## Chapter 4

# New Ruthenium Catalysts in the Intramolecular Carbene C($sp^3$)–H Insertion Leading to Pyrrolidines

The rich coordination chemistry of ruthenium and hence the diversity of ruthenium complexes have led to the development of a number of catalytic transformations that can be used for the rapid assembly of complex molecules with high atom economy.[69] In particular, the ruthenium carbenes collectively known as Grubbs catalysts have been extensively applied in metathesis reactions.[70] The outstanding performance of these reactions derives from the remarkable selectivity of Grubbs complexes for unsaturated reactants, which allows chemoselective targeting of alkenes and alkynes in intricate frameworks of organic functional groups. Moreover, a growing number of nonmetathetic catalytic transformations promoted by Grubbs carbene complexes have been described and after optimization some of them are showing synthetic utility.[71]

In parallel, as commented in the General Introduction, it has also been reported that the reaction of diazo compounds with different ruthenium complexes affords ruthenium carbene species that can participate, *inter alia*, in cyclopropanation[72] and C–H insertion reactions. Although in the last years ruthenium complexes have been increasingly used as alternatives to promote carbene C–H insertion starting from diazo compounds, in comparison with the well-established rhodium catalysts, ruthenium is a relative newcomer in this field, despite being considerably more cost-effective.

Regarding the ruthenium complexes used for C–H insertion of diazo compounds, their high structural diversity is remarkable. Thus, while most attention has centered on the use of $[RuCl_2(p\text{-cymene})]_2$,[36-40] some reports have shown that ruthenium(II)-porphyrins,[34,35] polystyrene-supported ruthenium nanoparticles[37] and some diRu(I,I)-complexes[41] can effectively catalyze intramolecular carbene C–H insertion. Very

[69] (a) *Ruthenium Catalysts and Fine Chemistry, in Topics in Organometallic Chemistry*, Bruneau, C. and Dixneuf, P. H. Eds., Springer-Verlag: Berlin; 2004. (b) *Ruthenium in Organic Synthesis*, Murahashi, S.-I. Ed., Wiley-VCH: Weinheim; 2005. (c) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem. Int. Ed.* **2005**, *44*, 6630.
[70] (a) *Handbook of Metathesis*, Grubbs, R. H. Ed., Wiley-VCH: Weinheim, 2003; Vol. 1-3. (b) Yet, L. *Organic Reactions*; John Wiley & Sons: Hoboken, NJ, 2016, Vol. 89, pp 1-1303. (c) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746. (d) Ogba, O. M.; Warner, N. C.; O'Leary, D. J. Grubbs, R. H. *Chem. Soc. Rev.* **2018**, *47*, 4510.
[71] (a) Alcaide, B.; Almendros, P.; Luna, A. *Chem. Rev.* **2009**, *109*, 3817. (b) Kotha, S.; Misra, S.; Sreevani, G.; Babu, B. V. *Curr. Org. Chem.* **2013**, *17*, 2776.
[72] Maas, G. *Chem. Soc. Rev.* **2004**, *33*, 183.

recently, the enantioselective intramolecular carbene insertion of α-diazoacetamides using a Ru(II)-Pheox catalyst has been also described.[42]

Considering the precedents outlined above and taking as a reference the previous work of the group, we were interested in establishing the feasibility of using different commercially available ruthenium complexes as catalysts to promote the C($sp^3$)–H insertion from γ-amino-tethered α-diazoesters leading to pyrrolidines. More concretely, we decided to study some Grubbs catalysts, as well as some chiral Ru(II)-complexes previously used in asymmetric hydrogenation reactions.

## 4.1. Grubbs Catalysts in Intramolecular Carbene C($sp^3$)–H Insertion Reactions From α-Diazoesters

As part of our ongoing research on the synthesis of nitrogen heterocycles, we have explored both ring-closing metathesis strategies[73] and intramolecular transition metal-catalyzed carbene C–H insertion reactions as annulation methodologies.[57-60] Ruthenium alkylidene complexes, which are the key intermediates in olefin metathesis, clearly resemble the ruthenium carbene species generated from diazo compounds. We therefore wondered if typical olefin metathesis catalysts could also be used to promote carbene C($sp^3$)–H insertion reactions from diazo derivatives and whether competition would arise between metathesis, cyclopropanation and C-H insertion in substrates bearing alkene and alkyne moieties.

To answer these questions, we selected the commercially available **Ru-1**, **Ru-2**, and **Ru-3** complexes (Figure 4.1) to be tested as potential catalysts to promote C–H insertion from γ-amino-tethered α-diazoesters leading to pyrrolidines.

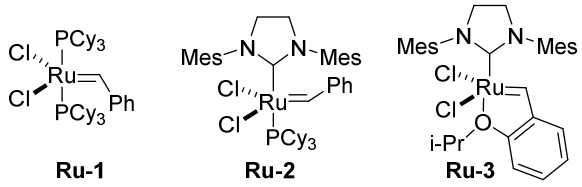


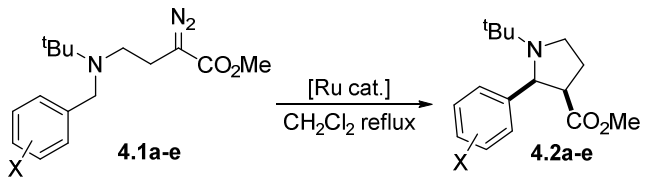

**Figure 4.1.**

We began our investigation by focusing on the reaction of *N*-benzyl-*N*-$^t$butyl-α-diazoesters **4.1a-e** (Table 4.1), comparing the efficiency of **Ru-1**, **Ru-2**, and **Ru-3** with that of [Ru(*p*-cymene)$Cl_2$]$_2$, which has been successfully used to promote similar insertion processes (Chapter 3). To our delight, treatment of **4.1a** with first generation Grubbs catalyst **Ru-1** in refluxing $CH_2Cl_2$ resulted in the stereoselective formation of the *cis*-pyrrolidine **4.2a** in excellent yield (entry 1, Table 4.1). Similar reactions were

[73] (a) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Tetrahedron* **2007**, *63*, 861. (b) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Chem. Commun.* **2009**, 3372. (c) Bennasar, M.-L.; Solé, D.; Zulaica, E.; Alonso, S. *Org. Lett.* **2011**, *13*, 2042. (d) Bennasar, M.-L.; Solé, D.; Roca, T.; Valldosera, M. *Tetrahedron* **2015**, *71*, 2246. (e) Solé, D.; Bennasar, M.-L.; Roca, T.; Valldosera, M. *Eur. J. Org. Chem.* **2016**, 1355.

observed with second generation Grubbs catalyst **Ru-2** (entry 2, Table 4.1) and Hoveyda-Grubbs catalyst **Ru-3** (entry 3, Table 4.1). Strikingly, all three catalysts were considerably more efficient than [Ru(*p*-cymene)$Cl_2$]$_2$ in promoting this C($sp^3$)–H insertion reaction (entry 4, Table 4.1). The same behavior was observed when starting from α-diazoesters **4.1b** and **4.1c** (entries 5-12, Table 4.1).

**Table 4.1.** C–H insertion reactions of α-diazoesters **4.1a-e.**[a]



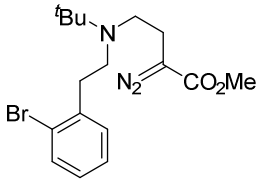
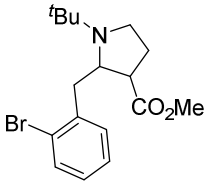
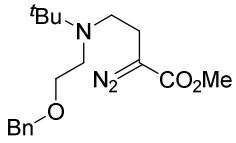
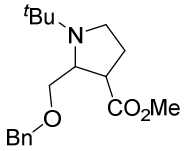
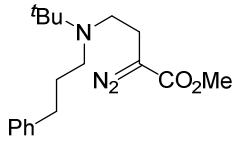
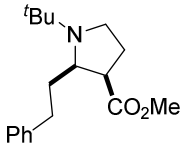
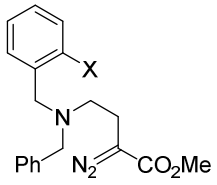
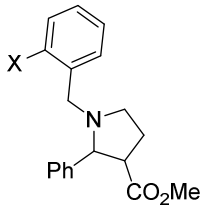

| Entry | 4.1 (X) | [Ru cat.] | dr | Products (%)[b] |
|---|---|---|---|---|
| 1 | **4.1a** (H) | **Ru-1** | >98:2 | **4.2a** (90) |
| 2 | **4.1a** (H) | **Ru-2** | >98:2 | **4.2a** (92) |
| 3 | **4.1a** (H) | **Ru-3** | >98:2 | **4.2a** (82) |
| 4 | **4.1a** (H) | [Ru(*p*-cymene)$Cl_2$]$_2$[c] | >98:2 | **4.2a** (69) |
| 5 | **4.1b** (4-Cl) | **Ru-1** | >98:2 | **4.2b** (89) |
| 6 | **4.1b** (4-Cl) | **Ru-2** | >98:2 | **4.2b** (80) |
| 7 | **4.1b** (4-Cl) | **Ru-3** | >98:2 | **4.2b** (74) |
| 8 | **4.1b** (4-Cl) | [Ru(*p*-cymene)$Cl_2$]$_2$[d] | >98:2 | **4.2b** (57) |
| 9 | **4.1c** (2-F) | **Ru-1** | >98:2 | **4.2c** (98) |
| 10 | **4.1c** (2-F) | **Ru-2** | >98:2 | **4.2c** (80) |
| 11 | **4.1c** (2-F) | **Ru-3** | >98:2 | **4.2c** (85) |
| 12 | **4.1c** (2-F) | [Ru(*p*-cymene)$Cl_2$]$_2$[d] | >98:2 | **4.2c** (70) |
| 13 | **4.1d** (2-Br) | **Ru-1** | >98:2 | **4.2d** (80) |
| 14 | **4.1d** (2-Br) | **Ru-2** | >98:2 | **4.2d** (62) |
| 15 | **4.1d** (2-Br) | **Ru-3** | >98:2 | **4.2d** (73) |
| 16 | **4.1d** (2-Br) | [Ru(*p*-cymene)$Cl_2$]$_2$[d] | | ---[e] |
| 17 | **4.1e** (2-MeO) | **Ru-1** | >98:2 | **4.2e** (60) |
| 18 | **4.1e** (2-MeO) | **Ru-2** | >98:2 | **4.2e** (81) |
| 19 | **4.1e** (2-MeO) | **Ru-3** | | ---[f] |
| 20 | **4.1e** (2-MeO) | [Ru(*p*-cymene)$Cl_2$]$_2$[d] | | ---[g] |

[a] Reaction conditions: Catalyst (3 mol%) in $CH_2Cl_2$ at reflux for 24 h. [b] Yields refer to products isolated by chromatography. [c] 31 h. [d] 48 h. [e] A 1:1 mixture of **4.1d** and **4.2d** was obtained. [f] A 1:1.4 mixture of **4.1e** and **4.2e** was obtained. [g] A 6:1 mixture of **4.1e** and **4.2e** was obtained.

In contrast, each ruthenium catalyst was differently affected by the presence of rather bulky *ortho*-substituents. Thus, **Ru-1** gave the highest yield when the substrate had an *ortho*-bromo group (entries 13-16, Table 4.1), but was less efficient in promoting the insertion from α-diazoester **4.1e**, which bears an *ortho*-methoxy substituent (entries 17-20, Table 4.1). On the other hand, when using **Ru-3** the reaction of **4.1e** (entry 19, Table 4.1) progressed more slowly than that of **4.1d** (entry 15, Table 4.1). Once again, [Ru(*p*-cymene)$Cl_2$]$_2$ afforded poor results (entries 16 and 20, Table 4.1).

To ascertain whether the efficiency of the C–H insertion depends on the activation inherent to the benzylic position, the reaction of α-diazoesters **4.3**, **4.5**, and **4.7** was explored (Table 4.2).

**Table 4.2.** C–H insertion reactions of α-diazoesters **4.3**, **4.5**, **4.7** and **4.9a-b**.[a]

| Entry | α-Diazoester | [Ru cat.] | Product yield (%)[b] |
|---|---|---|---|
| |  | |  |
| 1 | **4.3** | **Ru-1** | **4.4** (98, *cis*/*trans* 1.5:1) |
| 2 | **4.3** | **Ru-2** | **4.4** (92, *cis*/*trans* 1:1) |
| 3 | **4.3** | **Ru-3** | **4.4** (87, *cis*/*trans* 1:1) |
| |  | |  |
| 4 | **4.5** | **Ru-1** | **4.6** (91, *cis*/*trans* 1:1.4) |
| 5 | **4.5** | **Ru-2** | **4.6** (80, *cis*/*trans* 1:1.7) |
| 6 | **4.5** | **Ru-3** | **4.6** (82, *cis*/*trans* 1:1.3) |
| |  | |  |
| 7 | **4.7** | **Ru-1** | **4.8** (70) |
| 8 | **4.7** | **Ru-3** | ---[c] |
| |  | |  |
| 9 | **4.9a**, X = I | **Ru-1** | **4.10a** (87, *cis*/*trans* 6:1) |
| 10 | **4.9a**, X = I | **Ru-2** | **4.10a** (79, *cis*/*trans* 12:1) |
| 11 | **4.9a**, X = I | **Ru-3** | **4.10a** (95, *cis*/*trans* 3:1) |
| 12 | **4.9b**, X = F | **Ru-1** | **4.10b** (86, *cis*/*trans* 4.4:1)[d] |
| 13 | **4.9b**, X = F | **Ru-2** | **4.10b** (73, *cis*/*trans* 7:1)[e] |
| 14 | **4.9b**, X = F | **Ru-3** | **4.10b** (60, *cis*/*trans* 2.3:1)[f] |

[a] Reaction conditions: Catalyst (3 mol%) in $CH_2Cl_2$ at reflux for 24 h. [b] Yields refer to products isolated by chromatography. [c] A 5:1 mixture of **4.7** and **4.8** was obtained. [d] A 8:1 mixture of **4.10b** and the regioisomeric pyrrolidine **4.10b'** was obtained (See the Experimental Part). [e] A 2.8:1 mixture of **4.10b** and **4.10b'** was obtained. [f] A 2.5:1 mixture of **4.10b** and **4.10b'** was obtained.

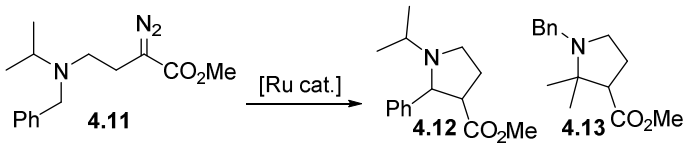
The three Grubbs catalysts regioselectively promoted the insertion reaction of **4.3** (entries 1-3, Table 4.2) to give pyrrolidine **4.4** (*cis*/*trans* mixtures). Similar results

were observed when these catalysts were used with *N*-(benzyloxyethyl) α-diazoester **4.5** (entries 4-6, Table 4.2). In contrast, treatment of **4.7** with **Ru-1** resulted in both regio- and stereoselective insertion to give *cis*-pyrrolidine **4.8** in 70% yield (entry 7, Table 4.2), while in the presence of **Ru-3** a slow reaction was observed (entry 8, Table 4.2). These results therefore indicate that the Grubbs catalysts can promote carbene C–H insertion into less activated C($sp^3$)–H bonds, and that remote electronic effects may accelerate the reaction.

Interestingly, the Grubbs catalysts were able to discriminate between the two secondary benzylic C($sp^3$)–H bonds of α-diazoesters **4.9a** and **4.9b**, probably due to a combination of steric and electronic effects. Thus, the reactions of **4.9a** regioselectively afforded pyrrolidine **4.10a** (*cis*/*trans* mixtures) in good yields (entries 9-11, Table 4.2). In contrast, the reactions of **4.9b** provided **4.10b** as the major product along with minor amounts of the pyrrolidine arising from the insertion into a C–H bond at the 2-fluorobenzyl position (entries 12-14, Table 4.2).

Seeking more information about the Grubbs catalyst-mediated carbene C–H insertion, we then explored the reaction of α-diazoester **4.11**, which bears an isopropyl group instead of the *N*-$^t$butyl substituent (Table 4.3). This study would afford some additional data about the substitution effects on the selectivity of the insertion.

**Table 4.3.** C–H insertion reactions of α-diazoester **4.11**.[a]




| Entry | [Ru cat.] | Products yield (%)[b] |
|---|---|---|
| 1 | **Ru-1** | **4.12** (61, *cis*/*trans* 5.8:1), **4.13** (32) |
| 2 | **Ru-2** | **4.12** (56, *cis*/*trans* 7.8:1), **4.13** (41) |
| 3 | **Ru-3** | **4.12** (36, *cis*/*trans* 3.6:1), **4.13** (58) |

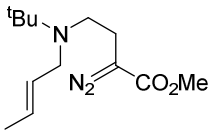
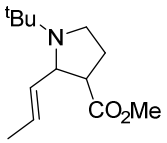
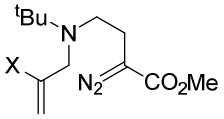
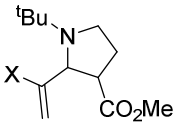
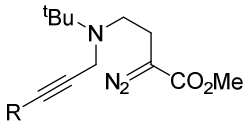
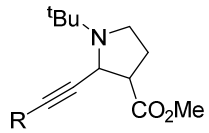
[a] Reaction conditions: Catalyst (3 mol%) in $CH_2Cl_2$ at reflux for 24 h. [b] Yields refer to products isolated by chromatography.

The use of the three Grubbs catalysts to promote the decomposition of **4.11** led to mixtures of pyrrolidines **4.12**, arising from the insertion into the benzylic C–H bond,

and **4.13**, which results from the insertion into the tertiary C($sp^3$)–H bond (entries 1-3, Table 4.3). While **Ru-1** and **Ru-2** gave **4.12** as the major product, **Ru-3** led predominantly to **4.13**.

The C-H insertion catalyzed by Grubbs complexes was also suitable for allylic and propargylic C($sp^3$)–H bonds (Table 4.4).

**Table 4.4.** C–H insertion reactions of α-diazoesters **4.14**, **4.16a-c** and **4.18a-c**.[a]

| Entry | α-Diazoester | [Ru cat.] | Products yield (%)[b] |
|---|---|---|---|
| |  | |  |
| 1 | **4.14** | **Ru-1** | **4.15** (70, *cis*/*trans* 6:1) |
| 2 | **4.14** | **Ru-3** | **4.15** (52, *cis*/*trans* 5:1) |
| |  | |  |
| 3 | **4.16a**, X = Me | **Ru-1** | **4.17a** (93, *cis*/*trans* 4:1) |
| 4 | **4.16a**, X = Me | **Ru-2** | **4.17a** (98, *cis*/*trans* 2:1) |
| 5 | **4.16a**, X = Me | **Ru-3** | **4.17a** (89, *cis*/*trans* 5.6:1) |
| 6 | **4.16b**, X = Br | **Ru-1** | **4.17b** (98, *cis*/*trans* 10:1) |
| 7 | **4.16b**, X = Br | **Ru-2** | **4.17b** (40, *cis*/*trans* 11:1)[c] |
| 8 | **4.16b**, X = Br | **Ru-3** | **4.17b** (70, *cis*/*trans* 10:1)[d] |
| 9 | **4.16c**, X = I | **Ru-1** | **4.17c** (52, *cis*/*trans* 7:1) |
| 10 | **4.16c**, X = I | **Ru-2** | ---[e] |
| 11 | **4.16c**, X = I | **Ru-3** | ---[e] |
| |  | |  |
| 12 | **4.18a**, R = H | **Ru-1** | **4.19a** (70, *cis*/*trans* 6:1) |
| 13 | **4.18a**, R = H | **Ru-2** | **4.18a** |
| 14 | **4.18a**, R = H | **Ru-3** | **4.19a** (88, *cis*/*trans* 7:1) |
| 15 | **4.18b**, R = Me | **Ru-1** | **4.19b** (89, *cis*/*trans* 3:1) |
| 16 | **4.18b**, R = Me | **Ru-2** | ---[f] |
| 17 | **4.18b**, R = Me | **Ru-3** | **4.19b** (75, *cis*/*trans* 4:1) |
| 18 | **4.18c**, R = TMS | **Ru-1** | **4.19c** (87, *cis*/*trans* 4:1) |
| 19 | **4.18c**, R = TMS | **Ru-2** | **4.19c** (62, *cis*/*trans* 4.5:1) |
| 20 | **4.18c**, R = TMS | **Ru-3** | **4.19c** (80, *cis*/*trans* 7:1) |

[a] Reaction conditions: Catalyst (3 mol%) in $CH_2Cl_2$ at reflux for 24 h. [b] Yields refer to products isolated by chromatography. [c] The cyclopropanation product (50%) was also obtained (See the Experimental Part). [d] The cyclopropanation product (20%) was also obtained. [e] Complex mixture. [f] A 1.3:1 mixture of **4.18b** and **4.19b** was obtained.

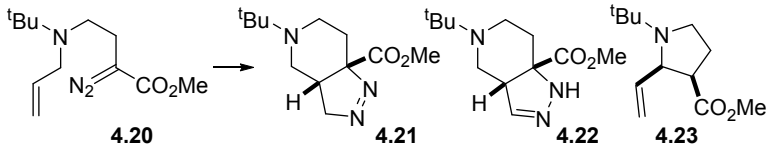
Thus, α-diazoester **4.14** chemoselectively afforded pyrrolidine **4.15** (*cis*/*trans* mixture) in yields of 70% with **Ru-1** (entry 1, Table 4.4) and 52% with **Ru-3**

(entry 2, Table 4.4). Notably, no product resulting from the possible ring-closing metathesis[74] and cyclopropanation was observed in either reaction.

Gem-disubstituted alkenes **4.16a**-**c** also underwent C–H insertion to give pyrrolidines under the action of Grubbs catalysts. Starting from α-diazoester **4.16a**, the three catalysts chemoselectively promoted C–H insertion to give **4.17a** in good yields (entries 3-5, Table 4.4). In contrast, while the insertion reaction from bromo alkene **4.16b** was selectively promoted by **Ru-1** (entry 6, Table 4.4), the use of either **Ru-2** or **Ru-3** led to the formation of significant amounts of the corresponding cyclopropanation product (entries 7-8, Table 4.4).[75] On the other hand, for iodo alkene **4.16c**, only **Ru-1** was able to promote the C–H insertion (entry 9, Table 4.4).

The Grubbs catalysts were also used to promote insertion into propargylic C($sp^3$)–H bonds of α-diazoesters bearing either terminal or internal alkynes (entries 12-20, Table 4.4), **Ru-1** and **Ru-3** being far more active than **Ru-2**.

Finally, *N*-allyl-α-diazoester **4.20** was prepared (Figure 4.2). This diazo derivative proved to be thermally unstable and in $CH_2Cl_2$ solution at room temperature evolved to pyrazolo[4,3-*c*]pyridine **4.21** through an intramolecular dipolar cycloaddition reaction.[76]




**4.20** **4.21** **4.22** **4.23**

**Figure 4.2.**

However, treatment of **4.20** with **Ru-1** in $CH_2Cl_2$ at reflux afforded a 1:2:1 mixture of **4.21**, **4.22** (arising from a 1,3-hydrogen shift from **4.21**),[76] and the C–H insertion product **4.23**. The use of **Ru-2** and **Ru-3** led to only trace amounts of **4.23** along with

[74] For RCM involving electron-deficient alkylidene species, see: Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210.
[75] Pan, X.-H.; Jiang, P.; Jia, Z.-H.; Xu, K.; Cao, J.; Chen, C.; Shen, M.-H.; Xu, H.-D. *Tetrahedron* **2015**, *71*, 5124.
[76] Brown, D. S.; Elliot, M. C.; Moody, C. J.; Mowlem, T. J.; Marino Jr., J. P.; Padwa, A. P. *J. Org. Chem.* **1994**, *59*, 2447.

**4.21** and **4.22**. Once again, no product from the ring-closing metathesis was detected in any of the reaction mixtures.

To shed light on the reaction mechanism and selectivity of the C–H insertion catalyzed by Grubbs complexes, Density Functional Theory (DFT) calculations were carried out. To this end, the process involving **4.1a** and the **Ru-1** catalyst was explored (Figure 4.3). The process begins with the formation of the corresponding ruthenacarbene intermediate **INT0** with the concomitant release of $N_2$. Our calculations indicate that the formation of **INT0**, where the new carbene ligand replaces a phosphine in **Ru-1**, is strongly favored ($\Delta\Delta G$ = 29.2 kcal/mol) over the formation of **INT0'**, where the carbene ligands are interchanged. From **INT0**, the zwitterionic intermediate **INT1-cis** is produced in a highly exergonic process ($\Delta G_R$ = –8.3 kcal/mol) via the transition state **TS1-cis** ($\Delta G^{\neq}$ = 11.1 kcal/mol). This step can be viewed as a 1,5-hydrogen migration that is not directly assisted by the metal, therefore resembling the mechanism involved in the $[RuCl_2(p\text{-cymene})]_2$–catalyzed process previously described (see Figure 3.7) as well as a Pd(II)-C–H activation process previously reported by our group.[59] Interestingly, the analogous transformation leading to the isomer **INT1-trans** is both kinetically ($\Delta\Delta G^{\neq}$ = 7.4 kcal/mol) and thermodynamically ($\Delta\Delta G_R$ = 4.4 kcal/mol) disfavored over the process involving **INT1-cis**, which is fully consistent with the complete stereoselectivity observed experimentally. Finally, the transformation ends up with the highly exergonic ($\Delta G_R$ = –26.2 kcal/mol) formation of the observed pyrrolidine **4.2a**. This final step proceeds via **TS2-cis**, a saddle point associated with the formation of the new C–C bond and the concomitant regeneration of the active Ru(II)-catalyst, with a rather low activation barrier of 10.5 kcal/mol.

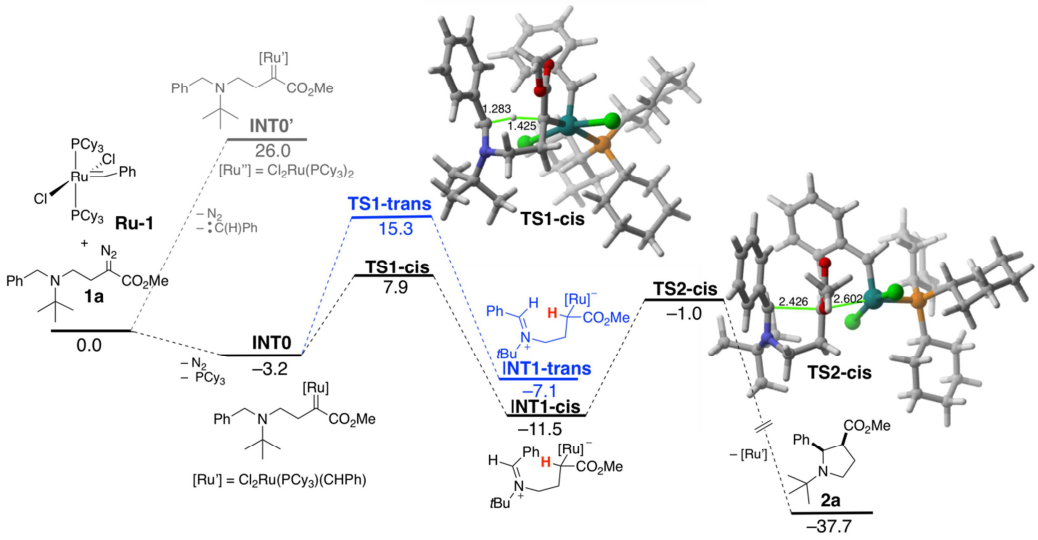



**Figure 4.3.** Computed reaction profile for the formation of **4.2a** from **4.1a**. Relative free energies (ΔG, at 298 K) and bond lengths are given in kcal/mol and angstroms, respectively. All data have been computed at the PCM($CH_2Cl_2$)-B3LYP-D3/def2-TZVPP//PCM($CH_2Cl_2$)-B3LYP-D3/def2-SVP level. Atom colors: N = blue, O = red, C = gray, P = orange, Ru = turquoise.

In addition, we wished to understand why the alternative metathesis reaction is not competitive in substrates that also have a reactive unsaturated C–C bond. Our calculations suggest that the formation of the key metallacyclobutane intermediate from the substrate bearing an allyl substituent is strongly disfavored (ΔΔG = 32.4 kcal/mol) over the formation of the zwitterionic intermediate involved in the C–H insertion reaction (Figure 4.4).

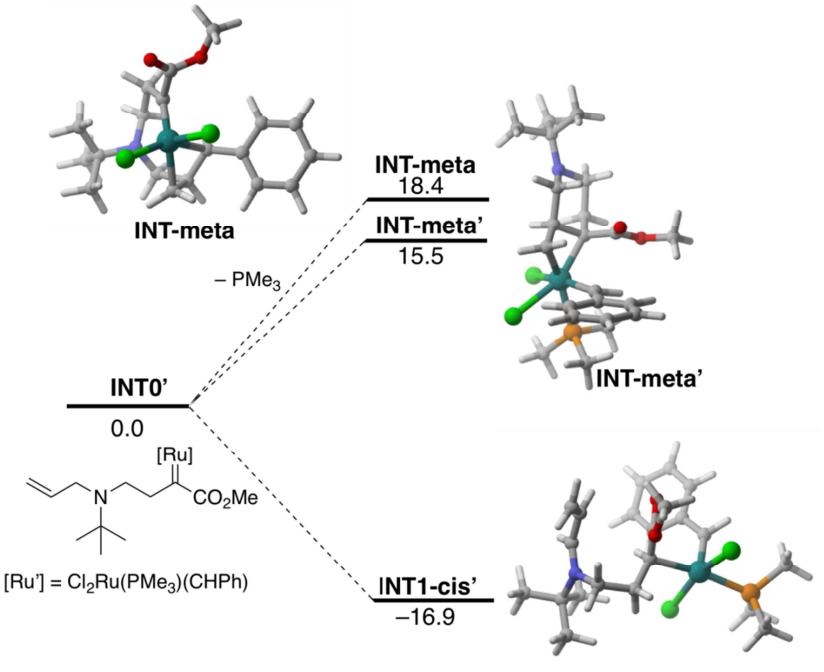



**Figure 4.4.** Comparative computed reaction profile for the metathesis versus C–H activation reaction from the ruthenacarbene formed upon reaction of **4.20** (see main text) and **Ru-1'**. Relative free energies (ΔG, at 298 K) and bond lengths are given in kcal/mol and angstroms, respectively. All data have been computed at the PCM($CH_2Cl_2$)-B3LYP-D3/def2-TZVPP//PCM($CH_2Cl_2$)-B3LYP-D3/def2-SVP level. Atom colors: N = blue, O = red, C = gray, P = orange, Ru = turquoise.

Finally, it is interesting to note that although a wide range of functional groups are well tolerated under metathesis conditions, the use of substrates with a strong Lewis base such as an amine usually deactivates the catalyst.[77] In contrast, not only does the amine moiety not hinder the carbene C–H insertion catalyzed by Grubbs complexes, but it seems crucial for the success of the reaction, which nicely agrees with the computed reaction profile depicted in Figure 4.3. In this context, it should be noted that the reaction of the *p*-toluene sulfonamide analogue of **4.20** with **Ru-1** resulted in the exclusive formation of the corresponding pyrazolo[4,3-*c*]pyridine, arising from the intramolecular cycloaddition reaction between the diazo moiety and the alkene double bond.

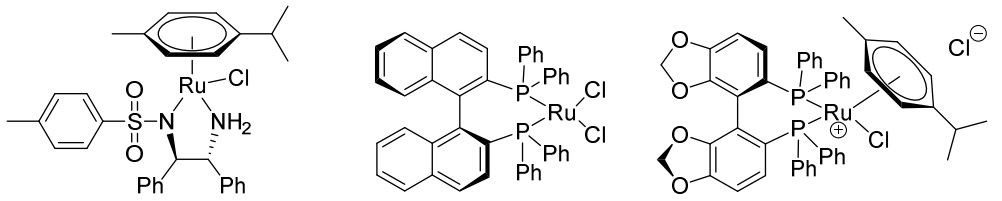
[77] See, for example: (a) P'Pool, S. J.; Schanz, H.-J. *J. Am. Chem. Soc.* **2007**, *129*, 14200. (b) Lafaye, K.; Nicolas, L.; Guérinot, A.; Reymond, S.; Cossy, J. *Org. Lett.* **2014**, *16*, 4972.

In summary, in this work we have described the first examples of Grubbs complexes used to catalyze carbene C–H insertion from diazo derivatives. On the whole, the first generation Grubbs catalyst **Ru-1** was the most versatile, although it did not always give the highest yield. Our studies clearly demonstrate not only that Grubbs complexes constitute a useful alternative to promote intramolecular carbene C–H insertion, but also that no competition from the possible metathesis reactions arises when starting from substrates with alkene or alkyne moieties.

## 4.2. Exploratory Studies on the Use of Chiral Ruthenium Catalysts for the Asymmetric Synthesis of Pyrrolidines

As mentioned in the General Introduction, and demonstrated in the previous section, the ruthenium catalysts used so far to promote carbene C–H insertion from diazo derivatives show considerable structural diversity. This variability contrasts with the homogeneity of dirhodium(II)-catalysts, which are mainly based on either carboxylate or carboxamide ligands.

To obtain further insight into the Ru(II)-catalyzed carbene C($sp^3$)–H insertion, we decided to evaluate the effectiveness of some structurally diverse and commercially available Ru(II)-complexes to promote the C–H insertion leading to pyrrolidines. This evaluation would consider several chiral Ru(II)-complexes (RuCl(*p*-cymene)[(*R*,*R*)-Ts-DPEN], (*S*)-BINAP-$RuCl_2$ and [RuCl(*p*-cymene)((*R*)-segphos)]Cl, see Figure 4.5) commonly used to perform asymmetric hydrogenation reactions.[78] These sorts of catalysts are interesting because they could be useful in developing an enantioselective pyrrolidine synthesis. Moreover, this study would provide structural information on what allows a Ru(II)-complex to be active in the carbene C($sp^3$)–H insertion.




**RuCl(*p*-cymene)[(*R*,*R*)-Ts-DPEN]**
**Ru-4**

**(*S*)-BINAP-$RuCl_2$**
**Ru-5**

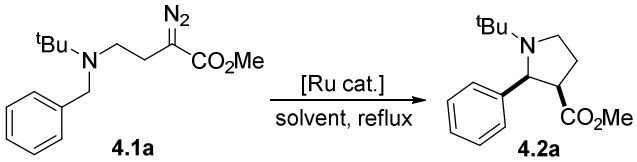
**[RuCl(*p*-cymene)((*R*)-segphos)]Cl**
**Ru-6**

**Figure 4.5.**

We began our investigation by applying **Ru-4**, **Ru-5** and **Ru-6** as catalysts to promote the decomposition of *N*-benzyl-*N*-$^t$butyl-α-diazoesters **4.1a** (Table 4.5).

[78] See, for example: (a) Ager, D. J.; Laneman, S. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3327. (b) Balázsik, K.; Szöllösi, G.; Berkesi, O.; Szalontai, G.; Fülöp, F.; Bartók, M. *Top Catal* **2012**, *55*, 880.

**Table 4.5.** Ru(II)-catalyzed reactions of α-diazoester **4.1a**.[a]




**4.1a** **4.2a**

| Entry | [TM cat.] (mol%) ligand (mol%) | Solvent | Product Yield[b] | ee |
|---|---|---|---|---|
| 1 | **Ru-4** (3) | $CH_2Cl_2$ | **4.1a**/**4.2a** (10:1)[c] | --- |
| 2 | **Ru-4** (3) | $CHCl_3$ | **4.2a** (50%) | ND[d] |
| 3 | **Ru-4** (3) | THF | **4.2a** (83%)[e] | 0 |
| 4 | **Ru-5** (3) | $CH_2Cl_2$[f] | **4.1a**/**4.2a** (3.4:1)[c] | --- |
| 5 | **Ru-5** (3) | THF | **4.2a** (80%) | 0 |
| 6 | **Ru-6** (3) | $CHCl_3$ | **4.1a**/**4.2a** (1.8:1)[c] | --- |
| 7 | **Ru-6** (3) | THF | **4.2a** (45%)[e] | 33% |
| 8 | [Ru(*p*-cymene)$Cl_2$]$_2$ (3) (*R*)-BINAP (6) | THF | **4.2a** (45%) | 0 |
| 9 | [Ru(*p*-cymene)$Cl_2$]$_2$ (3) (*R*,*R*)-Me-DUPHOS (6) | THF | **4.2a** (70%) | 25% |
| 10 | [Ru(*p*-cymene)$Cl_2$]$_2$ (3) (*S*,*S*)-CHIRAPHOS (6) | THF | **4.2a** (79%) | 39% |
| 11 | [Ru(*p*-cymene)$Cl_2$]$_2$ (3) (-)-DIPAMP (6) | THF | **4.2a** (84%) | ND |
| 12 | [Ru(*p*-cymene)$Cl_2$]$_2$ (3) (*R*)-MONOPHOS (6) | THF | **4.2a** (71%) | ND |

[a] Reaction conditions: Catalyst/ligand (see table) in the indicated solvent at reflux for 24 h. [b] Yields refer to products isolated by chromatography. [c] Ratio determined by $^1$H NMR. [d] Not determined. [e] $^1$H NMR analysis of the reaction mixture showed a ≈10:1 *cis*/*trans* ratio. [f] 12 h.

When **4.1a** was treated with **Ru-4** in dichloromethane at reflux for 24 h, mainly unchanged material was recovered, although a small amount of pyrrolidine **4.2a** was observed in the reaction mixture (entry 1, Table 4.5). The starting material was completely consumed when the reaction was run in $CHCl_3$ at reflux, which afforded **4.2a** in 50% yield (entry 2, Table 4.5). Changing the solvent to THF enhanced the formation of **4.2a**, which was isolated in 83% yield but without any enantioselectivity (entry 3, Table 4.5). Similar results were obtained when using **Ru-5** as the catalyst to promote the decomposition of **4.1a**. Thus, major amounts of the starting material were recovered when the reaction was run with **Ru-5** in dichloromethane (entry 4, Table 4.5), while changing the solvent to THF yielded **4.2a** in 80% yield, once again as a racemic mixture (entry 5, Table 4.5).

On the other hand, treatment of **4.1a** with **Ru-6** in $CHCl_3$ at reflux led to a 1.8:1 mixture of the starting material and **4.2a** (entry 6, Table 4.5). The complete consumption of the starting material was observed when the reaction was run with **Ru-6** in THF. Under these reaction conditions, **4.2a** was isolated in 45% yield and 33% enantiomeric excess (entry 7, Table 4.5).

These results confirm the structural tolerance of the Ru(II)-catalysts in the carbene C($sp^3$)–H insertion. Moreover, although enantioselection was only observed in one case, these results also show that the proper selection of catalysts and reaction conditions could allow the development of an enantioselective reaction. In this context, it should be noted that in 2019, when the studies described here had been finished, Chanthamath and Iwasa reported the first example of an enantioselective Ru(II)-catalyzed intramolecular C($sp^3$)–H insertion carbene insertion. In this work the authors used a Ru(II)-Pheox catalyst to promote carbene insertion of $\alpha$-diazoacetamides leading to $\gamma$-lactams (Figure 1.22).[42]

With these data in hand, in order to improve the enantioselectivity of the C–H insertion, we decided to study some additional chiral catalytic systems. Although the structure of the active catalytic species generated from **Ru-6** is not known, it probably incorporates both the *p*-cymene and phosphine ligands. We therefore proceeded to test the catalytic activity of different combinations of $[RuCl_2(p\text{-cymene})]_2$ and chiral ligands (Figure 4.6).

The use of (*R*)-BINAP as the ligand afforded **4.2a** in a yield similar to that of **Ru-6**, but without any enantioselection (entry 8, Table 4.5). Better results were obtained with the bidentate phosphines (*R*,*R*)-Me-DUPHOS (entry 9, Table 4.5) and (*S*,*S*)-CHIRAPHOS (entry 10, Table 4.5), the latter affording **4.2a** in 79% yield and 39% enantiomeric excess. Finally, the use of (-)-DIPAMP (entry 11, Table 4.5) and the phosphoramidite ligand (*R*)-MONOPHOS (entry 12, Table 4.5) afforded pyrrolidine **4.2a** in 84% and 71% yield, respectively.

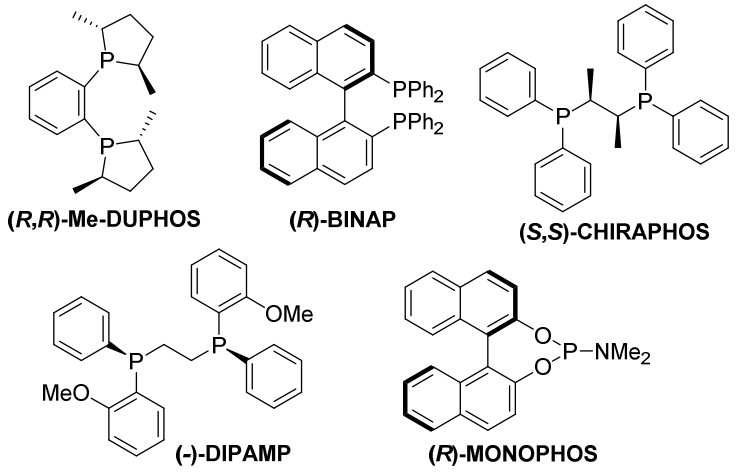



**Figure 4.6.**

In summary, in this preliminary study we have explored the use of different chiral Ru(II)-catalytic systems in order to develop an enantioselective version of the C($sp^3$)–H insertion leading to pyrrolidines. The results obtained demonstrate that it is possible to obtain enantioselection by using catalytic systems that combine the *p*-cymene and chiral bidentate phosphines. To gain more insight into the reaction mechanism and enantioselectivity of the insertion, further exploration of different chiral phosphine ligands and DFT computational studies will be carried out in the future.

## Chapter 5

# Transition Metal-Catalyzed Intramolecular Carbene $C_{Ar}$–H Functionalization of γ-Amino-α-diazoesters for the Synthesis of Tetrahydroquinolines

The transition metal-catalyzed intramolecular aromatic C–H functionalization of α-diazocarbonyl compounds[3d] constitutes a powerful method of annulation of the benzene nucleus, with considerable appeal in medicinal heterocyclic chemistry. A number of successful reactions involving the formation of [6,5]-bicycles have been reported, allowing the elaboration of both carbocyclic and heterocyclic backbones, including the oxindole,[7,31,32a,32c,38-40,79] indanone[80] and benzo-γ-sultam systems.[81] Traditionally, these intramolecular aromatic substitution reactions from α-diazocarbonyl compounds have been carried out in the presence of rhodium(II) catalysts,[31,32a,32c,80,81] although in recent times other transition metals, especially ruthenium,[38-40] have proved useful.

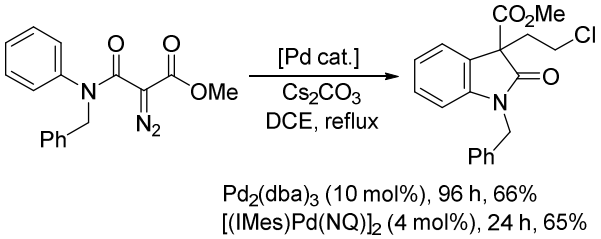
In contrast, the use of the intramolecular aromatic C–H functionalization of α-diazocarbonyl compounds for the construction of [6,6]-bicycles has been less successful, probably because of the competition from the so-called Buchner reaction.[82] Nevertheless, rhodium-based catalysts have been effectively applied to selectively promote intramolecular aromatic C–H functionalization of α-diazo-β-dicarbonyl compounds to construct isoquinolinones,[83] dihydroquinolinones[84] and chromanones.[85]

As commented in the General Introduction, all the above processes, often inaccurately referred to as aromatic C–H insertions,[28] differ mechanistically from the aliphatic version in that they generally involve the electrophilic addition of the corresponding metal carbene intermediate to the aromatic ring, followed by a 1,2-proton migration (see, for example, Figure 1.14).[30]

As part of a research program aimed at exploring the use of different transition-metal catalysts as alternatives to the widely used rhodium(II) carboxylates in carbene C–H insertion, our group has reported that palladium catalysts efficiently promote

[79] Son, S. I.; Lee, W. K.; Choi, J.; Ha, H.-J. *Green Chem.* **2015**, *17*, 3306.
[80] Watanabe, N.; Ohtake, Y.; Hashimoto, S.-I.; Shiro, M.; Ikegami, S. *Tetrahedron Lett*. **1995**, *36*, 1491.
[81] Yang, Z.; Xu, J. *Chem. Commun.* **2014**, *50*, 3616.
[82] See, for example: Chen, K.-H.; Chiang, Y.-J.; Zhu, J.-L. *Org. Biomol. Chem.* **2018**, *16*, 8353.
[83] Park, C. P.; Nagle, A.; Yoon, C. H.; Chen, C.; Jung, K. W. *J. Org. Chem.* **2009**, *74*, 6231.
[84] Ma, B.; Chen, F.-L.; Xu, X.-Y.; Zhang, Y.-N.; Hu, L.-H. *Adv. Synth. Catal.* **2014**, *356*, 416.
[85] Zhang, X.; Lei, M.; Zhang, Y.-N.; Hu, L.-H. *Tetrahedron* **2014**, *70*, 3400.

$C_{Ar}(sp^2)$–H functionalization of α-diazo- α-(methoxycarbonyl)acetanilides to form oxindoles. Thus, by using $Pd_2(dba)_3$ as the catalyst, our group developed a one-pot methodology to prepare 3-(chloroethyl)oxindoles by means of a sequential C–H insertion/alkylation process (Figure 5.1).[58]




$Pd_2(dba)_3$ (10 mol%), 96 h, 66%
$[(IMes)Pd(NQ)]_2$ (4 mol%), 24 h, 65%

**Figure 5.1.**

In order to improve the efficiency of the carbene insertion of α-diazoacetanilides, some other palladium catalysts bearing non-phosphine ligands were also tested for the tandem insertion/alkylation reaction. In this study, it was found that the use of $[(IMes)Pd(NQ)]_2$ required a notably shorter reaction time and lower catalyst loading than $Pd_2(dba)_3$ (Figure 5.1).[60]

Previous DFT calculations reported by our group suggested that the Pd(0)-catalyzed $C_{Ar}(sp^2)$–H insertion of α-diazo- α-(methoxycarbonyl)acetanilides to give oxindoles proceeds via a genuine stepwise mechanism involving a palladium-mediated 1,5-hydrogen migration from the initially generated pallada(0)carbene complex, followed by a reductive elimination. It was also shown that the complete chemoselectivity of the process, which exclusively produces oxindoles over β-lactams, takes place mainly under kinetic control (Figure 5.2).[58,60]

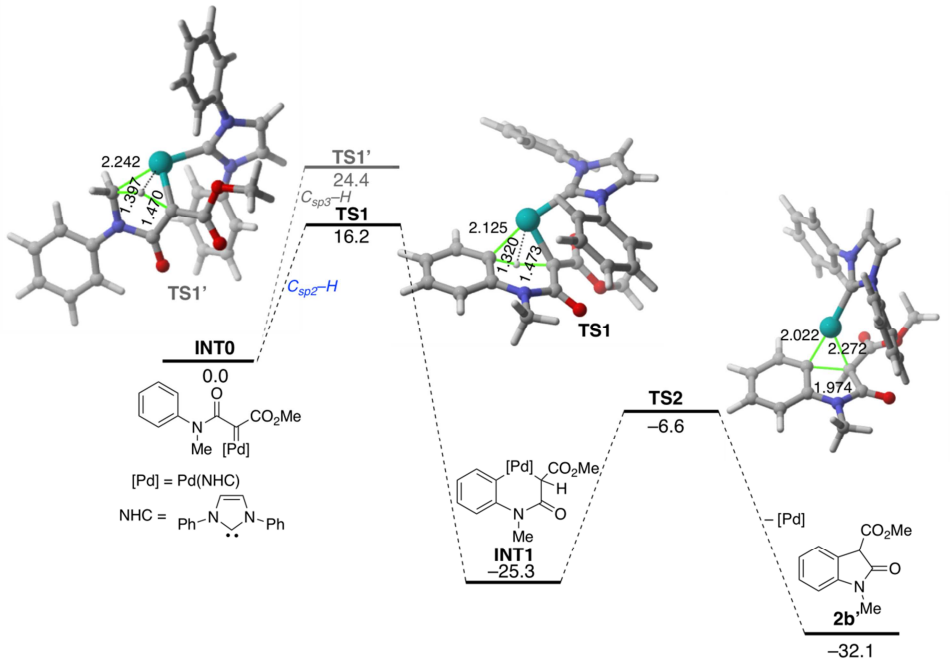
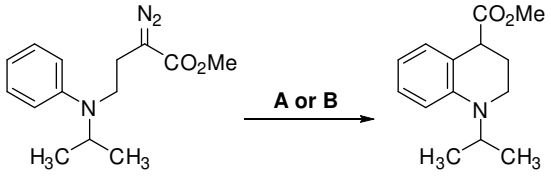



**Figure 5.2.** Computed reaction profile for the transformation of pallada(0)carbene **INT0** into oxindole **2b'**: Relative free energies and bond distances are given in kcal/mol and angstroms, respectively. All data have been computed at the PCM(dichloroethane)-B3LYP-D3/def2-TZVPP//PCM(dichloroethane)-B3LYP-D3/def2-SVP level. Atom colors: N = blue, O = red, C = gray, Pd = turquoise.

In our previous studies on the transition metal-catalyzed reactions of γ-amino-α-diazoesters reported in Chapter 3, we found that the use of either $Pd_2(dba)_3$ or $[(IMes)Pd(NQ)]_2$ to catalyze the decomposition of *N*-isopropyl α-diazoester **5.1a** resulted in the chemoselective functionalization at the arylic C($sp^2$)–H bond to give tetrahydroquinoline **5.2a** (Figure 5.3).




**5.1a** **5.2a**

**A:** $Pd_2(dba)_3$ (2.5 mol%), $CHCl_3$, reflux, 24 h, **5.2a** (80%)
**B:** $[(IMes)Pd(NQ)]_2$ (2.5 mol%), $CHCl_3$, reflux, 24 h, **5.2a** (75%)

**Figure 5.3.**

With these data in hand, we decided to further explore the construction of tetrahydroquinolines by transition metal-catalyzed decomposition of γ-anilino-α-diazoesters. The extensive bioactivity of tetrahydroquinolines, including antitumor, antiviral, antibacterial, antimalarial and antifungal activity, is well documented, and the development of efficient procedures for their preparation is therefore of considerable interest.[86,87,88]

The aim of the current work was to investigate the feasibility of using both palladium(0) and Grubbs catalysts to promote the intramolecular carbene $C_{Ar}(sp^2)$–H functionalization leading to tetrahydroquinolines and to identify differences in the reactivities and selectivities between the two transition metals.

Table 5.1 gathers the results of the transition metal-catalyzed $C_{Ar}(sp^2)$–H functionalization of diverse *N*-isopropylanilino α-diazoesters. We began by testing the use of Grubbs catalysts **Ru-1**, **Ru-2** and **Ru-3** (Figure 4.1) to promote the annulation reaction from **5.1a**. Gratifyingly, treatment of **5.1a** with first generation Grubbs catalyst **Ru-1** resulted in the chemoselective formation of **5.2a** in good yield (entry 3, Table 5.1). Similar chemoselectivity and a slightly lower yield were observed with second generation Grubbs catalyst **Ru-2** (entry 4, table 5.1), but when Hoveyda-Grubbs catalyst **Ru-3** was used, competition from the $C(sp^3)$–H insertion led to the formation of significant amounts of pyrrolidine **5.3a** (entry 5, Table 5.1).

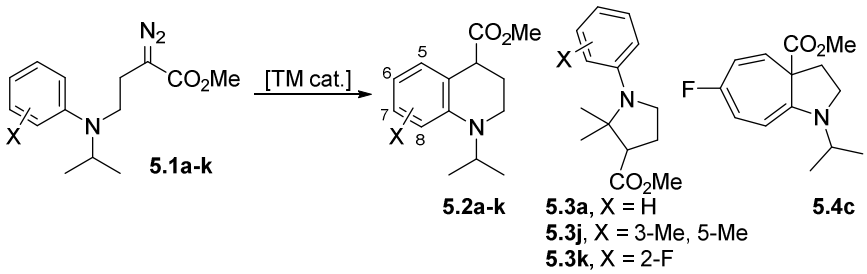
With this information in hand, in order to investigate the scope of the $C_{Ar}(sp^2)$–H functionalization reaction for the preparation of tetrahydroquinoline-4-carboxylic acid esters, $Pd_2(dba)_3$, $[(IMes)Pd(NQ)]_2$ and **Ru-1** were then tested as catalysts with a variety of γ-anilino- α-diazoesters bearing different substituents at the aromatic ring.

[86] (a) Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. *Chem. Rev.* **2011**, *111*, 7157. (b) Muthukrishnan, I.; Sridharan, V.; Menéndez, J. C. *Chem. Rev.* **2019**, *119*, 5057.

[87] Tetrahydroquinoline-4-carboxylic acid esters have shown activity as neurotropic agents: (a) Goli, N.; Mainkar, P. S.; Kotapalli, S. S.; Tejaswini, K.; Ummanni, R.; Chandrasekhar, S. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 1714.

[88] For potential therapeutic uses for some metabolic disorders, see: (a) Bissantz, C.; Dehmlow, H.; Martin, R. E.; Obst Sander, U.; Richter, H.; Ullmer, C. U.S. Pat. Appl. Publ. US 20100105906 A1 20100429. (b) Milanova, R. U.S. Pat. Appl. Publ.US 20060020135 A1 20060126.

**Table 5.1.** TM-catalyzed reactions of α-diazoesters **5.1a-k**.




| Entry | 5.1 (X) | [TM cat.] | Products (yield)[a] |
|---|---|---|---|
| 1 | **5.1a** (H) | $Pd_2(dba)_3$[b] | **5.2a**, X = H (80%) |
| 2 | **5.1a** (H) | $[(IMes)Pd(NQ)]_2$[c] | **5.2a**, X = H (75%) |
| 3 | **5.1a** (H) | **Ru-1**[d] | **5.2a**, X = H (82%) |
| 4 | **5.1a** (H) | **Ru-2**[d] | **5.2a**, X = H (68%) |
| 5 | **5.1a** (H) | **Ru-3**[d] | **5.2a**, X = H/**5.3a** (3:1, 53%) |
| 6 | **5.1b** (4-Me) | $Pd_2(dba)_3$[b] | **5.2b**, X = 6-Me (64%) |
| 7 | **5.1b** (4-Me) | $[(IMes)Pd(NQ)]_2$[c] | **5.2b**, X = 6-Me (70%) |
| 8 | **5.1b** (4-Me) | **Ru-1**[d] | **5.2b**, X = 6-Me (87%) |
| 9 | **5.1c** (4-F) | $Pd_2(dba)_3$[b] | **5.2c**, X = 6-F (38%)/**5.4c** (15%) |
| 10 | **5.1c** (4-F) | $[(IMes)Pd(NQ)]_2$[c] | **5.2c**, X = 6-F (68%) |
| 11 | **5.1c** (4-F) | **Ru-1**[d] | **5.2c**, X = 6-F (97%) |
| 12 | **5.1d** (4-OMe) | $Pd_2(dba)_3$[b] | **5.2d**, X = 6-OMe (55%) |
| 13 | **5.1d** (4-OMe) | $[(IMes)Pd(NQ)]_2$[c] | **5.2d**, X = 6-OMe (69%) |
| 14 | **5.1d** (4-OMe) | **Ru-1**[d] | **5.2d**, X = 6-OMe (88%) |
| 15 | **5.1e** (3-OMe) | $Pd_2(dba)_3$[b] | **5.2e**, X = 7-OMe/X = 5-OMe (40%, 3.7:1) |
| 16 | **5.1e** (3-OMe) | $[(IMes)Pd(NQ)]_2$[c] | **5.2e**, X = 7-OMe/X = 5-OMe (70%, 3.7:1) |
| 17 | **5.1e** (3-OMe) | **Ru-1**[d] | **5.2e**, X = 7-OMe/X = 5-OMe (86%, 3.7:1) |
| 18 | **5.1f** (3-Cl) | $[(IMes)Pd(NQ)]_2$[c] | **5.2f**, X = 7-Cl/X = 5-Cl (68%, 3:1) |
| 19 | **5.1f** (3-Cl) | **Ru-1**[d] | **5.2f**, X = 7-Cl/X = 5-Cl (82%, 3:1) |
| 20 | **5.1g** (3-I) | $[(IMes)Pd(NQ)]_2$[c] | **5.2g**, X = 7-I/X = 5-I (70%, 8.5:1) |
| 21 | **5.1g** (3-I) | **Ru-1**[d] | **5.2g**, X = 7-I/X = 5-I (81%, 3.5:1) |
| 22 | **5.1h** (3-$CO_2$Me) | $[(IMes)Pd(NQ)]_2$[c] | **5.2h**, X = 7-$CO_2$Me/X = 5-$CO_2$Me (75%, >19:1) |
| 23 | **5.1h** (3-$CO_2$Me) | **Ru-1**[d] | **5.2h**, X = 7-$CO_2$Me/X = 5-$CO_2$Me (90%, >19:1) |
| 24 | **5.1i** (3-$NO_2$) | $[(IMes)Pd(NQ)]_2$[c] | **5.2i**, X = 7-$NO_2$/X = 5-$NO_2$ (48%, >19:1) |
| 25 | **5.1i** (3-$NO_2$) | **Ru-1**[d] | **5.2i**, X = 7-$NO_2$/X = 5-$NO_2$ (94%, >19:1) |
| 26 | **5.1j** (3-Me, 5-Me) | $[(IMes)Pd(NQ)]_2$[c] | **5.2j**, X = 5-Me, 7-Me (82%) |
| 27 | **5.1j** (3-Me, 5-Me) | **Ru-1**[d] | **5.2j**, X = 5-Me, 7-Me/**5.3j** (3:1, 88%) |
| 28 | **5.1k** (2-F) | $[(IMes)Pd(NQ)]_2$[c] | **5.2k**, X = 8-F/**5.3k** (1:1, 64%) |
| 29 | **5.1k** (2-F) | **Ru-1**[d] | **5.2k**, X = 8-F/**5.3k** (1:3.5, 98%) |

[a] Yields refer to products isolated by chromatography, and for entries in which a product mixture was obtained, the yield refers to the combined yield. [b] Catalyst (5 mol%) in DCE at reflux for 24 h. [c] Catalyst (2.5 mol%) in $CHCl_3$ at reflux for 24 h. [d] Catalyst (3 mol%) in $CH_2Cl_2$ at reflux for 24 h.

The examples in Table 5.1 confirm the generality and functional group tolerance of these reactions. As can be seen, no competition from the C($sp^3$)–H insertion was observed when starting from *para*- and *meta*-substituted *N*-isopropylanilines (entries 6-25, Table 5.1). Thus, when using either $[(IMes)Pd(NQ)]_2$ or **Ru-1** as catalysts, the *para*-substituted anilines **5.1b-d** (entries 6-14, Table 5.1) chemoselectively underwent

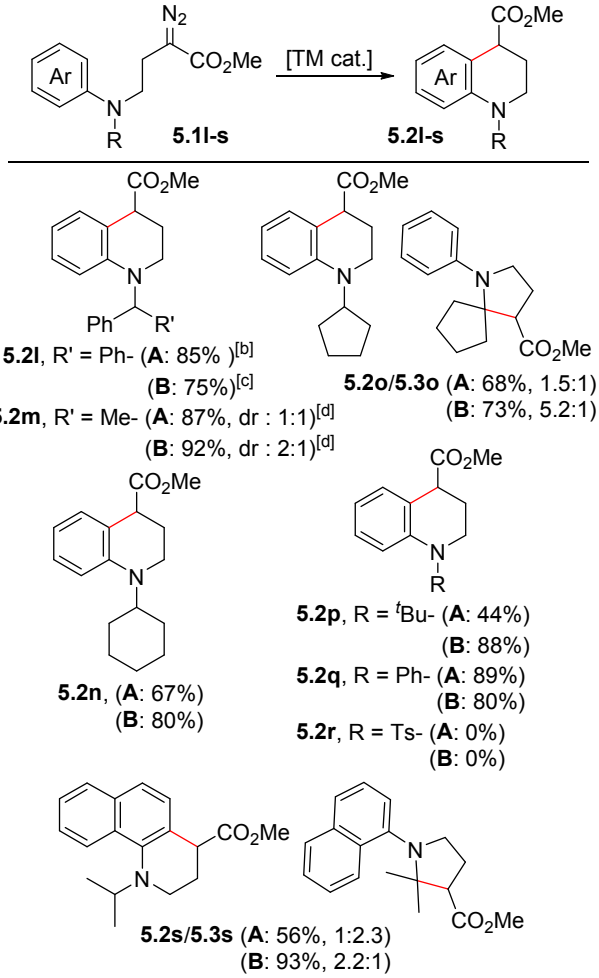
$C_{Ar}(sp^2)$–H functionalization to give the corresponding tetrahydroquinolines regardless of the nature of the substituent. In contrast, whereas the use of $Pd_2(dba)_3$ selectively led to tetrahydroquinolines **5.2b** and **5.2d** (entries 6 and 12, Table 5.1), when starting from the *para*-fluoro aniline **5.1c**, a mixture of tetrahydroquinoline **5.2c** and the Buchner product **5.4c** was observed (entry 9, Table 5.1). For *para*-substituted anilines, **Ru-1** invariably afforded the best results, whereas the least efficient catalyst was $Pd_2(dba)_3$.

*meta*-Substituted anilines **5.1e-i** also underwent chemoselective $C_{Ar}(sp^2)$–H functionalization to give the corresponding tetrahydroquinolines with either the Pd(0)- or **Ru-1** catalysts, the latter once again affording the highest reaction yields (entries 15-25, Table 5.1). With these substrates, the regioselectivity of the insertion (5-X/7-X ratio) seems to be controlled by a combination of steric and electronic effects. Thus, similar moderate regioselectivities were obtained in the reactions of anilines **5.1e** and **5.1f**, which bear a *meta*-methoxy and *meta*-chloro substituent, respectively, using either $[(IMes)Pd(NQ)]_2$ or **Ru-1** (entries 15-19, Table 5.1). However, with the *meta*-iodo substituted aniline **5.1g**, the Pd(0)-catalyst afforded better regioselectivity than **Ru-1** (entries 20-21, Table 5.1). On the other hand, in the reactions of anilines **5.1h** and **5.1i**, which bear the highly electron-withdrawing groups *meta*-$CO_2Me$ and *meta*-$NO_2$, respectively, almost complete regioselectivity was observed with both $[(IMes)Pd(NQ)]_2$ and **Ru-1** (entries 22-25, Table 5.1).

The $C_{Ar}(sp^2)$–H functionalization from dimethylaniline **5.1j** was also selectively promoted by $[(IMes)Pd(NQ)]_2$, while the use of **Ru-1** led to the formation of significant amounts of pyrrolidine **5.3j**, resulting from the $C(sp^3)$–H insertion (entries 26-27, Table 5.1). In contrast, competition between $C_{Ar}(sp^2)$–H and $C(sp^3)$–H insertion was observed in the reactions of *ortho*-fluoroaniline **5.1k** in the presence of $[(IMes)Pd(NQ)]_2$ or **Ru-1** (entries 28-29, Table 5.1). Interestingly, as in the reaction of **5.1j**, tetrahydroquinoline formation was enhanced by the use of the Pd(0)-catalyst, which afforded a 1:1 mixture of **5.2k** and **5.3k**. The high tendency of *ortho*-substituted aniline **5.1k** to undergo $C(sp^3)$–H functionalization, which is in line with our previously reported results (see chapter 3), can be mainly ascribed to steric factors.

The $C_{Ar}(sp^2)$–H functionalization was not limited to *N*-isopropylanilines but also proved suitable for anilines bearing other substituents at the nitrogen atom (Table 5.2). Thus, *N*-benzhydrylaniline **5.1l** chemoselectively afforded tetrahydroquinoline **5.2l** in 85% and 75% reaction yield in the presence of $[(IMes)Pd(NQ)]_2$ or **Ru-1**, respectively.

**Table 5.2.** TM-catalyzed $C_{Ar}(sp^2)$–H functionalization of α-diazoesters **5.1l-s**.[a]




[a] Yields refer to products isolated by chromatography, and for entries in which a product mixture was obtained, the yield refers to the combined yield. [b] **A**: $[(IMes)Pd(NQ)]_2$ (2.5 mol%) in $CHCl_3$ at reflux for 24 h. [c] **B**: **Ru-1** (3 mol%) in $CH_2Cl_2$ at reflux for 24 h. [d] dr = diastereomeric ratio.

Similarly, the reaction of *N*-(1-phenylethyl)aniline **5.1m** in the presence of either $[(IMes)Pd(NQ)]_2$ or **Ru-1** chemoselectively afforded tetrahydroquinoline **5.2m** (mixture of stereoisomers) in good yields.

Both catalysts selectively promoted $C_{Ar}(sp^2)$–H functionalization of *N*-cyclohexylaniline **5.1n** to give **5.2n**, and although their use with *N*-cyclopentylaniline **5.1o** led to mixtures of tetrahydroquinoline **5.2o** and spirocyclic pyrrolidine **5.3o**, the former was obtained in an acceptable yield of 61% when using **Ru-1**. In the presence of either $[(IMes)Pd(NQ)]_2$ or **Ru-1**, *N*-*tert*-butyl α-diazoester **5.1p** and *N*,*N*-diphenyl α-diazoester **5.1q** also underwent $C_{Ar}(sp^2)$–H functionalization to give tetrahydroquinolines **5.2p** and **5.2q**, respectively, in good yields. However, both catalysts failed to promote the C–H functionalization reaction of *p*-toluene sulfonamide **5.1r**. On the other hand, in the reaction of α-diazoester **5.1s**, the use of **Ru-1** afforded tetrahydrobenzo[*h*]quinolone **5.2s** in 64% yield, whereas $[(IMes)Pd(NQ)]_2$ reversed the regioselectivity, providing pyrrolidine **5.3s** as the main product together with minor amounts of **5.2s**.

To shed light on the reaction mechanism and selectivity of the Pd(0)- and Grubbs catalyst-promoted functionalizations described above, density functional theory (DFT) calculations were carried out. To this end, we first explored the process involving **5.1a** (Figure 5.4) which, in the presence of $[(IMes)Pd(NQ)]_2$, leads to the formation of tetrahydroquinoline **5.2a** (see entry 2, Table 5.1). Similar to the related Pd(0)-mediated C–H insertions of α-diazo-α-(methoxycarbonyl)acetanilides commented above, our calculations started from the corresponding pallada(0)-carbene intermediate **INT0**, formed by the reaction of the diazo compound **5.1a** and a model Pd(0)-catalyst, where the bulky mesyl groups in the NHC ligand were replaced by phenyl groups.

This species evolves into the seven-membered palladacycle **INT1** through the transition state **TS1** in a highly exergonic transformation ($\Delta G_R$ = –25.3 kcal/mol). As shown in Figure 5.4, this saddle point is associated with a palladium-mediated 1,6-H migration from the phenyl group to the carbene carbon atom, which results in the formal oxidation of the transition metal. Then, **INT1** is transformed into the observed tetrahydroquinoline **5.2a** through a reductive elimination reaction via **TS2**. This final exergonic step ($\Delta G_R$ = –10.4 kcal/mol) forms the new C–C bond and releases the active catalytic species Pd(NHC), which is then able to enter in a new catalytic cycle.

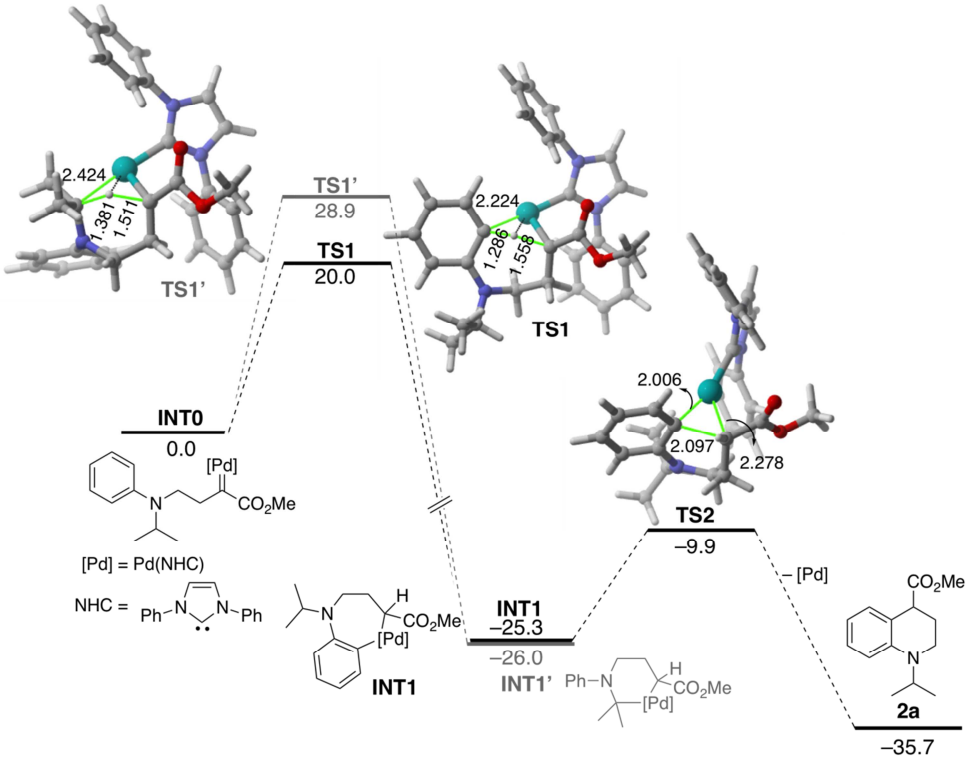



**Figure 5.4.** Computed reaction profile for the formation of tetrahydroquinoline **5.2a** mediated by the Pd(0)-catalyst. Relative free energies ($\Delta G_{298}$, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data were computed at the PCM($CHCl_3$)-B3LYP-D3/def2-TZVPP//PCM($CHCl_3$)-B3LYP-D3/def2-SVP level. Atom colors: N = blue, O = red, C = gray, Pd = turquoise.

We also explored the possible C($sp^3$)–H activation from the initial pallada(0)-carbene. A similar Pd-mediated 1,5-H migration was found, leading to the corresponding six-membered palladacycle **INT1'**. However, the associated activation barrier involving **TS1'** is clearly much higher than that computed for the $C_{Ar}$($sp^2$)–H activation involving **TS1** ($\Delta\Delta G^{\neq}$ = 8.9 kcal/mol), which is fully consistent with the complete selectivity observed experimentally (see Table 5.1).

The process affording the same tetrahydroquinoline (**5.2a**) from **5.1a** mediated by the first generation Grubbs catalyst (Table 5.1, entry 3) was studied next. Similar to the above palladium-mediated transformation and related C($sp^3$)–H activations promoted by this ruthenium catalyst (see Chapter 4), our calculations also start from the

analogous ruthenacarbene **INT0-Ru** (in which the bulky $PCy_3$ phosphine ligand was replaced by $PMe_3$, see Figure 5.5). We located a similar Ru-assisted 1,6-H migration reaction. However, the rather high barrier required to reach the corresponding transition state (**TS1''-Ru**, $\Delta G^{\neq}$ = 56.4 kcal/mol) makes this reaction unfeasible. Alternatively, we found that **INT0-Ru** can easily evolve (computed barrier of only 5.5 kcal/mol) into the bicyclic intermediate **INT1-Ru** via **TS1-Ru**. This saddle point is associated with the formation of the new C–C bond and this reaction step can therefore be viewed as an electrophilic addition of the metal carbene intermediate to the aromatic ring in a typical $S_EAr$ reaction. Intermediate **INT1-Ru** is then transformed into the observed reaction product **5.2a** through a direct 1,2-proton migration via **TS2-Ru**, which releases the active ruthenium catalyst in a highly exergonic transformation ($\Delta G_R$ = –41.0 kcal/mol). Another alternative is that this 1,2-proton migration can proceed stepwise with the assistance of a chloride ligand attached to the transition metal. Thus, the proton first migrates to the chloride ligand via **TS2'-Ru** forming **INT2-Ru**, and then moves to its final position, affording **5.2a** via **TS3-Ru**. Not surprisingly, our calculations indicate that the chloride-assisted proton transfer is slightly favored over the direct 1,2-migration.

Finally, we also considered the possible C($sp^3$)–H activation from the **INT0-Ru**, which proceeds via the expected ruthenium-assisted 1,5-H migration reaction. Once again, the barrier associated with reaching the corresponding saddle point **TS1'-Ru** ($\Delta G^{\neq}$ = 14.4 kcal/mol) is found to be much higher than that involving **TS1-Ru** ($\Delta\Delta G^{\neq}$ = 8.9 kcal/mol), which renders this alternative C($sp^3$)–H activation kinetically noncompetitive, as experimentally observed.

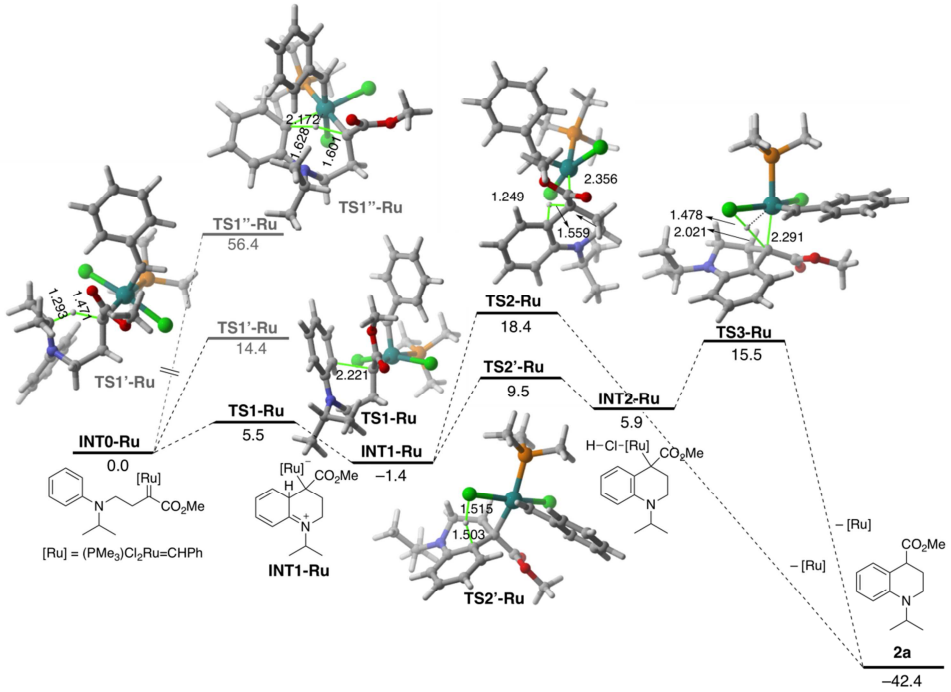



**Figure 5.5.** Computed reaction profile for the formation of tetrahydroquinoline **5.2a** mediated by the ruthenium catalyst. Relative free energies ($\Delta G_{298}$, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data were computed at the PCM($CH_2Cl_2$)-B3LYP-D3/def2-TZVPP//PCM($CH_2Cl_2$)-B3LYP-D3/def2-SVP level. Atom colors: N = blue, O = red, C = gray, P = orange, Ru = turquoise.

In summary, in this Chapter we have reported our studies on the implementation of the transition metal-catalyzed intramolecular carbene C–H functionalization of α-diazoesters for the preparation of tetrahydroquinolines. Although Pd(0) and Grubbs catalysts proved effective for this purpose, the first generation Grubbs catalyst was more versatile, despite not always affording the highest yields or selectivities. Starting from *N*-isopropylaniline substrates, the insertion occurred selectively on the $C_{Ar}(sp^2)$–H bond to give the tetrahydroquinoline-4-carboxylic acid esters in good yields. The reaction was not limited to substrates with an *N*-isopropyl group but also proved suitable for anilines bearing other secondary alkyl groups at the nitrogen atom, as well as for the *N*-*tert*-butyl and *N*-phenyl anilines. According to DFT calculations, the mechanism involved in the $C_{Ar}(sp^2)$–H functionalization process strongly depends on the nature of the transition metal. Whereas the Pd(0)-catalyzed reaction involves a Pd-

mediated 1,6-H migration from the $C_{Ar}(sp^2)$–H bond to the carbene carbon atom, followed by a reductive elimination process, in the Grubbs catalyst-promoted reaction an initial electrophilic addition of the ruthena-carbene intermediate to the aromatic ring and subsequent 1,2-proton migration are operative.

## Chapter 6

# Preliminary Studies on the Transition Metal-Catalyzed Decomposition of δ-(Arylamino)- and β-(Arylamino)-α-diazoesters

In Chapters 3, 4 and 5 we have presented our studies on the transition metal-catalyzed decomposition of γ-amino-α-diazoesters. In these studies, we have explored how the reactions are affected by the substituents on the γ-amino moiety and by the catalyst type, exploring the use of palladium, rhodium and ruthenium catalysts. We have shown that, although the chemoselectivity of the carbene insertion reaction, C($sp^3$)–H insertion *versus* $C_{Ar}$($sp^2$)–H functionalization, is mainly governed by the nature of the substrates, it can be indeed modified by the adequate selection of catalyst and reaction conditions.

As a continuation of this work, we decided to explore how the transition metal-catalyzed carbene reactions are affected by the length of the tether connecting the nitrogen atom and the α-diazoester moiety. To this end, the higher homolog δ-amino-α-diazoester **6.1**, as well as the lower homolog β-amino-α-diazoester **6.2** were selected (Figure 6.1).

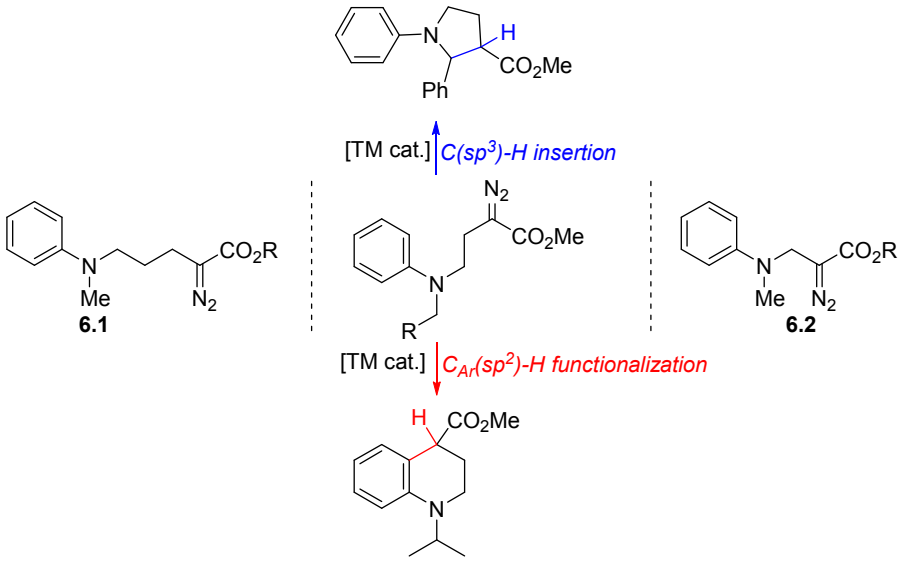



**Figure 6.1.**

To begin the study of the transition metal-catalyzed decomposition of δ-amino-α-diazoesters, we used α-diazoester **6.1a**, and we initially chose as catalysts the Pd(0)-complex [(IMes)Pd(NQ)]$_2$, the Grubbs complex **Ru-1** and [Ru(*p*-cymene)Cl$_2$]$_2$. Considering the preferential formation of six-membered over seven-membered rings, we would

have expected the formation of the piperidine[89] from the carbene C($sp^3$)–H insertion (Figure 6.2). However, when **6.1a** was treated with a catalytic amount of $[(IMes)Pd(NQ)]_2$ (0.03 mol%) in $CHCl_3$ at reflux for 24 h, the formation of the C–H insertion product was not observed. Instead, a complex reaction mixture was obtained, from which pyrrolidine **6.3a** was the only identifiable product (≤25% yield).

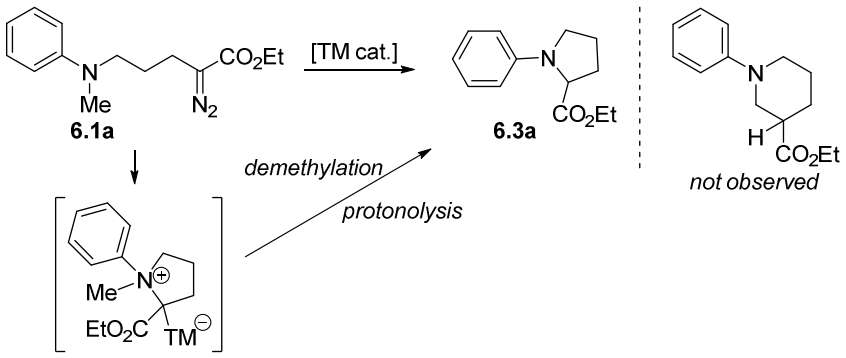



**Figure 6.2.**

Pyrrolidine **6.3a** likely results from the nucleophilic attack of the aniline nitrogen atom to the pallada(0)carbene to give an ammonium ylide intermediate,[90] followed by subsequent demethylation[91] and protonolysis. It is well known in the literature that metal carbenes derived from diazocarbonyl compounds react with amines to form transient ammonium ylides, which can undergo subsequent intramolecular rearrangement. Although reports of rearrangement reactions of ammonium ylides generated from metal carbenes are less frequent in the literature than those of their oxygen and sulfur counterparts, the synthetic potential of nitrogen ylides has been demonstrated for both inter- and intramolecular processes. Thus, for

[89] For the synthesis of tetrahydropyrans by Rh(II)-catalyzed C–H insertion of δ-(alkyloxy)-α-diazoesters, see: Ito, M.; Kondo, Y.; Nambu, H.; Anada, M.; Takeda, K.; Hashimoto, S. *Tetrahedron Lett.* **2015**, *56*, 1397.

[90] For some recent examples of Rh(II)-catalyzed formation of ammonium ylides, see: (a) Muroni, D.; Saba, A.; Culeddu, N. *Tetrahedron* **2006**, *62*, 1459. (b) Pramanik, M. M. D.; Nagode, S. B.; Kant, R.; Rastogi, N. *Org. Biomol. Chem.* **2017**, *15*, 7369. (c) Zhu, J.; Li, R.; Su, Y.; Gu, P. *J. Org. Chem.* **2019**, *84*, 5813.

[91] For related oxygen dealkylations, see: Chen, Z.-S.; Huang, X.-Y.; Chen, L.-H.; Gao, J.-M.; Ji, K. *ACS Catal.* **2017**, *7*, 7902.

example, intramolecular [1,2]-shift[92] and [2,3]-sigmatropic rearrangement[93] of ammonium ylides have been reported in decomposition reactions of amino-tethered α-diazocarbonyl compounds catalyzed by either copper or rhodium complexes.[94]

Moreover, we have previously reported that the $[(IMes)Pd(NQ)]_2$-catalyzed nucleophilic attack of the inner pyridine nitrogen to the transient carbene generated from an α-diazo-α-(ethoxycarbonyl)amide carbene gives a stable mesoionic imidazopyridine (Figure 6.3).[60]

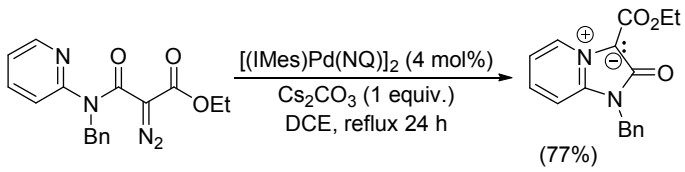



**Figure 6.3.**

However, it should be noted that, to the best of our knowledge, the dealkylation of the transient ammonium ylides[91] is unprecedented and clearly contrasts with the [1,2]-phenyl shift observed in a related *N*-methyl-*N*-phenylammonium ylide (Figure 6.4).[95]

[92] (a) West, F. G.; Glaeske, K. W.; Naidu, B. N. *Synthesis* **1993**, 977. *(b)* West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1993**, *115*, 1177. (c) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420. (d) West, F. G.; Naidu, B. N. *J. Org. Chem.* **1994**, *59*, 6051. (e) Naidu, B. N.; West, F. G. *Tetrahedron* **1997**, *53*, 16565. (f) Beall, L. S.; Padwa, A. *Tetrahedron Lett.* **1998**, *39*, 4159. (g) Moody, C. J.; Miah, S.; Slawin, A. M.; Mansfield, D. J.; Richards, I. C. *Tetrahedron* **1998**, *54*, 9689. (h) Padwa, A.; Beall, L. S.; Eidell, C. K.; Worsencroft, K. J. *J. Org. Chem.* **2001**, *66*, 2414. (i) Muroni, D.; Saba, A.; Culeddu, N. *Tetrahedron: Asymmetry* **2004**, *15*, 2609. (j) Mucedda, M.; Muroni, D.; Saba, A.; Manassero, C. *Tetrahedron* **2007**, *63*, 12232. (k) Rosset, I. G.; Dias, R. M. P.; Pinho, V. D.; Burtoloso, A. C. B. *J. Org. Chem.* **2014**, *79*, 6748.

[93] (a) Clark, J. S.; Hodgson, P. B. *Tetrahedron Lett.* **1995**, *36*, 2519. (b) Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Street, L. J. *J. Chem. Soc., Perkin Trans 1* **2001**, 3312. (c) Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Blake, A. J.; Cooke, P. A.; Street, L. J. *J. Chem. Soc., Perkin Trans 1* **2001**, 3325. (d) Clark, J. S.; Middleton, M. D. *Org. Lett.* **2002**, *4*, 765. (e) Roberts, E.; Sançon, J. P.; Sweeney, J. B. *Org. Lett.* **2005**, *7*, 2075.

[94] For the catalyst-free [2,3]-sigmatropic rearrangement of ammonium ylides, see: Li, F.; He, F.; Koenigs, R. M. *Synthesis* **2019**, *51*, 4348.

[95] Padwa, A.; Snyder, J. P.; Curtis, E. A.; Sheehan, S. M.; Worsencroft, K. J. Kappe, C. O. *J. Am. Chem. Soc.* **2000**, *122*, 8155.

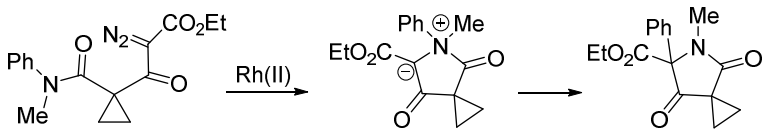



**Figure 6.4.**

Since pyrrolidine **6.3a** results from the nucleophilic interception of the transient pallada(0)carbene by the aniline nitrogen, we wondered if the use of the more electrophilic Pd(II)-complexes as catalysts could enhance its formation. Unfortunately, treatment of **6.1a** with $[Pd(allyl)Cl]_2$ (0.03 mol%), $Pd(TFA)_2$ (0.05 mol%) or $Pd(OAc)_2$ (0.1 mol%)/AcONa (1 equiv.) as the catalysts in refluxing $CHCl_3$ afforded similar reactions, the best result being obtained when using $Pd(allyl)Cl]_2$, which afforded **6.3a** in 35% yield.

On the other hand, treatment of **6.1a** with **Ru-1** (0.03 mol%) in $CH_2Cl_2$ at reflux for 24 h afforded a very complex reaction mixture in which the starting material and pyrrolidine **6.3a** (≈ 1:1 ratio) were identified. When the reaction was performed with $[Ru(p\text{-cymene})Cl_2]_2$ (0.03 mol%) in $CHCl_3$ at reflux for 24 h, in the presence of DBU (1 equiv.) to facilitate the demethylation step by nucleophilic attack to the ammonium ylide intermediate, **6.3a** was isolated in 40% yield. Interestingly, the use of DBU together with $[Pd(allyl)Cl]_2$ (*vide supra*) resulted in the deactivation of the catalyst, the starting material being recovered unchanged.

The formation of pyrrolidine **6.3a** as the main product with either palladium or ruthenium catalysts revealed a new scenario, and we decided to center our efforts in improving this unexpected reaction. To this end, we focused on the use of iron salts as the catalyst.[96,97] Iron is one of the most abundant elements on the Earth and is emerging as an important metal for carbene transfer reactions from α-diazocarbonyl

[96] For the hemin-catalyzed formation of sulfonium ylides and subsequent rearrangement, see: (a) Xu, X.; Li, C.; Tao, Z.; Pan, Y. *Green Chem.* **2017**, **19**, 1245. (b) Xu, X.; Li, C.; Xiong, M.; Tao, Z.; Pan, Y. *Chem. Commun.* **2017**, *53*, 6219.

[97] For the hemin-catalyzed formation of sulfonium ylides and subsequent dealkylation, see: (a) Empel, C.; Hock, K. J.; Koenigs, R. M. *Chem. Commun.* **2019**, *55*, 338. (b) Yan, X.; Li, C.; Xu, X.; He, Q.; Zhao, X.; Pan, Y. *Tetrahedron* **2019**, *75*, 3081.

compounds.[43-45,98] In particular, due to the higher electrophilicity of iron-carbenes, the iron-catalyzed carbene insertion of α-diazocarbonyl compounds into X–H bonds has been demonstrated to be a highly efficient transformation.[46-47]

Table 6.1 gathers the results of the iron-catalyzed decomposition of α-diazoesters **6.1a** and **6.1b**. Treatment of **6.1a** with equimolar amounts of $Fe(acac)_3$ and DBU in DCE at reflux resulted in ca. 50% of conversion, to give alkene **6.4a**, arising from the 1,2-H migration of the metal carbene intermediate, as the main product, together with small amounts of **6.3a** (entry 1, Table 6.1). In contrast, when the reaction was performed with $FeCl_2$ (1.5 equiv.), complete conversion of the starting material was observed and **6.3a** was isolated in 65% yield (entry 2, Table 6.1). Unfortunately, the use of substoichiometric quantities of $FeCl_2$ not only resulted in the recovery of some starting material, but also in the formation of significant amounts of alkene **6.4a** (entry 3, Table 6.1). Similarly, when the reaction was performed with $FeCl_3$, a mixture of starting material, pyrrolidine **6.3a** and alkene **6.4a** was obtained (entry 4, Table 6.1).

When $FeSO_4$ was used to promote the decomposition of **6.1a**, the yield of **6.3a** increased up to 82% (entry 5, Table 6.1). A similar result was obtained when the reaction was performed starting from α-diazoester **6.1b**, which afforded pyrrolidine **6.3b** in 83% yield (entry 7, Table 6.1). Interestingly, when the reaction of **6.1b** was run in the absence of DBU but under otherwise the same conditions, ca. 70% conversion was observed to give alkene **6.4b** as the only reaction product (entry 8, Table 6.1).

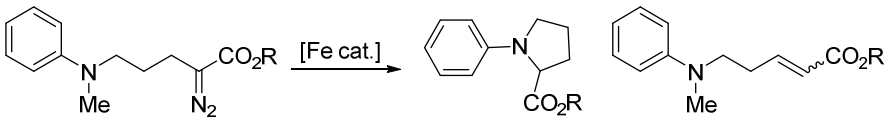
The partial conversion of the starting material and the different course of the latter reaction compared to that of entry 7, suggest that DBU could be acting as a ligand[99] in the $FeSO_4$-promoted decomposition of α-diazoesters. We therefore decided to explore the reaction in the presence of some ligands currently used in iron-catalyzed

[98] For some recent examples, see: (a) Vargas, D. A.; Khade, R. L.; Zhang, Y.; Fasan, R. *Angew. Chem. Int. Ed.* **2019**, *58*, 10148. (b) Hernán-Gomez, A.; Rodríguez, M.; Parella, T.; Costas, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 13904. (c) Zhang, R. K.; Chen, K.; Huang, X.; Wohlschlager, L.; Renata, H.; Arnold, F. H. *Nature* **2019**, *565*, 67.

[99] (a) Fournier, D.; Romagné, M.-L.; Pascual, S.; Montembault, V.; Fontaine, L. *Eur. Polym. J.* **2005**, *41*, 1576. (b) Adimurthy, S.; Malakar, C. C.; Beifuss, U. *J. Org. Chem.* **2009**, *74*, 5648. (c) Wei, W.; Hu, X.-Y.; Yan, X.-W.; Zhang, Q.; Cheng, M.; Ji, J.-X. *Chem. Commun.,* **2012**, *48*, 305.

transformations. However, when using either bpy (entry 9, Table 6.1) or TMEDA (entry 10, Table 6.1) as the ligands in the $FeSO_4$-promoted decomposition of **6.1b**, the formation of the pyrrolidine was completely suppressed. Instead, mixtures of unreacted starting material together with alkene **6.4b** were obtained.

**Table 6.1.** Fe-promoted decomposition of α-diazoesters **6.1a**-**b**.[a]




**6.1a** (R:Et) **6.3a** (R:Et) **6.4a** (R:Et)
**6.1b** (R:Me) **6.3b** (R:Me) **6.4b** (R:Me)

| Entry | 6.1 | [Fe] (mol%) | Additives (equiv.) | Products ratio[b] | Products (yield)[c] |
|---|---|---|---|---|---|
| 1 | **6.1a** | $Fe(acac)_3$ (100) | DBU (1) | **6.1a**/**6.4a**, ≈1:1[d] | --- |
| 2 | **6.1a** | $FeCl_2$ (150) | DBU (1) | --- | **6.3a** (65%) |
| 3 | **6.1a** | $FeCl_2$ (50) | DBU (1) | **6.1a**/**6.3a**/**6.4a**, ≈1.5:1:1 | --- |
| 4 | **6.1a** | $FeCl_3$ (150) | DBU (1) | --- | **6.1a** (10%)<br>**6.3a** (20%)<br>**6.4a** (10%)[e] |
| 5 | **6.1a** | $FeSO_4{\cdot}7H_2O$ (150) | DBU (1) | --- | **6.3a** (82%) |
| 6 | **6.1a** | $Fe(BF_4)_2{\cdot}6H_2O$ (150) | DBU (1) | **6.1a**/**6.4a**, ≈1:1 | --- |
| 7 | **6.1b** | $FeSO_4{\cdot}7H_2O$ (150) | DBU (1) | --- | **6.3b** (83%) |
| 8 | **6.1b** | $FeSO_4{\cdot}7H_2O$ (150) | --- | | **6.1b** (30%)<br>**6.4b** (49%)[e] |
| 9 | **6.1b** | $FeSO_4{\cdot}7H_2O$(150) | bpy (1) | --- | **6.1b** (43%)<br>**6.4b** (52%)[e] |
| 10 | **6.1b** | $FeSO_4{\cdot}7H_2O$ (150) | TMEDA (1) | --- | **6.1b** (35%)<br>**6.4b** (63%)[e] |
| 11 | **6.1b** | **---** | DBU (1) | **---** | **6.1b** (40%)<br>**6.4b** (52%)[e] |
| 12 | **6.1b** | $FeSO_4{\cdot}7H_2O$ (50) | DBU (0.5) | --- | **6.1b** (6%)<br>**6.3b** (52%)<br>**6.4b** (35%)[e] |
| 13 | **6.1b** | $Fe(ClO_4)_2{\cdot}xH_2O$ (150) | DBU (1) | --- | **6.4b** (46%)[e] |
| 14 | **6.1b** | $Fe(CF_3SO_3)_2$ (150) | DBU (1) | --- | **6.4b** (78%)[f] |
| 15 | **6.1b** | $FeBr_2$ (150) | DBU (1) | --- | **6.3b** (91%) |
| 16 | **6.1b** | $FeBr_2$ (70) | DBU (0.7) | --- | **6.3b** (89%) |
| 17 | **6.1b** | $FeBr_2$ (70) | DBU (0.7)[g] | --- | **6.1b** (15%)<br>**6.3b** (70%) |
| 18 | **6.1b** | $FeBr_2$ (50) | DBU (0.5) | --- | **6.3b** (89%) |
| 19 | **6.1b** | $FeBr_2$ (30) | DBU (0.3) | --- | **6.1b** (10%)<br>**6.3b** (54%)<br>**6.4b** (20%)[e] |
| 20 | **6.1b** | $FeBr_2$ (50) | --- | --- | **6.3b** (90%) |
| 21 | **6.1b** | $FeBr_2$ (30) | DBU (0.3)<br>KBr (0.4)[h] | --- | **6.1b** (48%)<br>**6.3b** (27%)<br>**6.4b** (9%)[e] |

[a] Reaction conditions: [Fe]/additives (see table) in DCE at reflux for 24 h. [b] Ratio determined by $^1H$ NMR. [c] Yields refer to products isolated by chromatography. [d] Small amounts of **6.3a** were also observed in the crude reaction mixture. [e] ≈1:1 *Z*/*E* isomers. [f] ≈2.5:1 *Z*/*E* isomers. [g] $CHCl_3$ at reflux for 24 h. [h] DCE at 75 °C (bath temperature) for 48 h.

On the other hand, the formation of considerable amounts of alkenes **6.4a-b** in the reactions with an incomplete conversion of the starting material (see, for example, entries 4, 9 and 10, Table 6.1) suggests that these by-products could be formed, at least in part, by thermal reaction of the diazoesters and therefore without participation of the transition metal. Thus, to further confirm the thermal formation of alkenes and also the role of iron in the carbene reaction leading to pyrrolidines, the thermal decomposition was evaluated. In the absence of iron salts but otherwise the same reaction conditions, α-diazoester **6.1b** afforded a 1:1.3 mixture of the starting material and alkene **6.4b** (entry 11, Table 6.1). This result clearly supports the essential role of the transition metal for the pyrrolidine formation.

Unfortunately, when substoichiometric loadings of $FeSO_4$ and DBU were used to promote the decomposition of **6.1b**, significant amounts of the starting material were recovered together with pyrrolidine **6.3b** and alkene **6.4b** (entry 12, Table 6.1).

With this information in hand, some additional Fe(II)-salts were tested to promote the decomposition of α-diazoesters **6.1a-b**. Treatment of **6.1a** with $Fe(BF_4)_2$ resulted in the exclusive formation of alkene **6.4a** (entry 6, Table 6.1). Similarly, treatment of **6.1b** with either $Fe(ClO_4)_2$ (entry 13, Table 6.1) or $Fe(CF_3SO_3)_2$ (entry 14, Table 6.1) also resulted in the exclusive formation of alkene **6.4b**.

On the contrary, the use of $FeBr_2$ to promote the decomposition reaction of **6.1b** afforded **6.3b** in 91% yield (entry 15, Table 6.1). Interestingly, **6.3b** was obtained in a similar yield when the reaction was run with 70 mol% of $FeBr_2$ (entry 16, Table 6.1). On the other hand, when the reaction was performed in refluxing $CHCl_3$ under otherwise the same reaction conditions, some of the starting material was recovered together with pyrrolidine **6.3b** (entry 17, Table 6.1). The amount of $FeBr_2$ could be reduced to 50 mol% without any effect on the cyclization reaction (entry 18, Table 6.1). However, lower $FeBr_2$ loadings resulted in the formation of significant amounts of alkene **6.4b** (entry 19, Table 6.1). To our surprise, and contrary to what we observed in the reactions

with $FeSO_4$, when using $FeBr_2$ the presence of DBU was not needed to successfully promote the cyclization (entry 20, Table 6.1).

The latter results seem to indicate that in the reactions promoted by $FeBr_2$ the nucleophile necessary for the demethylation step could be the bromide anion. We therefore decided to perform the decomposition of **6.1b** using 30 mol% of $FeBr_2$ in the presence of 40 mol% of KBr, which would ensure a stoichiometric amount of bromide anion and thus allow the complete consumption of the α-diazoester. However, under these reaction conditions a mixture of the starting material, pyrrolidine **6.3b** and alkene **6.4b** was obtained (entry 21, Table 6.1).

Based on this information, we propose a mechanism for the $FeBr_2$-promoted cyclization of α-diazoesters leading to pyrrolidines, which would explain why 50 mol% of $FeBr_2$ is needed to successfully promote the reaction (Figure 6.5).

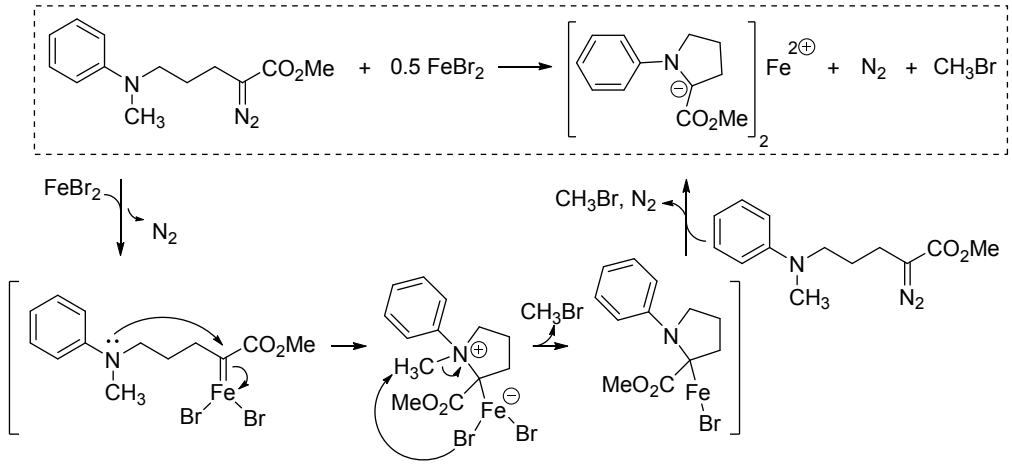



**Figure 6.5.**

The reaction would begin with the initial Fe(II)-carbene complex formed upon reaction of $FeBr_2$ with the α-diazoester. This carbene would evolve to the ammonium ylide complex via nucleophilic attack of the aniline nitrogen atom to the carbene carbon atom. Subsequent nucleophilic attack of one of the coordinated bromide ligands to the methyl at the ammonium moiety would eliminate $CH_3Br$ and afford a Fe(II) enolate,

which also bears a bromide anion. This Fe(II) species would then enter in a new cycle with a second molecule of the α-diazoester to give a Fe(II) salt with two ester enolate anions. Final protonolysis of this enolate during the work-up would lead to the observed pyrrolidine.

With this information in hand, without further optimization, we decided to explore the scope of the Fe(II)-mediated cyclization reaction leading to *N*-aryl proline derivatives. Similarly to **6.1a** and **6.1b**, *N*-Methyl α-diazoesters **6.1c** and **6.1d** afforded pyrrolidines **6.3c** and **6.3d**, respectively, in high yields when submitted to the optimized reaction conditions (Figure 6.6).

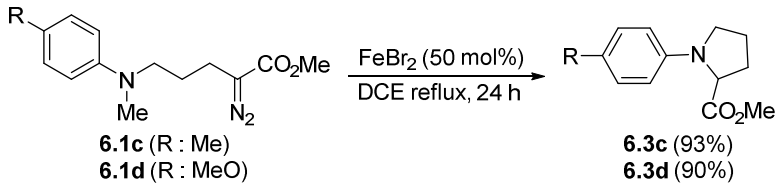



**Figure 6.6.**

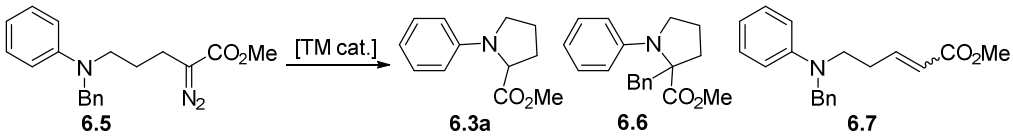
The studies were also extended to the decomposition of α-diazoesters **6.5** and **6.8**, bearing an *N*-benzyl and *N*-allyl group, respectively (Tables 6.2 and 6.3).

Treatment of α-diazoester **6.5** with $FeBr_2$ (150 mol%) and DBU (1 equiv.) in DCE at reflux (entry 1, Table 6.2) afforded pyrrolidines **6.3a** (57%) and **6.6** (38%), arising from the initially formed ammonium ylide intermediate through debenzylation or a [1,2]-benzyl shift, respectively (Figure 6.7). The same result was obtained when the reaction was run with $FeSO_4$ and DBU in DCE at reflux (entry 2, Table 6.2).

Reducing the loading of both $FeBr_2$ and DBU to 50 mol% resulted in the isolation of significant amounts of alkene **6.7** together with pyrrolidines **6.3a** and **6.6**, the latter being the main reaction product (entry 3, Table 6.2). As expected, the use of 60 mol% of $FeBr_2$ and DBU avoided the formation of the alkene (entry 4, Table 6.2). In contrast, changing the solvent from DCE to toluene resulted in the exclusive formation of alkene **6.7** (entry 5, Table 6.2). Interestingly, when the reaction was run in DCE at reflux

without DBU, the three products were once again formed, but the yield of the debenzylated pyrrolidine **6.3a** was increased up to 73% (entry 6, Table 6.2).

**Table 6.2.** TM-promoted decomposition of α-diazoester **6.5**.[a]




| Entry | [TM] (mol%) | Additives (equiv.) | Solvent | Products (yield)[b] |
|---|---|---|---|---|
| 1 | $FeBr_2$ (150) | DBU (1) | DCE | **6.3a** (57%)<br>**6.6** (38%) |
| 2 | $FeSO_4 \cdot 7H_2O$ (150) | DBU (1) | DCE | **6.3a** (56%)<br>**6.6** (38%) |
| 3 | $FeBr_2$ (50) | DBU (0.5) | DCE | **6.3a** (20%)<br>**6.6** (59%)<br>**6.7** (16%)[c] |
| 4 | $FeBr_2$ (60) | DBU (0.6) | DCE | **6.3a** (30%)<br>**6.6** (57%) |
| 5 | $FeBr_2$ (50) | DBU (0.5) | Toluene[d] | **6.5** (25%)<br>**6.7** (43%)[c] |
| 6 | $FeBr_2$ (50) | --- | DCE | **6.3a** (73%)<br>**6.6** (13%)<br>**6.7** (10%)[c] |
| 7 | $[Ru(p\text{-cymene})Cl_2]_2$ (5) | --- | $CHCl_3$ | **6.7**[c],[e] |
| 8 | $[Pd(allyl)Cl]_2$ (8) | --- | $CHCl_3$ | **6.3a** (9%)<br>**6.6** (79%)<br>**6.7** (8%)[c] |

[a] Reaction conditions: [TM]/additives (see table) at reflux for 24 h. [b] Yields refer to products isolated by chromatography. [c] ≈1:1 *Z*/*E* isomers. [d] 90 °C (bath temperature). [e] Complex mixture, the yield was not quantified.

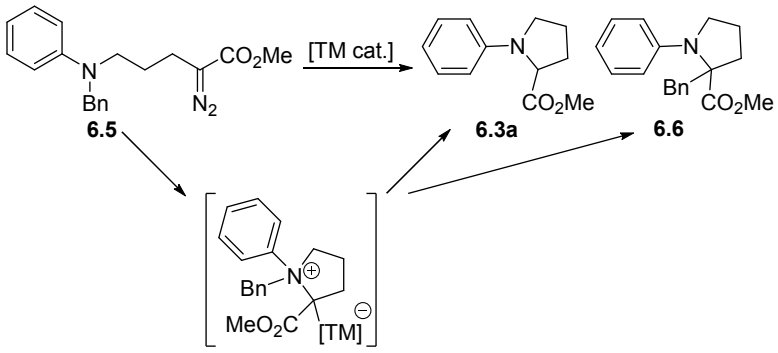


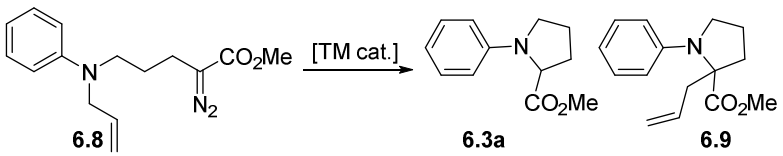

**Figure 6.7.**

As the formation of pyrrolidine **6.6** does not require the participation of any nucleophile, we decided to return to the use of ruthenium and palladium catalysts,

hoping to avoid the debenzylation and therefore favor the [1,2]-benzyl shift. While in the presence of a catalytic amount of [Ru(*p*-cymene)$Cl_2$]$_2$, alkene **6.7** was the only reaction product (entry 7, Table 6.2), when using [Pd(allyl)Cl]$_2$, pyrrolidine **6.6** was obtained in 79% yield (entry 8, Table 6.2).[100]

*N*-Allyl α-diazoester **6.8** showed a similar behavior to the *N*-benzyl derivative when submitted to the different transition metal complexes (Table 6.3).

**Table 6.3.** TM-promoted decomposition of α-diazoester **6.8**.[a]




**6.8** **6.3a** **6.9**

| Entry | [TM] (mol%) | Additives (equiv.) | Solvent | Products (yield)[b] |
|---|---|---|---|---|
| 1 | $FeBr_2$ (150) | DBU (1) | DCE | **6.3a** (60%)<br>**6.9** (20%) |
| 2 | $FeBr_2$ (60) | DBU (0.6) | DCE | **6.3a** (49%)<br>**6.9** (45%) |
| 3 | [Pd(allyl)Cl]$_2$ (8) | --- | $CHCl_3$ | **6.9** (69%)[c] |

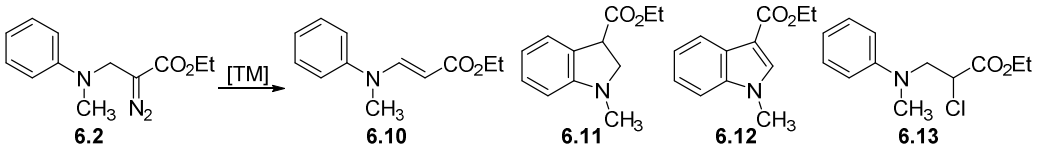
[a] Reaction conditions: [TM]/additives (see table) at reflux for 24 h. [b] Yields refer to products isolated by chromatography. [c] Small amounts of **6.3a** and the corresponding alkene were also observed in the crude reaction mixture.

Thus, when **6.8** was treated with an excess of $FeBr_2$ in the presence of DBU, a mixture of the deallylated pyrrolidine **6.3a** and pyrrolidine **6.9** arising from the [1,2]-allyl shift was obtained, the former being the main reaction product (entry 1, Table 6.3). The use of substoichiometric amounts of $FeBr_2$ and DBU resulted in an increase of the [1,2]-allyl shift product (entry 2, Table 6.3). On the other hand, when using [Pd(allyl)Cl]$_2$, pyrrolidine **6.9** was obtained in 69% yield (entry 3, Table 6.3).

In parallel to the studies with δ-amino-α-diazoesters, we also began to explore the reactivity of β-amino-α-diazoester **6.2** with different transition metal complexes.

[100] For the palladium-catalyzed formation of sulfonium ylides and subsequent rearrangement, see: Greenman, K. L.; Carter, D. S.; Van Vranken, D. L. *Tetrahedron* **2001**, *57*, 5219.

**Table 6.4.** TM-promoted decomposition of α-diazoester **6.2**.[a]




| Entry | [TM] (mol%)/Additives (mol%) | Solvent | Products ratio[b] |
|---|---|---|---|
| 1 | **Ru-1** (3) | $CH_2Cl_2$ | **6.10**/**6.11**/**6.12**, ≈1:0.15:0.2 |
| 2 | **Ru-2** (3) | $CH_2Cl_2$ | **6.10**/**6.11**/**6.12**, ≈1:0.1:0.2 |
| 3 | [Ru(*p*-cymene)$Cl_2$]$_2$ (3) | $CH_2Cl_2$ | **6.10**/**6.12**, ≈1:0.15 |
| 4 | [(IMes)Pd(NQ)]$_2$ (3) | $CHCl_3$ | **6.10**[c] |
| 5 | [Pd(allyl)Cl]$_2$ (8) | $CHCl_3$ | **6.10**[c] |
| 6 | $FeCl_2$ (100)/DBU(100) | DCE | **6.2**/**6.10**/**6.13**, ≈1:1:0.7 |
| 7 | Fe($CF_3SO_3$)$_2$ (100) | DCE | --- |

[a] Reaction conditions: [TM]/additives (see table) at reflux for 24 h. [b] Ratio determined by $^1$H NMR. [c] Yield not determined.

In our preliminary studies with this α-diazoester (Table 6.4), we observed its high tendency to undergo 1,2-H migration[101] to give alkene **6.10**, probably due to the stability of the latter, resulting from the delocalization of the vinylogous amide system. In fact, regardless of the transition metal employed to promote the decomposition of **6.2**, the formation of the alkene was always the main reaction pathway. Thus, treatment of **6.2** with Grubbs complexes (entries 1-2, Table 6.4) resulted in the major formation of alkene **6.10** together with minor amounts of indoline **6.11**, which arises from the $C_{Ar}(sp^2)$–H functionalization, and indole **6.12**, which is formed by dehydrogenation of **6.11**. A similar result was obtained when using [Ru(*p*-cymene)$Cl_2$]$_2$ as the catalyst (entry 3, Table 6.4). On the other hand, in the presence of either [(IMes)Pd(NQ)]$_2$ (entry 4, Table 6.4) or [Pd(allyl)Cl]$_2$ (entry 5, Table 6.4), the alkene was the only identifiable reaction product.

When using stoichiometric amounts of $FeCl_2$ and DBU, partial conversion of the starting material to give alkene **6.10** and α-chloroester **6.13** was observed (entry 6, Table 6.4). Finally, the use of Fe($CF_3SO_3$)$_2$ resulted in the complete disintegration of the α-diazoester (entry 7, Table 6.4).

[101] For the Rh(II)-catalyzed decomposition of related β-amino α-diazoesters, see: Muthusamy, S.; Gunanathan, C.; Babu, S. A. *Synthesis* **2002**, 471.

In summary, in this preliminary study we have explored the transition metal-promoted decomposition of δ-amino-α-diazoesters and β-amino-α-diazoesters. The transition metal-mediated reactions of δ-(arylamino)-α-diazoesters lead to the formation of a transient ammonium ylide intermediate, from which subsequent dealkylation or a [1,2]-shift affords the corresponding *N*-phenyl proline alkyl esters. On the other hand, in the presence of transition-metal complexes, the β-(arylamino)-α-diazoester shows a high tendency to undergo 1,2-H migration to give the corresponding vinylogous amide. Further exploration of different transition-metal complexes and DFT computational studies will be carried out in the future to gain more insight into the mechanisms of the above reactions as well as to optimize the synthesis of proline derivatives.

# Chapter 7

# Conclusions

In this Thesis, we have experimentally studied the transition metal-catalyzed decomposition of amino-tethered α-diazoesters. From this study, the following conclusions can be drawn:

1. The use of Pd-, Rh(II)- and Ru(II)-based catalysts has been explored in the transition metal-catalyzed intramolecular carbene C($sp^3$)–H insertion of γ-amino-α-diazoesters leading to pyrrolidines.

   Although the outcome of the reaction was highly substrate-dependent, in general, it was possible to control the chemoselectivity of the process towards pyrrolidines by adequate catalyst selection. Thus, the Pd(0)-catalysts were as efficient as $[Rh(Ph_3CCO_2)_2]_2$ in promoting the C($sp^3$)–H insertion of *ortho*-substituted anilines. In contrast, for anilines bearing *meta*- and *para*-substituents, the Rh(II)-catalyst provided the best chemoselectivities and reaction yields.

   On the other hand, [Ru(*p*-cymene)$Cl_2$]$_2$ was the most efficient catalyst for the insertion reaction of the *N*-benzyl-*N*-phenyl and *N*,*N*-dibenzyl α-diazoesters, while the C($sp^3$)–H insertion of the *N*-benzylsulfonamide substrate was only promoted by $[Rh(Ph_3CCO_2)_2]_2$.

   According to density functional theory (DFT) calculations carried out in collaboration with Prof. Israel Fernández from the "Universidad Complutense de Madrid", the mechanism involved in the Pd(0)- and Ru(II)-catalyzed C($sp^3$)–H insertions differs considerably from that typically proposed for the Rh(II)-catalyzed transformation. Whereas the Pd(0)-catalyzed reaction involves a Pd-mediated 1,5-H migration from the C($sp^3$)–H bond to the carbene carbon atom leading to the formal oxidation of the transition metal, a Ru(II)-promoted Mannich type reaction involving a zwitterionic intermediate seems to be operative in the Ru(II)-catalyzed transformation.

   Our experimental and computational studies show that, regardless of the transition metal-catalytic system [Pd, Rh(II) or Ru(II)], the success of C($sp^3$)–H insertion relies on the presence of a heteroatom at the γ position of the α-diazoester.

2. Some structurally diverse and commercially available Ru(II)-complexes have been explored as catalysts to promote the carbene C($sp^3$)–H insertion of α-diazoesters leading to pyrrolidines.

   We have demonstrated that the Grubbs catalysts are a useful alternative to promote intramolecular carbene C($sp^3$)–H insertion of γ-amino-α-diazoesters. Overall, the first generation Grubbs catalyst proved to be the most efficient in promoting the cyclization. Our studies clearly showed that no competition arises from the possible metathesis and cyclopropanation reactions on substrates bearing alkene and alkyne moieties.

   DFT calculations showed that the Grubbs-catalyzed C($sp^3$)–H insertion proceeds through an identical mechanism to that described previously for the [Ru(*p*-cymene)$Cl_2$]$_2$-catalyzed reaction.

   On the other hand, preliminary results on the use of different chiral Ru(II)-catalytic systems to promote the C($sp^3$)–H insertion leading to pyrrolidines suggest that it should be possible to develop an enantioselective version of the Ru(II)-catalyzed insertion reaction.

3. A synthesis of tetrahydroquinoline-4-carboxylic acid esters has been developed via the transition metal-catalyzed intramolecular aromatic C–H functionalization of γ-anilino-α-diazoesters. Both [(IMes)Pd(NQ)]$_2$ and the first generation Grubbs catalyst proved effective for this purpose. The ruthenium catalyst was found to be the most versatile, although in a few cases the palladium complex afforded better yields or selectivities.

   According to DFT calculations, the Pd(0)- and Ru(II)-catalyzed $C_{Ar}$($sp^2$)–H functionalization proceeds through rather different reaction mechanisms. Thus, the Pd(0)-catalyzed reaction involves a Pd-mediated 1,6-H migration from the $C_{Ar}$($sp^2$)–H bond to the carbene carbon atom, followed by a reductive elimination process. In contrast, an electrophilic addition of the ruthenacarbene intermediate

to the aromatic ring and subsequent 1,2-proton migration are operative in the Grubbs catalyst-promoted reaction.

4. The transition metal-promoted decomposition of δ-(arylamino)-α-diazoesters has been explored. To this end, we used some diverse palladium and ruthenium complexes as well as different iron salts. The reaction of δ-(arylamino)-α-diazoesters with the transition metal always led to the formation of a transient ammonium ylide intermediate, which underwent subsequent dealkylation or [1,2]-alkyl shift to afford the corresponding pyrrolidines.

   $FeBr_2$ provided the best results in the dealkylative cyclization of *N*-methyl δ-(arylamino)-α-diazoesters leading to *N*-aryl proline alkyl esters. On the other hand, $[Pd(allyl)Cl]_2$ was more efficient in promoting the cyclization/[1,2]-alkyl shift to afford 2-alkyl-*N*-arylproline alkyl esters starting from *N*-alkyl δ-(arylamino)-α-diazoesters.

# Chapter 8

## Experimental Part

## 8.1. General Methods

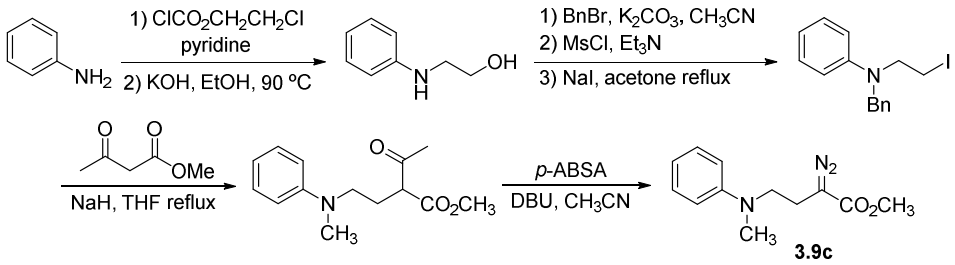
All commercially available reagents were used without further purification. All reactions were carried out under an argon atmosphere. TLC was carried out on $SiO_2$ (silica gel 60 $F_{254}$, Merck), and the spots were located with UV light or 1% aqueous $KMnO_4$. Flash chromatography was carried out on $SiO_2$ (silica gel 60, SDS, 230-400 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous $Na_2SO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. $^1$H- and $^{13}$C-NMR spectra were recorded using $Me_4Si$ as the internal standard, with a Varian Mercury 400 instrument. Chemical shifts are reported in ppm downfield (δ) from $Me_4Si$ for $^1$H- and $^{13}$C- NMR. HRMS were obtained using a LC/MSD TOF mass spectrometer.

## 8.2. Experimental Part of Chapter 3

### Experimental procedures and characterization data for the starting materials

α-Diazoesters **3.1**, **3.5a-i** and **3.9a-b** have been previously reported.[57]

**Methyl 2-diazo-4-(*N*-benzyl-*N*-phenylamino)butanoate (3.9c).**




Pyridine (1.13 mL, 13.95 mmol) and 2-chloroethylchloroformate (1.1 mL, 10.73 mmol) were added, under argon, to a solution of aniline (1.0 g, 10.73 mmol) in $CH_2Cl_2$ (30 mL). The resulting solution was stirred at room temperature overnight, washed three times with water, dried, filtered and concentrated to give an orange oil. This oil was dissolved in EtOH (30 mL), and KOH (2.4 g, 42.92 mmol) was added at room temperature. The resulting suspension was stirred at 90 ºC for 5 h. The reaction mixture was cooled to room temperature and partitioned between water and $CH_2Cl_2$. The aqueous layer was

extracted with $CH_2Cl_2$. The combined organic extracts were washed with water, dried, filtered and concentrated to give 2-(phenylamino)ethanol (1.38 g), which was used in the next step without purification.

To a cooled (0 ºC) solution of the crude 2-(*N*-phenylamino)ethanol (1.38 g) in $CH_3CN$ (60 mL) were added benzyl bromide (2.55 mL, 21.46 mmol) and $K_2CO_3$ (2.97 g, 21.46 mmol). The mixture was stirred at 60 ºC overnight, concentrated *in vacuo* and the residue was partitioned between water and $CH_2Cl_2$. The organic extracts were dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 1:3) to give 2-(*N*-benzyl-*N*-phenylamino)ethanol (1.6 g, 66% for the two steps).

2-(*N*-Benzyl-*N*-phenylamino)ethanol (1.6 g, 7.04 mmol) and triethylamine (1.3 mL, 9.15 mmols) were dissolved in $CH_2Cl_2$ (9 mL), and methanesulfonyl chloride (0.6 mL, 7.74 mmols) was added dropwise at 0 ºC. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was poured into water and ice, basified with a saturated $NaHCO_3$ aqueous solution, and extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried, filtered and concentrated to give the crude 2-(*N*-benzyl-*N*-phenylamino)ethyl methanesulfonate as a yellow oil, which was used in the next step without purification.

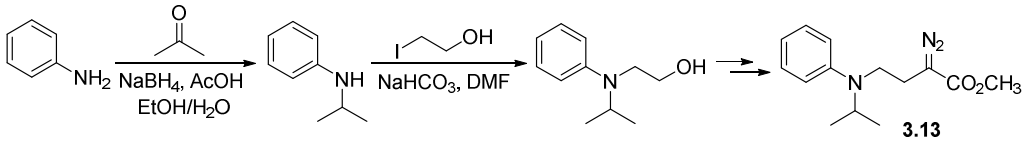
A mixture of the crude 2-(*N*-benzyl-*N*-phenylamino)ethyl methanesulfonate and NaI (21 g, 140.8 mmols) in acetone (53 mL) was stirred at reflux overnight. The resulting mixture was concentrated *in vacuo* and the residue was partitioned between water and $Et_2O$. The organic extracts were washed with water, dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 9:1) to give *N*-(2-iodoethyl)-*N*-benzylaniline (2.4 g, quantitative) as an orange oil.

A solution of methyl 3-oxobutanoate (4.6 mL, 42.6 mmols) in dry THF (45 mL) was added dropwise, under an argon atmosphere, to a stirred suspension of NaH (1.7 g of a 60% suspension in mineral oil, 42.6 mmols) in dry THF (45 mL) at room temperature. After the mixture became clear (5 min), a solution of *N*-(2-iodoethyl)-*N*-benzylaniline (2.4 g, 7.1 mmols) in dry THF (145 mL) was added dropwise, and the mixture was stirred

at 80 ºC for 96 h. The reaction mixture was poured into a saturated ammonium chloride aqueous solution and ice, and then extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 9:1) to give *N*-(2-iodoethyl)-*N*-benzylaniline (1.49 g, 62%) and methyl 2-acetyl-4-(*N*-benzyl-*N*-phenylamino)butanoate (713 mg, 31%) as a yellow oil.

To a solution of methyl 2-acetyl-4-(*N*-benzyl-*N*-phenylamino)butanoate (713 mg, 2.19 mmols) and DBU (0.49 mL, 3.29 mmols) in dry acetonitrile (11 mL) was added dropwise a solution of *p*-ABSA (0.68 g, 2.85 mmols) in dry acetonitrile (4 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was purified by chromatography ($SiO_2$, $CH_2Cl_2$) to give **3.9c** (0.51 g, 75%) as a yellow oil. $^1$H RMN ($CDCl_3$, 400 MHz) δ 2.59 (m, 2H), 3.61 (m, 2H), 3.75 (s, 3H), 4.55 (s, 2H), 6.71 (tt, *J* = 7.2 and 0.8 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 2H), 7.18-7.32 (m, 7H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 22.1 ($CH_2$), 49.4 ($CH_2$), 52.1 ($CH_3$), 54.8 ($CH_2$), 112.7 (2 CH), 117.1 (CH), 126.8 (2 CH), 127.1 (CH), 128.7 (2 CH), 129.5 (2 CH), 138.7 (C), 148.1 (C), 167.9 (C). C=$N_2$ was not observed. IR (NaCl) ν 2080, 1692 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{18}H_{20}N_3O_2$: 310.1550 $[M + H]^+$; found: 310.1547.

**Methyl 2-diazo-4-(*N*-isopropyl-*N*-phenylamino)butanoate (3.13).**




**3.13**

A solution of aniline (1.0 g, 10.74 mmol) in ethanol (12 mL) and water (12 mL) was cooled in an ice bath. Sodium acetate trihydrate (2.64 g, 32.2 mmol), acetic acid (9.8 mL), acetone (4 mL, 53.8 mmol) and $NaBH_4$ (2.0 g, 53.6 mmol) were slowly added, and the mixture was stirred at room temperature for 30 min. The reaction mixture, which was maintained at 0 ºC by using an ice bath, was basified by addition of 10% NaOH aqueous solution, and then was extracted with $Et_2O$. The organic extracts were washed with brine, dried, filtered and concentrated to give the crude *N*-isopropylaniline as a yellow oil, which was used in the next step without purification.

A solution of crude *N*-isopropylaniline, 2-iodoethanol (3.0 mL, 38.4 mmol) and $NaHCO_3$ (1.1 g, 12.8 mmol) in DMF (16 mL) was stirred at 80 ºC for 24 h. The reaction mixture was partitioned between water and $Et_2O$, and the organic extracts were carefully washed with brine. The organic extracts were dried, filtered and concentrated. To remove the excess of 2-iodoethanol, the residue was dissolved in acetonitrile (12 mL) and dimethylamine (22 mL of a 2M solution in THF) was added. The mixture was stirred at 80 ºC in a sealed tube overnight. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water and $CH_2Cl_2$. The organic extracts were washed with water, dried, filtered and concentrated to give crude 2-[*N*-isopropyl-*N*-phenylamino]ethanol (1.61 g, 83%) as a yellow oil, which was used in the next step without purification.

2-[*N*-Isopropyl-*N*-phenylamino]ethanol (1.61 g, 9.0 mmol) and triethylamine (1.6 mL, 11.6 mmols) were dissolved in $CH_2Cl_2$ (11 mL), and methanesulfonyl chloride (0.76 mL, 9.82 mmols) was added dropwise at 0 ºC. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was poured into water and ice, basified with a saturated $NaHCO_3$ aqueous solution, and extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried, filtered and concentrated to give the crude 2-(*N*-isopropyl-*N*-phenylamino)ethyl methanesulfonate as a yellow oil, which was used in the next step without purification.

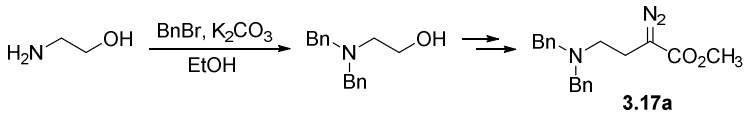
A mixture of the crude 2-(*N*-isopropyl-*N*-phenylamino)ethyl methanesulfonate and NaI (26.8 g, 178 mmols) in acetone (67 mL) was stirred at reflux overnight. The resulting mixture was concentrated *in vacuo* and the residue was partitioned between water and $Et_2O$. The organic extracts were washed with water, dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 9:1) to give *N*-(2-iodoethyl)-*N*-isopropylaniline (1.6 g, 62%) as an orange oil.

A solution of methyl 3-oxobutanoate (3.6 mL, 33.2 mmols) in dry THF (28 mL) was added dropwise, under an argon atmosphere, to a stirred suspension of NaH (0.84 g of a 60% suspension in mineral oil, 33.2 mmols) in dry THF (28 mL) at room temperature. After the mixture became clear (5 min), a solution of *N*-(2-iodoethyl)-*N*-isopropylaniline (1.6 g, 5.53 mmols) in dry THF (28 mL) was added dropwise, and the mixture was stirred

at 80 ºC for 96 h. The reaction mixture was poured into a saturated ammonium chloride aqueous solution and ice, and then extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 9:1) to give *N*-(2-iodoethyl)-*N*-isopropylaniline (0.48 g, 30%) and methyl 2-acetyl-4-(*N*-isopropyl-*N*-phenylamino)butanoate (0.56 g, 37%) as a yellow oil.

To a solution of methyl 2-acetyl-4-(*N*-isopropyl-*N*-phenylamino)butanoate (0.56 g, 2.0 mmols) and DBU (0.4 mL, 3.0 mmols) in dry acetonitrile (910 mL) was added dropwise a solution of *p*-ABSA (0.62 g, 2.6 mmols) in dry acetonitrile (9 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was purified by chromatography ($SiO_2$, $CH_2Cl_2$) to give **3.13** (0.36 g, 68%) as a yellow oil. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.16 (d, *J* = 6.8 Hz, 6H), 2.49 (m, 2H), 3.33 (m, 2H), 3.78 (s, 3H), 3.99 (septuplet, *J* = 6.8 Hz, 1H), 6.74 (tt, *J* = 7.2 and 1.0 Hz, 1H), 6.81-6.85 (m, 2H), 7.20-7.26 (m, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 20.1 (2 $CH_3$), 23.4 ($CH_2$), 42.2 ($CH_2$), 50.4 (CH), 52.1 ($CH_3$), 115.0 (2 CH), 117.7 (CH), 129.4 (2 CH), 148.5 (C), 168.2 (C). C=$N_2$ was not observed. IR (NaCl) ν 2082, 1693 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{14}H_{20}N_3O_2$: 262.1550 $[M + H]^+$; found: 262.1548.

**Methyl 2-diazo-4-(*N,N*-dibenzylamino)butanoate (3.17a).**




**3.17a**

Benzyl bromide (3.0 mL, 25.78 mmol) and $K_2CO_3$ (3.56 g, 25.78 mmol) were added, under argon, to a solution of 2-aminoethanol (0.74 mL, 12.28 mmol) in EtOH (75 mL). The resulting mixture was stirred at reflux for 3 h. The solvent was removed *in vacuo* and the residue was partitioned between dichloromethane and water. The combined organic extracts were dried, filtered and concentrated, and the residue was purified by chromatography ($SiO_2$, $CH_2Cl_2$-MeOH 97:3) to give 2-(*N*,*N*-dibenzylamino)ethanol (1.86 g, 63%) as a colorless oil.

2-(*N*,*N*-Dibenzylamino)ethanol (0.85 g, 3.52 mmol) and triethylamine (0.74 mL, 5.28 mmols) were dissolved in $CH_2Cl_2$ (7 mL), and methanesulfonyl chloride (0.6 mL, 7.74 mmols) was added dropwise at 0 ºC. The resulting solution was stirred at room temperature for 3 h. The reaction mixture was poured into water and ice, basified with a saturated $NaHCO_3$ aqueous solution, and extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried, filtered and concentrated to give the crude *N*-(2-chloroethyl)-*N*,*N*-dibenzylaniline (0.92 g) as a yellow oil, which was used in the next step without purification.

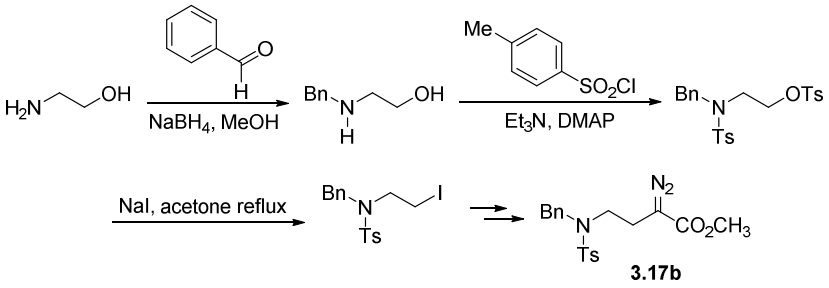
A mixture of the crude *N*-(2-chloroethyl)-*N*,*N*-dibenzylaniline and NaI (2.1 g, 14.08 mmols) in acetone (30 mL) was stirred at reflux for 24 h. The resulting mixture was concentrated *in vacuo* and the residue was partitioned between water and $Et_2O$. The organic extracts were washed with water, dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 9:1) to give *N*-(2-iodoethyl)-*N*,*N*-dibenzylaniline (0.77 g, 62%) as an orange oil.

A solution of methyl 3-oxobutanoate (1.66 mL, 15.36 mmols) in dry THF (13 mL) was added dropwise, under an argon atmosphere, to a stirred suspension of NaH (615 mg of a 60% suspension in mineral oil, 15.36 mmols) in dry THF (13 mL) at room temperature. After the mixture became clear (5 min), a solution of *N*-(2-iodoethyl)-*N*,*N*-dibenzylaniline (0.9 g, 2.56 mmols) in dry THF (13 mL) was added dropwise, and the mixture was stirred at 80 ºC for 96 h. The reaction mixture was poured into a saturated ammonium chloride aqueous solution and ice, and then extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 9:1) to give methyl 2-acetyl-4-(*N,N*-dibenzylamino)butanoate (414 mg, 48%) as a colorless oil.

To a solution of methyl 2-acetyl-4-(*N,N*-dibenzylamino)butanoate (0.25 g, 0.74 mmols) and DBU (0.17 mL, 1.1 mmols) in dry acetonitrile (5 mL) was added dropwise a solution of *p*-ABSA (0.23 g, 0.96 mmols) in dry acetonitrile (5 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was purified by chromatography ($SiO_2$, $CH_2Cl_2$) to give **3.17a** (200 mg, 88%) as a yellow oil. $^1$H RMN ($CDCl_3$, 400 MHz) δ 2.40 (t, *J* = 6.4 Hz, 2H), 3.63 (t, *J* = 6.4 Hz, 2H), 3.60

(s, 4H), 3.66 (s, 3H), 7.22-7.36 (m, 10H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 22.2 ($CH_2$), 51.8 ($CH_2$), 51.9 ($CH_3$), 58.8 (2 $CH_2$), 127.1 (CH), 128.4 (2 CH), 128.9 (2 CH), 139.4 (C), 167.9 (C). C=$N_2$ was not observed. IR (NaCl) ν 2081, 1694 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{19}H_{22}N_3O_2$: 324.11707 $[M + H]^+$; found: 324.1699.

**Methyl 2-diazo-4-(*N*-benzyl-*N*-(*p*-toluenesulfonyl)amino)butanoate (3.17b).**




**3.17b**

A solution of benzaldehyde (0.96 mL, 9.44 mmol) in methanol (53 mL) was cooled in an ice bath. 2-Aminoethanol (0.54 mL, 8.97 mmol) was added, and the mixture was stirred at room temperature for 8h. Sodium borohydride (0.7 g, 18.8 mmol) was added slowly to the reaction mixture, which was maintained at 0 ºC by using an ice bath. After the addition, the mixture was stirred at room temperature for 12 h. The reaction was cooled in an ice bath and quenched by addition of 6M HCl aqueous solution until the pH was adjusted to ≈ 4. The solvent was removed under reduced pressure and the residue was dissolved in water, and then washed with $CH_2Cl_2$ to remove the organic impurities. The aqueous phase was adjusted to pH ≈ 10 by using solid $Na_2CO_3$, and then was extracted with $CH_2Cl_2$. The organic extracts were dried, filtered and concentrated to give crude 2-(*N*-benzylamino)ethanol (0.84 g, 62%) as a colorless oil, which was used in the next step without purification.

To a solution of 2-(*N*-benzylamino)ethanol (0.84 g, 5.55 mmol) in $CH_2Cl_2$ (36 mL), were added *p*-toluenesulfonyl chloride (2.33 g, 12.21 mmol), $Et_3N$ (3.88 mL, 27.75 mmol) and DMAP (170 mg, 1.39 mmol). The mixture was stirred at room temperature for 48 h, and then washed with 1M HCl aqueous solution and saturated $NaHCO_3$ aqueous solution. The organic layer was dried, filtered and concentrated to give crude 2-[*N*-benzyl-*N*-(*p*-

toluenesulfonyl)amino]ethyl *p*-toluenesulfonate, which was used in the next step without purification.

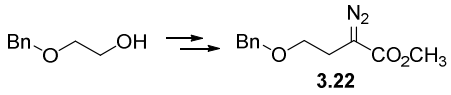
The crude sulfonate (5.55 mmol) was dissolved in acetone (42 mL) and NaI (16.6 g, 111 mmol) was added. The mixture was heated at reflux for 24 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water and $Et_2O$. The organic extracts were washed with water, dried, filtered and concentrated. The solvent was removed to give *N*-benzyl-*N*-(2-iodoethyl)-*p*-toluenesulfonamide, which was used in the next step without purification.

A solution of methyl 3-oxobutanoate (3.6 mL, 33.3 mmols) in dry THF (28 mL) was added dropwise, under an argon atmosphere, to a stirred suspension of NaH (0.8 g of a 60% suspension in mineral oil, 33.3 mmols) in dry THF (28 mL) at room temperature. After the mixture became clear (5 min), a solution of crude *N*-benzyl-*N*-(2-iodoethyl)-*p*-toluenesulfonamide (5.55 mmol) in dry THF (28 mL) was added dropwise, and the mixture was stirred at 80 ºC for 96 h. The reaction mixture was poured into a saturated ammonium chloride aqueous solution and ice, and then extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 9:1) to give *N*-benzyl-*N*-(2-iodoethyl)-*p*-toluenesulfonamide (0.63 g, 27.5%) and methyl 2-acetyl-4-(*N*-benzyl-*N*-(*p*-toluenesulfonyl)amino)butanoate (0.82 g, 37%) as a colorless oil.

To a solution of methyl 2-acetyl-4-(*N*-benzyl-*N*-(*p*-toluenesulfonyl)amino)butanoate (0.82 g, 2.2 mmols) and DBU (0.44 mL, 2.94 mmols) in dry acetonitrile (9 mL) was added dropwise a solution of *p*-ABSA (0.61 g, 2.54 mmols) in dry acetonitrile (8.5 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was purified by chromatography ($SiO_2$, $CH_2Cl_2$) to give **3.17b** (540 mg, 63%) as a yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.33 (t, *J* = 6.8 Hz, 2H), 2.45 (s, 3H), 3.21 (t, *J* = 6.8 Hz, 2H), 3.62 (s, 3H), 4.27 (s, 2H), 7.26-7.36 (m, 7H), 7.71-7.75 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 21.7 ($CH_3$), 24.3 ($CH_2$), 46.8 ($CH_2$), 51.9 ($CH_3$), 53.6 ($CH_2$), 127.5 (2 CH), 128.2 (CH), 128.8 (2 CH), 128.9 (2 CH), 130.0 (2 CH), 136.1 (C), 136.2 (C), 143.7 (C), 167.5 (C). C=$N_2$ was not observed. IR (NaCl) ν

1087, 1692 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{19}H_{25}N_4O_4S$: 405.1591 $[M + NH_4]^+$; found: 405.1590.

**Methyl 4-(benzyloxy)-2-diazobutanoate (3.22).**




**3.22**

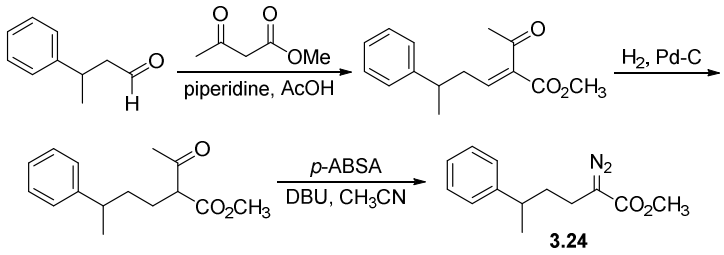
2-(Benzyloxy)ethanol (1.0 g, 6.57 mmol) and triethylamine (0.86 mL, 8.54 mmols) were dissolved in $CH_2Cl_2$ (8.5 mL), and methanesulfonyl chloride (0.56 mL, 7.23 mmols) was added dropwise at 0 ºC. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was poured into water and ice, basified with a saturated $NaHCO_3$ aqueous solution, and extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried, filtered and concentrated to give the crude 2-(benzyloxy)ethyl methanesulfonate as a yellow oil, which was used in the next step without purification.

A mixture of the crude 2-(benzyloxy)ethyl methanesulfonate and NaI (19.7 g, 131.9 mmols) in acetone (49 mL) was stirred at reflux overnight. The resulting mixture was concentrated *in vacuo* and the residue was partitioned between water and $Et_2O$. The organic extracts were washed with water, dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 9:1) to give benzyl (2-iodoethyl) ether as an orange oil, which was used in the next step without purification.

$K_2CO_3$ (2.22 g, 16.05 mmol) was added to a solution of crude benzyl (2-iodoethyl) ether and methyl 3-oxobutanoate (1.1 mL, 9.9 mmols) in acetone (40 mL) and the mixture was then heated under reflux for 27 h under a nitrogen atmosphere. The mixture was cooled to room temperature and then evaporated *in vacuo*. The residue was diluted with water and extracted with $Et_2O$. The combined organic extracts were dried and then concentrated. The residue was purified by chromatography ($SiO_2$, hexanes-EtOAc 10%) to give 2-[2-(benzyloxy)ethyl]-3-oxobutyric acid methyl ester (1.15 g, 70% for the three steps) as a colorless oil.

To a solution of 2-[2-(benzyloxy)ethyl]-3-oxobutyric acid methyl ester (0.55 g, 2.2 mmol) and DBU (0.5 mL, 3.28 mmols) in dry acetonitrile (11 mL) was added dropwise a solution of *p*-ABSA (0.68 g, 2.84 mmols) in dry acetonitrile (9.5 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was purified by chromatography ($SiO_2$, $CH_2Cl_2$) to give **3.22** (470 mg, 91%) as a yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.58 (t, *J* = 6.0 Hz, 2H), 3.63 (t, *J* = 6.0 Hz, 2H), 3.75 (s, 3H), 4.52 (s, 2H), 7.25-7.37 (m, 5H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 24.4 ($CH_2$), 52.0 ($CH_3$), 68.5 ($CH_2$), 73.3 ($CH_2$), 127.7 (2 CH), 127.8 (CH), 128.6 (2 CH), 138.2 (C), 168.0 (C). C=$N_2$ was not observed. IR (NaCl) ν 2086, 1692 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{12}H_{15}N_2O_3$: 235.1077 $[M + H]^+$; found: 235.1073.

**Methyl 2-diazo-5-phenylhexanoate (3.24).**




**3.24**

To a cooled (0 ºC) solution of 3-phenylbutyraldehyde (0.25 mL, 1.69 mmol) and methyl 3-oxobutanoate (0.2 mL, 1.85 mmols) in $CH_2Cl_2$ (1 mL), were added piperidine (17 μL, 0.17 mmol) and acetic acid (9.7 μL, 0.17 mmol). After stirring for 30 min, the reaction mixture was warmed up to room temperature and stirred for another 30 min, at which time it was diluted with $Et_2O$ and water, and extracted with $Et_2O$. The combined organic extracts were washed with saturated $NaHCO_3$ aqueous solution and brine, dried, filtered and concentrated to give methyl 2-acetyl-5-phenyl-2-hexenoate (mixture of *Z/E* isomers), which was used in the next step without purification.

A mixture of crude methyl 2-acetyl-5-phenyl-2-hexenoate (1.69 mmol) and palladium on carbon (85 mg, 20% w/w) was stirred in methanol (8 mL) for 24 h at room temperature under hydrogen delivered from a balloon. The mixture was filtered through Celite, dried

and concentrated under reduced pressure to give the α-substituted β-ketoester (400 mg), which was used in the next step without purification.

To a solution of the α-substituted β-ketoester (400 mg) and DBU (0.38 mL, 2.53 mmols) in dry acetonitrile (8.5 mL) was added dropwise a solution of *p*-ABSA (0.53 g, 2.2 mmols) in dry acetonitrile (7.5 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was purified by chromatography ($SiO_2$, $CH_2Cl_2$) to give **3.24** (170 mg, 43% for the three steps) as a yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, *J* = 6.8 Hz, 3H), 1.77-1.83 (m, 2H), 2.18-2.22 (m, 2H), 2.74 (sept, *J* = 6.8 Hz, 1H), 3.73 (s, 3H), 7.16-7.22 (m, 3H), 7.27-7.32 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 21.7 ($CH_3$), 22.6 ($CH_2$), 36.0 ($CH_2$), 39.4 (CH), 52.0 ($CH_3$), 126.4 (CH), 127.1 (2 CH), 128.7 (2 CH), 146.5 (C), 168.1 (C). C=$N_2$ was not observed. IR (NaCl) ν 2085, 1731 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{13}H_{17}O_2$: 205.1223 $[M - N_2 + H]^+$; found: 205.1222.

**Representative procedure for the $Pd_2(dba)_3$-catalyzed cyclization reactions (Table 3.2, Entry 1).** A mixture of diazoester **3.5a** (60 mg, 0.17 mmol), $Pd_2(dba)_3$ (3.8 mg, 0.004 mmol), and $Cs_2CO_3$ (110 mg, 0.34 mmol) in $CHCl_3$ (10 mL) was stirred at reflux under Argon atmosphere for 24 h. The reaction mixture was partitioned between a saturated $NaHCO_3$ aqueous solution and $Et_2O$. The organic extracts were dried and concentrated. The residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 97:3) to give pyrrolidine **3.6a** (50 mg, 89%) as a colorless oil.

**Representative procedure for the [(IMes)Pd(NQ)]$_2$-catalyzed cyclization reactions (Table 3.2, Entry 2).** A mixture of diazoester **3.5a** (50 mg, 0.14 mmol), [(IMes)Pd(NQ)]$_2$ (4.0 mg, 0.0035 mmol) in $CHCl_3$ (10 mL) was stirred at reflux under Argon atmosphere for 24 h. The reaction mixture was concentrated and the residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 97:3) to give pyrrolidine **3.6a** (39.5 mg, 85%).

**Representative procedure for the $[Rh(Ph_3CCO_2)_2]_2$-catalyzed cyclization reactions (Table 3.2, Entry 3).** A mixture of diazoester **3.5a** (50 mg, 0.14 mmol), $[Rh(Ph_3CCO_2)_2]_2$ (4.0 mg, 0.003 mmol) in $CH_2Cl_2$ (5 mL) was stirred at room temperature under Argon atmosphere for 5 h. The reaction mixture was concentrated and the residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 97:3) to give pyrrolidine **3.6a** (32.5 mg, 70%).

**Representative procedure for the $[Ru(p\text{-cymene})Cl_2]_2$-catalyzed cyclization reactions (Table 3.2, Entry 4).** A mixture of diazoester **3.5a** (50 mg, 0.14 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (2.6 mg, 0.004 mmol) in toluene (3 mL) was stirred at 40 ºC under Argon atmosphere for 24 h. The reaction mixture was concentrated and the residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 97:3) to give pyrrolidine **3.6a** (30.5 mg, 66%) and aniline **3.8a** (4 mg, 9%).

**Characterization data for compounds of Tables 3.1-3.4 and Figures 3.5, 3.8 and 3.9**

Pyrrolidines **3.2**, **3.6a-i** and **3.10a**-**b**, and tetrahydroquinoline**s 3.3** and **3.7f-g** have been previously described.[57]

**Methyl 2-[(*N*-methyl-*N*-phenylamino)methyl]acrylate (3.4).** Yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.99 (s, 3H), 3.80 (s, 3H), 4.17 (s, 2H), 5.56 (m, 1H), 6.25 (m, 1H), 6.65-6.73 (m, 3H), 7.19-7.26 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 38.5 ($CH_3$), 52.0 ($CH_3$), 54.0 ($CH_2$), 112.1 (2 CH), 116.7 (CH), 125.2 ($CH_2$), 129.3 (2 CH), 135.9 (C), 149.2 (C), 167.2 (C). IR (NaCl) ν 1716 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{12}H_{16}NO_2$: 206.1176 $[M + H]^+$; found: 206.1178.

**Methyl 2-{(*N*-methyl-*N*-[(2-methyl)phenyl]amino)methyl}acrylate (3.4').** Yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3H), 2.65 (s, 3H), 3.73 (s, 3H), 3.75 (t, *J* = 1.6 Hz, 2H), 5.90 (q, *J* = 1.6 Hz, 1H), 6.32 (q, *J* = 1.6 Hz, 1H), 6.96 (td, *J* = 7.6 and 1.6 Hz, 1H), 7.06 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.12-7.17 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 18.4 ($CH_3$), 41.4 ($CH_3$), 51.9 ($CH_3$), 56.9 ($CH_2$), 120.0 (CH), 123.2 (CH), 126.1 ($CH_2$),

126.6 (CH), 131.3 (CH), 133.0 (C), 137.4 (C), 152.2 (C), 167.5 (C). IR (NaCl) ν 1722 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{13}H_{18}NO_2$: 220.1332 $[M + H]^+$; found: 220.1328.

**Methyl 4-[(2-iodophenyl)amino]butanoate (3.8a).** Orange oil. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 2.00 (quintuplet, *J* = 7.2 Hz, 2H), 2.46 (t, *J* = 7.2 Hz, 2H), 3.23 (q, *J* = 7.2 Hz, 2H), 3.70 (s, 3H), 6.44 (ddd, *J* = 8.4, 7.6 and 1.6 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 7.20 (dd, *J* = 8.4 and 7.6 Hz, 1H), 7.65 (dd, *J* = 7.6 and 1.6 Hz, 1H). IR (NaCl) ν 1737 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{11}H_{15}INO_2$: 320.0142 $[M + H]^+$; found: 320.0141.

**Methyl 4-[(2-chlorophenyl)amino]butanoate (3.8c).** Significant signals from a 10:1 mixture of **6c** and **8c** obtained from the crude reaction mixture corresponding to entry 12 of Table 2. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.96-2.03 (m, 2H), 2.46 (t, *J* = 7.2 Hz, 2H), 3.24 (q, *J* = 6.4 Hz, 2H), 3.69 (s, 3H), 6.62 (ddd, *J* = 8.0, 7.6 and 1.2 Hz, 1H), 6.66 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.13 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.24 (dd, *J* = 7.6 and 1.2 Hz, 1H).

**Methyl 4-[(3-chlorophenyl)amino]butanoate (3.8f).** Significant signals from the crude reaction mixture corresponding to entry 24 of Table 2. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.97-2.03 (m, 2H), 2.47 (t, *J* = 7.2 Hz, 2H), 3.23 (q, *J* = 7,2 Hz, 2H), 3.68 (s, 3H).

**Methyl 4-[(4-chlorophenyl)amino]butanoate (3.8h).** Orange oil. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.94 (quintuplet, *J* = 6.8 Hz, 2H), 2.43 (t, *J* = 6.8 Hz, 2H), 3.15 (t, *J* = 6.8 Hz, 2H), 3.68 (s, 3H), 6.48-6.54 (m, 2H), 6.09-7.13 (m, 2H). $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) δ 24.7 ($CH_2$), 31.8 ($CH_2$), 43.6 ($CH_2$), 51.9 ($CH_3$), 113.9 (2 CH), 122.1 (C), 129.2 (2 CH), 146.8 (C), 174.0 (C). HRMS (ESI-TOF) cald for $C_{11}H_{15}ClNO_2$: 228.0785 $[M + H]^+$; found: 228.0807.

**Methyl *cis*-1,2-diphenylpyrrolidine-3-carboxylate (*cis*-3.10c).** Yellow oil. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 2.18 (dtd, *J* = 12.8, 6.4 and 1.0 Hz, 1H), 2.57 (dddd, *J* = 12.8, 12.0, 10.8 and 8.4 Hz, 1H), 3.40 (s, 3H), 3.46 (ddd, *J* = 10.8, 9.2 and 6.4 Hz, 1H), 3.50 (ddd, *J* = 12.0, 9.2 and 6.4 Hz, 1H), 3.85 (td, *J* = 8.4 and 1.0 Hz, 1H), 4.99 (d, *J* = 8.4 Hz, 1H), 6.49 (dd, *J* = 8.4 and 1.2 Hz, 2H), 6.65 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.10-7.30 (m, 7H). $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) δ 25.1 ($CH_2$), 48.0 ($CH_2$), 50.3 (CH), 51.6 ($CH_3$), 64.7

(CH), 112.4 (2 CH), 116.6 (CH), 127.1 (2 CH), 127.9 (CH), 128.5 (2 CH), 129.2 (2 CH), 140.2 (C), 146.5 (C), 171.2 (C). IR (NaCl) ν 1735 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{18}H_{20}NO_2$: 282.1489 $[M + H]^+$; found: 282.1490.

**Methyl *trans*-1,2-diphenylpyrrolidine-3-carboxylate (*trans*-3.10c).** Yellow oil. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 2.25 (dddd, *J* = 12.8, 9.2, 8.0 and 7.2 Hz, 1H), 2.36 (ddt, *J* = 12.8, 7.2 and 3.2 Hz, 1H), 3.02 (dt, *J* = 7.2 and 3.2 Hz, 1H), 3.58 (td, *J* = 9.2 and 7.2 Hz, 1H), 3.73 (s, 3H), 3.75 (ddd, *J* = 9.2, 8.0 and 3.2 Hz, 1H), 5.04 (d, *J* = 3.2 Hz, 1H), 6.48 (dd, *J* = 8.8 and 1.2 Hz, 2H), 6.65 (tt, *J* = 7.2 and 1.2 Hz, 1H), 7.10-7.15 (m, 2H), 7.21-7.34 (m, 5H). $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) δ 26.3 ($CH_2$), 48.4 ($CH_2$), 52.4 ($CH_3$), 53.5 (CH), 65.8 (CH), 112.9 (2 CH), 116.5 (CH), 126.0 (2 CH), 127.3 (CH), 128.9 (2 CH), 129.1 (2 CH), 143.2 (C), 146.8 (C), 174.0 (C). IR (NaCl) ν 1736 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{18}H_{20}NO_2$: 282.1489 $[M + H]^+$; found: 282.1486.

**Methyl *N*-benzyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (3.11).** Yellow oil. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 2.10 (dddd, *J* = 13.2, 10.8, 5.6 and 4.4 Hz, 1H), 2.32 (dq, *J* = 13.2 and 4.0 Hz, 1H), 3.31 (dtd, *J* = 11.6, 4.4 and 1.2 Hz, 1H), 3.57 (ddd, *J* = 11.6, 10.8 and 4.0 Hz, 1H), 3.73 (s, 3H), 3.84 (t, *J* = 4.8 Hz, 1H), 4.51 (s, 2H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.61 (td, *J* = 7.6 and 0.8 Hz,1H), 7.04 (ddd, *J* = 8.0, 7.6 and 1.6 Hz, 1H), 7.12 (dd, *J* = 7.6 and 1.6 Hz, 1H), 7.21-7.34 (m, 5H). $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) δ 24.8 ($CH_2$), 42.8 (CH), 46.7 ($CH_2$), 52.3 ($CH_3$), 55.3 ($CH_2$), 111.8 (CH), 116.1 (CH), 118.0 (C), 126.7 (2 CH), 127.0 (CH), 128.7 (CH), 128.8 (2 CH), 130.2 (CH), 138.7 (C), 145.2 (C), 174.8 (C). IR (film) 1733 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{18}H_{20}NO_2$: 282.1489 $[M + H]^+$; found: 282.1494.

**Methyl 2-[(*N*-benzyl-*N*-phenylamino)methyl]acrylate (3.12).** Significant signals from the crude reaction mixture corresponding to entry 13 of Table 3. $^1H$ RMN ($CDCl_3$, 400 MHz) δ 3.78 (s, 3H), 4.28 (t, *J* = 1.6 Hz, 2H), 4.58 (s, 2H), 5.64 (q, *J* = 1.6 Hz, 1H), 6.29 (q, *J* = 1.6 Hz, 1H).

**Methyl *N*-isopropyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (3.14).** Colorless oil. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.17 (d, *J* = 6.4 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.94 (ddt, *J* = 12.8, 8.4 and 6.0 Hz, 1H), 2.28 (dq, *J* = 12.8 and 4.4 Hz, 1H), 3.18-3.16 (m,

2H), 3.70 (s, 3H), 3.76 (t, *J* = 4.8 Hz, 1H), 4.14 (septuplet, *J* = 6.4 Hz, 1H), 6.59 (td, *J* = 7.6 and 1.2 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 7.07-7.15 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 18.8 ($CH_3$), 19.5 ($CH_3$), 24.9 ($CH_2$), 37.1 ($CH_2$), 43.0 (CH), 47.2 (CH), 52.2 ($CH_3$), 111.5 (CH), 115.4 (CH), 118.9 (C), 128.6 (CH), 130.5 (CH), 145.2 (C), 174.9 (C). IR (NaCl) ν 1735 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{14}H_{20}NO_2$: 234.1489 [M + H]$^+$; found: 234.1490.

**Methyl 2-[(*N*-isopropyl-*N*-phenylamino)methyl]acrylate (3.15).** Colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.17 (d, *J* = 6.8 Hz, 6H), 3.82 (s, 3H), 4.00 (t, *J* = 2.0 Hz, 2H), 4.19 (septuplet, *J* = 6.8 Hz, 1H), 5.70 (q, *J* = 2.0 Hz, 1H), 6.29 (q, *J* = 2.0 Hz, 1H), 6.64-6.70 (m, 3H), 7.17-7.22 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 19.7 (2 $CH_3$), 45.8 ($CH_2$), 47.9 (CH), 52.0 ($CH_3$), 112.9 (2 CH), 116.6 (CH), 125.9 ($CH_2$), 129.3 (2 CH), 137.5 (C), 148.8 (C), 167.2 (C). IR (NaCl) ν 1716 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{14}H_{20}NO_2$: 234.1489 [M + H]$^+$; found: 234.1493.

**Methyl *N*-phenyl-2,2-dimethylpyrrolidine-3-carboxylate (3.16).** Significant signals from a 7:1 mixture of **14** and **16**. $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.09 (dtd, *J* = 12.4, 6.8 and 2.8 Hz, 1H), 2.29-2.36 (m, 1H), 2.92 (dd, *J* = 11.2 and 6.8 Hz, 1H), 3.38 (ddd, *J* = 9.6, 8.8 and 6.8 Hz, 1H), 3.43 (td, *J* = 8.8 and 2.8 Hz, 1H), 3.75 (s, 3H), 6.71 (tt, *J* = 7.2 and 1.2 Hz, 1H), 6.77-6.81 (m, 2H), 7.19-7.24 (m, 2H).

**Methyl *cis*-*N*-benzyl-2-phenylpyrrolidine-3-carboxylate (*cis*-3.18a).** $^1$H NMR ($CDCl_3$, 400 MHz, signals from a ≈ 2.8:1 mixture of *cis*-18 and *trans*-18) δ 1.92 (dddd, *J* = 12.4, 8.8, 6.8 and 1.6 Hz, 1H), 2.26 (ddd, *J* = 10.4, 8.8 and 6.4 Hz, 1H), 2.33-2.43 (m, 1H), 3.08 (s, 3H), 3.11 (d, *J* = 13.4 Hz, 1H), 3.18 (ddd, *J* = 8.4, 7.6 and 1.6 Hz, 1H), 3.27 (ddd, *J* = 10.4, 8.4 and 7.6 Hz, 1H), 3.81 (d, *J* = 9.6 Hz, 1H), 3.87 (d, *J* = 13.4 Hz, 1H), 7.20-7.51 (m, 10H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 2.8:1 mixture of *cis*-18 and *trans*-18) δ 26.4 ($CH_2$), 49.7 (CH), 51.3 ($CH_3$), 52.6 ($CH_2$), 57.7 ($CH_2$), 71.1 (CH), 126.9 (CH), 127.7 (CH), 128.2 (2 CH), 128.3 (2 CH), 128.6 (2 CH), 128.9 (2 CH), 139.1 (C), 139.7 (C), 173.7 (C). IR (film) 1736 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{19}H_{22}NO_2$: 296.1645 [M + H]$^+$; found: 296.1649.

**Methyl *trans*-*N*-benzyl-2-phenylpyrrolidine-3-carboxylate (*trans*-3.18a).** $^{1}$H NMR ($CDCl_3$, 400 MHz, signals from a ≈ 1:1 mixture of *cis* and *trans* isomers) δ 2.04 (dddd, *J* = 12.8, 8.8, 6.0 and 2.4 Hz, 1H), 2.15-2.24 (m, 1H), 2.33-2.43 (m, 1H), 2.92 (ddd, *J* = 11.2, 8.8 and 6.0 Hz, 1H), 3.05 (d, *J* = 13.4 Hz, 1H), 3.06-3.12 (masked m, 1H), 3.63 (s, 3H), 3.66 (d, *J* = 8.4 Hz, 1H), 3.80 (d, *J* = 13.4 Hz, 1H), 7.20-7.51 (m, 10H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 1:1 mixture of *cis* and *trans* isomers) δ 27.5 ($CH_2$), 51.9 ($CH_3$), 52.4 (CH), 52.5 ($CH_2$), 57.9 ($CH_2$), 72.6 (CH), 127.0 (CH), 127.8 (CH), 128.0 (2 CH), 128.4 (2 CH), 128.7 (2 CH), 128.8 (2 CH), 139.5 (C), 141.8 (C), 175.3 (C).

**Methyl 2-[(*N*,*N*-dibenzylamino)methyl]acrylate (3.19).** Colorless oil. $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 3.30 (t, *J* = 1.6 Hz, 2H), 3.58 (s, 4H), 3.71 (s, 3H), 6.00 (q, *J* = 1.6 Hz, 1H), 6.27 (q, *J* = 1.6 Hz, 1H), 7.20-7.40 (m, 10H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 51.9 ($CH_3$), 54.1 ($CH_2$), 58.3 (2 $CH_2$), 126.2 ($CH_2$), 127.1 (CH), 128.4 (2 CH), 128.7 (2 CH), 138.4 (C), 139.5 (C), 167.7 (C). IR (NaCl) ν 1724 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{19}H_{22}NO_2$: 296.1645 $[M + H]^+$; found: 296.1645.

**Methyl *cis*-*N*-(*p*-toluenesulfonyl)-2-phenylpyrrolidine-3-carboxylate (*cis*-3.18b).** Colorless oil. $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 1.98 (dtd, *J* = 12.8, 6.8 and 2.0 Hz, 1H), 2.36-2.47 (m, 1H), 2.41 (s, 3H), 3.10 (ddd, *J* = 11.6, 8.8 and 6.8 Hz, 1H), 3.30 (s, 3H), 3.42 (td, *J* = 10.0 and 6.8 Hz, 1H), 3.81 (ddd, *J* = 10.0, 8.0 and 2.0 Hz, 1H), 5.09 (d, *J* = 8.8 Hz, 1H), 7.12-7.15 (m, 2H), 7.21-7.27 (m, 5H), 7.60-7.63 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 21.7 ($CH_3$), 25.7 ($CH_2$), 48.0 ($CH_2$), 50.1 (CH), 51.7 ($CH_3$), 64.3 (CH), 127.3 (2 CH), 127.6 (2 CH), 128.0 (CH), 128.2 (2 CH), 129.7 (2 CH), 135.1 (C), 138.8 (C), 143.7 (C), 170.2 (C). IR (NaCl) ν 1735 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{19}H_{22}NO_4S$: 360.1264 $[M + H]^+$; found: 360.1265.

**Methyl (*Z*)-4-(*N*-benzyl-*p*-toluenesulfonamido)-2-butenoate (*Z*-3.20).** Colorless oil. $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 2.45 (s, 3H), 3.62 (s, 3H), 4.30 (s, 2H), 4.31 (dd, *J* = 6.0 and 2.0 Hz, 2H), 5.62 (dt, *J* = 11.6 and 2.0 Hz, 1H), 6.03 (dt, *J* = 11.6 and 6.0 Hz, 1H), 7.25-7.35 (m, 7H), 7.71-7.75 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 21.7 ($CH_3$), 47.0 ($CH_2$), 51.4 ($CH_3$), 53.1 ($CH_2$), 120.2 (CH), 127.5 (2 CH), 128.1 (CH), 128.7 (2 CH), 128.8 (2 CH), 130.0 (2 CH), 135.9 (C), 136.4 (C), 143.8 (C), 146.8 (CH), 166.4 (C). IR

(NaCl) ν 1720 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{19}H_{22}NO_4S$: 360.1264 $[M + H]^+$; found: 360.1263.

**Methyl (*E*)-4-(*N*-benzyl-*p*-toluenesulfonamido)-2-butenoate (*E*-3.20).** Significant signals from a ≈ 10:1 mixture of ***E*-3.20** and ***Z*-3.20** obtained from the crude reaction mixture corresponding to entry 7 of Table 4. $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.45 (s, 3H), 3.68 (s, 3H), 3.85 (dd, *J* = 6.0 and 1.6 Hz, 2H), 4.33 (s, 2H), 5.70 (dt, *J* = 16.0 and 1.6 Hz, 1H), 6.56 (dt, *J* = 16.0 and 6.0 Hz, 1H), 7.20-7.35 (m, 7H), 7.71-7.75 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 21.7 ($CH_3$), 47.6 ($CH_2$), 51.4 ($CH_3$), 51.8 ($CH_2$), 123.8 (CH), 127.4 (2 CH), 128.2 (CH), 128.7 (2 CH), 128.9 (2 CH), 130.1 (2 CH), 135.4 (C), 137.1 (C), 142.3 (CH), 143.9 (C), 166.1 (C).

**Methyl 4-(*N*-benzyl-*N*-(*p*-toluenesulfonyl)amino)-2-oxobutanoate (3.21).** Pale yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.45 (s, 3H), 2.95 (t, *J* = 7.2 Hz, 2H), 3.38 (t, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 4.30 (s, 2H), 7.26-7.36 (m, 7H), 7.71-7.74 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 21.7 ($CH_3$), 39.7 ($CH_2$), 42.8 ($CH_2$), 53.2 ($CH_3$), 53.4 ($CH_2$), 127.5 (2 CH), 128.2 (CH), 128.6 (2 CH), 129.0 (2 CH), 130.1 (2 CH), 136.0 (C), 136.2 (C), 143.9 (C), 160.5 (C), 192.0 (C). IR (NaCl) ν 1732, 1598 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{19}H_{25}N_2O_5S$: 393.1479 $[M + NH_4]^+$; found: 393.1473.

**Methyl *cis*-2-phenyltetrahydrofuran-3-carboxylate (*cis*-3.23).** An analytical sample of ***cis*-3.23** was obtained by additional flash chromatography of the 7:1 mixture of ***cis*-3.23/*trans*-3.23**. Pale yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.14-2.23 (m, 1H), 2.41-2.50 (m, 1H), 3.19 (s, 3H), 3.39 (td, *J* = 8.0 and 6.0 Hz, 1H), 3.94 (q, *J* = 8.0 Hz, 1H), 4.40 (td, *J* = 8.4 and 4.8 Hz, 1H), 5.14 (d, *J* = 8.0 Hz, 1H), 7.21-7.36 (m, 5H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 29.1 ($CH_2$), 50.3 (CH), 51.4 ($CH_3$), 68.7 ($CH_2$), 82.8 (CH), 126.3 (2 CH), 127.9 (CH), 128.1 (2 CH), 139.0 (C), 172.6 (C). IR (NaCl) ν 1735 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{12}H_{18}NO_3$: 224.1281 $[M + NH_4]^+$; found: 224.1278.

**Methyl *trans*-2-phenyltetrahydrofuran-3-carboxylate (*trans*-3.23).** An analytical sample of ***trans*-3.23** was obtained by additional flash chromatography of the 1:1.8 mixture of ***cis*-3.23/*trans*-3.23**. Pale yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.25-2.38 (m, 2H), 2.98 (dt, *J* = 8.8 and 7.2 Hz, 1H), 3.72 (s, 3H), 4.04 (dt, *J* = 8.4 and 7.2 Hz, 1H),

4.17 (ddd, *J* = 8.4, 7.2 and 6.0 Hz, 1H), 5.06 (d, *J* = 7.2 Hz, 1H), 7.23-7.36 (m, 5H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 30.9 ($CH_2$), 52.3 ($CH_3$), 52.4 (CH), 68.6 ($CH_2$), 83.5 (CH), 125.9 (2 CH), 127.9 (CH), 128.6 (2 CH), 141.5 (C), 174.0 (C).

**Methyl *Z*-5-phenyl-2-hexenoate (*Z*-3.25).** Colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.29 (d, *J* = 6.4 Hz, 3H), 2.83-2.94 (m, 2H), 3.00-3.10 (m, 1H), 3.70 (s, 3H), 5.75 (dt, *J* = 11.6 and 1.6 Hz, 1H), 6.12 (ddd, *J* = 11.6, 7.8 and 6.6 Hz, 1H), 7.16-7.32 (m, 5H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 22.2 ($CH_3$), 37.2 ($CH_2$), 40.0 (CH), 51.2 ($CH_3$), 120.2 (CH), 126.4 (CH), 127.2 (2 CH), 128.6 (2 CH), 146.4 (C), 149.1 (CH), 167.0 (C). IR (NaCl) ν 1723 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{13}H_{17}O_2$: 205.1223 $[M + H]^+$; found: 205.1222.

**Methyl *E*-5-phenyl-2-hexenoate (*E*-3.25).** Pale yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.29 (d, *J* = 6.8 Hz, 3H), 2.43 (dtd, *J* = 14.4, 7.6 and 1.6 Hz, 1H), 2.53 (dtd, *J* = 14.4, 7.0 and 1.6 Hz, 1H), 2.84-2.94 (m, 1H), 3.70 (s, 3H), 5.79 (dt, *J* = 15.6 and 1.6 Hz, 1H), 6.88 (ddd, *J* = 15.6, 7.6 and 7.2 Hz, 1H), 7.17-7.22 (m, 3H), 7.27-7.33 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 21.9 ($CH_3$), 39.3 (CH), 41.1 ($CH_2$), 51.6 ($CH_3$), 122.5 (CH), 126.5 (CH), 127.0 (2 CH), 128.7 (2 CH), 146.2 (C), 147.8 (CH), 167.1 (C).

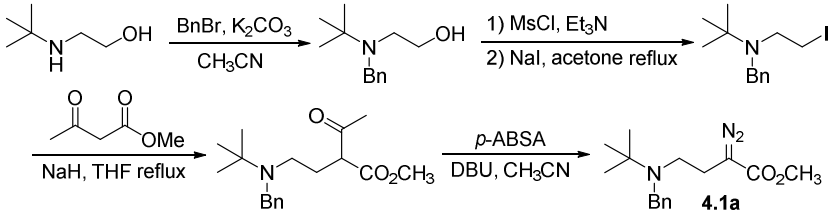
**Methyl 1-methyl-2,3-dihydroazulene-3a(1*H*)-carboxylate (3.26).** $^1$H NMR ($CDCl_3$, 400 MHz, 1.5:1 mixture of stereoisomers, only the most significant signals are described) δ 1.11 (d, *J* = 6.4 Hz, 3H minor stereoisomer), 1.31 (d, *J* = 6.8 Hz, 3H major stereoisomer), 3.47 (s, 3H minor stereoisomer), 3.49 (s, 3H major stereoisomer), 5.22 (d, *J* = 9.2 Hz, 1H minor stereoisomer), 5.30 (d, *J* = 9.6 Hz, 1H major stereoisomer), 6.20-6.34 (m, 2H major and 2H minor stereoisomer), 6.40-6.49 (m, 1H major and 1H minor stereoisomer), 6.53 (dd, *J* = 11.2 and 6.4 Hz, 1H major stereoisomer), 6.62 (dd, *J* = 11.2 and 6.4 Hz, 1H minor stereoisomer). IR (NaCl) ν 1731 cm$^{-1}$.

**Methyl 2-oxo-5-phenylhexanoate (3.27).** $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.28 (d, *J* = 6.8 Hz, 3H), 1.85-2.00 (m, 2H), 2.63-2.81 (m, 3H), 3.82 (s, 3H), 7.15-7.22 (m, 3H), 7.27-7.32 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 22.5 ($CH_3$), 31.3 ($CH_2$), 37.8 ($CH_2$), 39.4 (CH), 53.0 ($CH_3$), 126.5 (CH), 127.2 (2 CH), 128.8 (2 CH), 146.1 (C), 161.6 (C), 194.3 (C).

## 8.3. Experimental Part of Chapter 4

### Experimental procedures and characterization data for the starting materials

**METHOD A: Methyl 4-(*N*-benzyl-*N*-*tert*-butylamino)-2-diazobutanoate (4.1a).**




Benzyl bromide (2.3 mL, 19.5 mmol) and $K_2CO_3$ (3.5 g, 25.5 mmol) were added, under argon, to a solution of *N*-*tert*-butylethanolamine (1.5 g, 12.7 mmol) in $CH_3CN$ (26 mL). The resulting mixture was stirred at 80 ºC for 24 h. The solvent was removed *in vacuo* and the residue was partitioned between dichloromethane and water. The combined organic extracts were dried, filtered and concentrated, and the residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 4:1) to give 2-(*N*-benzyl-*N*-*tert*-butylamino)ethanol (2.3 g, 86%) as a colorless oil.

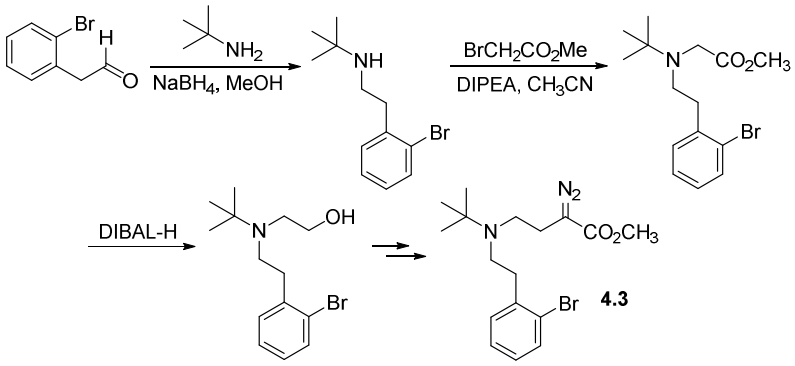
2-(*N*-Benzyl-*N*-*tert*-butylamino)ethanol (2.3 g, 11.0 mmol) and triethylamine (2.3 mL, 16.4 mmols) were dissolved in $CH_2Cl_2$ (22 mL), and methanesulfonyl chloride (1.8 mL, 23.3 mmols) was added dropwise at 0 ºC. The resulting solution was stirred at room temperature for 3 h. The reaction mixture was poured into water and ice, basified with a saturated $NaHCO_3$ aqueous solution, and extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried, filtered and concentrated. The residue was dissolved in acetone (82 mL), and NaI (16.5 g, 111 mmols) was added. The mixture was stirred at reflux for 24 h, concentrated *in vacuo* and the residue was partitioned between water and $Et_2O$. The organic extracts were washed with water, dried, filtered and concentrated to give *N*-benzyl-*N*-(2-iodoethyl)-*tert*-butylamine (3.4 g, quantitative), which was used in the next step without purification.

A solution of methyl 3-oxobutanoate (6.8 mL, 62.7 mmols) in dry THF (50 mL) was added dropwise, under an argon atmosphere, to a stirred suspension of NaH (1.5 g, 62.7 mmols) in dry THF (50 mL) at room temperature. After the mixture became clear (5

min), a solution of *N*-(2-iodoethyl)-*N*-benzyl-*tert*-butylamine (3.4 g) in dry THF (10 mL) was added dropwise, and the mixture was stirred at 80 ºC for 96 h. The reaction mixture was poured into a mixture of saturated ammonium chloride aqueous solution and ice, and extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 9:1) to give methyl 2-acetyl-4-(*N*-benzyl-*N*-*tert*-butylamino)butanoate (1.53 g, 47% for two steps) as a colorless oil.

To a solution of methyl 2-acetyl-4-(*N*-benzyl-*N*-*tert*-butylamino)butanoate (1.53 g, 5.0 mmols) and DBU (1.12 mL, 7.3 mmols) in dry acetonitrile (25 mL) was added dropwise a solution of *p*-ABSA (1.56 g, 6.5 mmols) in dry acetonitrile (22 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was purified by chromatography ($SiO_2$, $CH_2Cl_2$) to give **4.1a** (0.9 g, 62%) as a yellow oil. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.14 (s, 9H), 1.99 (t, *J* = 7.0 Hz, 2H), 2.73 (t, *J* = 7.0 Hz, 2H), 3.65 (s, 3H), 3.68 (s, 2H), 7.20 (ddt, *J* = 8.0, 6.4 and 1.6 Hz, 1H), 7.25-7.35 (m, 4H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 25.4 ($CH_2$), 27.4 (3 $CH_3$), 49.4 ($CH_2$), 51.8 ($CH_3$), 55.4 ($CH_2$), 55.5 (C), 68.1 (C), 126.6 (CH), 128.2 (2 CH), 128.4 (2 CH), 142.7 (C). One C was not observed. IR (NaCl) ν 2082, 1695 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{16}H_{24}N_3O_2$: 290.1863 $[M + H]^+$; found: 290.1867.

**METHOD B: Methyl 4-(*N*-[2-(2-bromophenyl)ethyl]-*N*-*tert*-butylamino)-2-diazobutanoate (4.3).**




A solution of 2-bromoacetaldehyde (1.3 g, 6.5 mmol) in methanol (14 mL) was cooled in an ice bath. *tert*-Butylamine (0.69 mL, 6.5 mmol) was added, and the mixture was stirred

at room temperature for 3 h. Sodium borohydride (0.3 g, 7.79 mmol) was added slowly to the reaction mixture, which was maintained at 0 ºC by using an ice bath. After the addition, the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was dissolved in water, and then extracted with $CH_2Cl_2$. The organic extracts were dried, filtered and concentrated to give crude *N*-[2-(2-bromophenyl)ethyl]-*tert*-butylamine (1.35 g) as a colorless oil, which was used in the next step without purification.

A solution of *N*-[2-(2-bromophenyl)ethyl]-*tert*-butylamine (1.35 g), diisopropylethylamine (1.4 mL, 8.0 mmol), and methyl bromoacetate (1.3 mL, 13.8 mmol) in acetonitrile (34 mL) was refluxed for 24 h. The solvent was removed in vacuo, and the residue was dissolved in dichloromethane and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried and concentrated. The residue was purified by chromatography ($SiO_2$, from hexanes to 9:1 hexanes/EtOAc) to give methyl 2-(*N*-[2-(2-bromophenyl)ethyl]-*N*-*tert*-butylamino)acetate (1.0 g, 47% for two steps) as a colorless oil.

To a cooled (-30 ºC) solution of methyl 2-(*N*-[2-(2-bromophenyl)ethyl]-*N*-*tert*-butylamino)acetate (1.0 g, 3.05 mmol) in $CH_2Cl_2$ (60 mL), DIBAL-H (5.2 mL of 25% solution in toluene, 7.8 mmol) was added dropwise. After 3 h at room temperature, the reaction mixture was poured into a saturated $NH_4Cl$ aqueous solution and stirring was continued for 1.5 h. The mixture was extracted with $CH_2Cl_2$ and the organic layer was washed with saturated $NaHCO_3$ aqueous solution. The organic extracts were dried and the solvent was removed under vacuum to give 2-(*N*-[2-(2-bromophenyl)ethyl]-*N*-*tert*-butylamino)ethanol (0.8 g), which was used in the next step without purification.

2-(*N*-[2-(2-Bromophenyl)ethyl]-*N*-*tert*-butylamino)ethanol (0.8 g) and triethylamine (0.56 mL, 4.1 mmols) were dissolved in $CH_2Cl_2$ (5 mL), and methanesulfonyl chloride (0.26 mL, 3.4 mmols) was added dropwise at 0 ºC. The resulting solution was stirred at room temperature for 3 h. The reaction mixture was poured into water and ice, basified with a saturated $NaHCO_3$ aqueous solution, and extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried, filtered and concentrated. The residue was dissolved in acetone (24 mL), and NaI (5 g, 31 mmols) was added. The mixture was

stirred at reflux for 24 h, concentrated *in vacuo* and the residue was partitioned between water and $Et_2O$. The organic extracts were washed with water, dried, filtered and concentrated to give *N*-[2-(2-bromophenyl)ethyl]-*N*-(2-iodoethyl)-*tert*-butylamine (0.87 g), which was used in the next step without purification.

A solution of methyl 3-oxobutanoate (1.4 mL, 12.7 mmols) in dry THF (11 mL) was added dropwise, under an argon atmosphere, to a stirred suspension of NaH (0.3 g, 12.7 mmols) in dry THF (11 mL) at room temperature. After the mixture became clear (5 min), a solution of *N*-[2-(2-bromophenyl)ethyl]-*N*-(2-iodoethyl)-*tert*-butylamine (0.87 g) in dry THF (11 mL) was added dropwise, and the mixture was stirred at 80 ºC for 96 h. The reaction mixture was poured into a mixture of saturated ammonium chloride aqueous solution and ice, and then extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 4:1) to give methyl 2-acetyl-4-(*N*-[2-(2-bromophenyl)ethyl]-*N*-*tert*-butylamino)butanoate (0.45 g, 37% for three steps) as a colorless oil.

To a solution of methyl 2-acetyl-4-(*N*-[2-(2-bromophenyl)ethyl]-*N*-*tert*-butylamino)butanoate (0.45 g, 1.1 mmols) and DBU (0.25 mL, 1.7 mmols) in dry acetonitrile (5 mL) was added dropwise a solution of *p*-ABSA (0.35 g, 1.5 mmols) in dry acetonitrile (5 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was purified by chromatography ($SiO_2$, $CH_2Cl_2$) to give **4.3** (324 mg, 75%) as a yellow oil. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.10 (s, 9H), 2.44 (t, *J* = 6.8 Hz, 2H), 2.69-2.74 (m, 2H), 2.79 (t, *J* = 6.8 Hz, 2H), 2.83-2.88 (m, 2H), 3.77 (s, 3H), 7.05 (ddd, *J* = 8.0, 6.0 and 3.2 Hz, 1H), 7.20-7.25 (m, 2H), 7.51 (dd, *J* = 8.0 and 0.8 Hz, 1H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 25.3 ($CH_2$), 27.5 (3 $CH_3$), 38.6 ($CH_2$), 49.0 ($CH_2$), 51.4 ($CH_2$), 52.0 ($CH_3$), 55.4 (C), 124.6 (C), 127.7 (CH), 127.9 (CH), 131.1 (CH), 132.9 (CH), 140.2 (C). Two C were not observed. IR (NaCl) ν 2083, 1693 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{17}H_{25}BrN_3O_2$: 382.1125 $[M + H]^+$; found: 382.1133.

**Methyl 4-[*N*-*tert*-butyl-*N*-(4-chlorobenzyl)amino]-2-diazobutanoate (4.1b). 4.1b** was obtained as a yellowish oil following Method A [(a) alkylation, 80%; (b) MsCl, $Et_3N$;

then NaI; (c) $CH_3COCH_2CO_2CH_3$, NaH, 50% two steps; (d) *p*-ABSA, DBU, 60%]. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.12 (s, 9H), 2.05 (t, *J* = 6.8 Hz, 2H), 2.72 (t, *J* = 6.8 Hz, 2H), 3.63 (s, 2H), 3.65 (s, 3H), 7.22-7.29 (m, 4H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 25.5 ($CH_2$), 27.4 (3 $CH_3$), 49.2 ($CH_2$), 51.9 ($CH_3$), 54.7 ($CH_2$), 55.6 (C), 66.4 (C), 128.3 (2 CH), 128.7 (C), 129.6 (2 CH), 141.3 (C). One C was not observed. IR (NaCl) ν 2083, 1694 cm$^{-1}$.

**Methyl 4-[*N*-*tert*-butyl-*N*-(2-fluorobenzyl)amino]-2-diazobutanoate (4.1c). 4.1c** was obtained as a yellowish oil following Method A [(a) alkylation; (b) MsCl, $Et_3N$; then NaI; (c) $CH_3COCH_2CO_2CH_3$, NaH, 56% three steps; (d) *p*-ABSA, DBU, 80%]. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.13 (s, 9H), 2.06 (t, *J* = 7.2 Hz, 2H), 2.76 (t, *J* = 7.2 Hz, 2H), 3.66 (s, 3H), 3.75 (s, 2H), 6.97 (ddd, *J* = 10.8, 8.0 and 1.2 Hz, 1H), 7.08 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.18 (dddd, *J* = 8.0, 7.6, 5.2 and 1.6 Hz, 1H), 7.50 (td, *J* = 7.6 and 1.6 Hz, 1H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 25.3 ($CH_2$), 27.3 (3 $CH_3$), 47.7 (d, *J* = 2.7 Hz, $CH_2$), 49.3 ($CH_2$), 51.9 ($CH_3$), 55.6 (C), 65.6 (C), 115.0 (d, *J* = 22.0 Hz, CH), 123.9 (d, *J* = 3.5 Hz, CH), 128.1 (d, *J* = 8.2 Hz, CH), 129.4 (d, *J* = 13.4 Hz, C), 130.9 (d, *J* = 4.6 Hz, CH), 160.9 (d, *J* = 245.1 Hz, C). One C was not observed. IR (NaCl) ν 2083, 1696 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{16}H_{23}FN_3O_2$: 308.1774 $[M + H]^+$; found: 308.1770.

**Methyl 4-[*N*-(2-bromobenzyl)-*N*-*tert*-butylamino]-2-diazobutanoate (4.1d). 4.1d** was obtained as a brownish oil following Method A [(a) alkylation, 70%; (b) MsCl, $Et_3N$; then NaI; (c) $CH_3COCH_2CO_2CH_3$, NaH, 25% two steps; (d) *p*-ABSA, DBU, 65%]. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.12 (s, 9H), 2.13 (t, *J* = 7.2 Hz, 2H), 2.80 (t, *J* = 7.2 Hz, 2H), 3.69 (s, 3H), 3.78 (s, 2H), 7.06 (ddd, *J* = 8.0, 7.6 and 1.6 Hz, 1H), 7.26 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.47 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.67 (dd, *J* = 7.6 and 1.6 Hz, 1H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 25.1 ($CH_2$), 27.3 (3 $CH_3$), 49.6 ($CH_2$), 51.9 ($CH_3$), 54.7 ($CH_2$), 55.7 (C), 66.5 (C), 123.1 (C), 127.2 (CH), 128.0 (CH), 130.6 (CH), 132.4 (CH), 141.6 (C), 168.1 (C). IR (NaCl) ν 2082, 1696 cm$^{-1}$.

**Methyl 4-[*N*-*tert*-butyl-*N*-(2-methoxybenzyl)amino]-2-diazobutanoate (4.1e). 4.1e** was obtained as a brownish oil following Method A [(a) alkylation, 68%; (b) MsCl, $Et_3N$; then NaI; (c) $CH_3COCH_2CO_2CH_3$, NaH, 23% two steps; (d) *p*-ABSA, DBU, 66%]. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.12 (s, 9H), 2.08 (t, *J* = 7.0 Hz, 2H), 2.76 (t, *J* = 7.0 Hz, 2H),

3.67 (s, 3H), 3.72 (s, 2H), 3.82 (s, 3H), 6.80 (dd, *J* = 8.0 and 1.2 Hz, 1H), 6.91 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.17 (tdd, *J* = 8.0, 7.6 and 1.6 Hz, 1H), 7.52 (dd, *J* = 7.6 and 1.6 Hz, 1H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 25.0 ($CH_2$), 27.3 (3 $CH_3$), 48.7 ($CH_2$), 49.4 ($CH_2$), 51.8 ($CH_3$), 55.3 ($CH_3$), 55.4 (C), 109.9 (CH), 120.4 (CH), 127.3 (CH), 129.9 (CH), 130.9 (C), 157.0 (C), 168.3 (C). One C was not observed. IR (NaCl) ν 2083, 1696 $cm^{-1}$.

**Methyl 4-(*N*-[2-(benzyloxy)ethyl]-*N*-*tert*-butylamino)-2-diazobutanoate (4.5). 4.5** was obtained from *N*-[2-(benzyloxy)ethyl]-*tert*-butylamine as a yellow oil following Method B [(a) $BrCH_2CO_2Me$; (b) DIBAL-H, 43% two steps; (c) MsCl, $Et_3N$; then NaI; (d) $CH_3COCH_2CO_2CH_3$, NaH, 18% two steps; (e) *p*-ABSA, DBU, 53%]. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.04 (s, 9H), 2.35 (t, *J* = 6.8 Hz, 2H), 2.69 (t, *J* = 6.8 Hz, 2H), 2.76 (t, *J* = 6.8 Hz, 2H), 3.45 (t, *J* = 6.8 Hz, 2H), 3.74 (s, 3H), 4.50 (s, 2H), 7.26-7.33 (m, 5H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 25.0 ($CH_2$), 27.2 (3 $CH_3$), 50.1 ($CH_2$), 50.7 ($CH_2$), 52.0 ($CH_3$), 55.2 (C), 72.1 ($CH_2$), 73.3 ($CH_2$), 127.7 (CH), 127.8 (2 CH), 128.5 (2 CH), 138.6 (C). Two C were not observed. IR (NaCl) ν 2083, 1693 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{18}H_{28}N_3O_3$: 334.2131 $[M + H]^+$; found: 334.2130.

**Methyl 4-(*N*-*tert*-butyl-*N*-[3-phenylpropyl]amino)-2-diazobutanoate (4.7). 4.7** was obtained from 3-phenylpropanal as a yellowish oil following Method B [(a) $^t$BuNH$_2$; then $NaBH_4$; (b) $BrCH_2CO_2Me$; (c) DIBAL-H; (d) MsCl, $Et_3N$; then NaI, 44% four steps; (e) $CH_3COCH_2CO_2CH_3$, NaH, 80% two steps; (f) *p*-ABSA, DBU, 68%]. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.03 (s, 9H), 1.71-1.79 (m, 2H), 2.31 (t, *J* = 6.8 Hz, 2H), 2.52 (t, *J* = 7.6 Hz, 2H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.66 (t, *J* = 6.8 Hz, 2H), 3.71 (s, 3H), 7.14-7.19 (m, 3H), 7.24-7.29 (m, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 25.6 ($CH_2$), 27.3 (3 $CH_3$), 32.9 ($CH_2$), 33.8 ($CH_2$), 49.1 ($CH_2$), 50.7 ($CH_2$), 52.0 ($CH_3$), 55.2 (C), 125.8 (CH), 128.4 (2 CH), 128.5 (2 CH), 142.4 (C), 169.2 (C). One C was not observed. IR (NaCl) ν 2082, 1694 $cm^{-1}$.

**Methyl 4-[*N*-benzyl-*N*-(2-iodobenzyl)amino]-2-diazobutanoate (4.9a). 4.9a** was obtained from *N*-(2-iodobenzyl)ethanolamine as a yellow oil following Method A [(a) alkylation; (b) MsCl, $Et_3N$; then NaI, 40% two steps; (c) $CH_3COCH_2CO_2CH_3$, NaH, 25%; (d) *p*-ABSA, DBU, 80%]. $^1$H RMN ($CDCl_3$, 400 MHz) δ 2.37 (t, *J* = 6.8 Hz, 2H), 2.65 (t, *J* = 6.8 Hz, 2H), 3.65 (s, 3H), 3.65 (s, 2H), 3.66 (s, 2H), 6.92 (td, *J* = 8.0 and 1.6

Hz, 1H), 7.20-7.35 (m, 6H), 7.50 (dd, *J* = 8.0 and 1.6 Hz, 1H), 7.80 (dd, *J* = 7.6 and 1.2 Hz, 1H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 22.2 ($CH_2$), 51.8 ($CH_2$), 51.9 ($CH_3$), 58.9 ($CH_2$), 63.1 ($CH_2$), 66.4 (C), 100.4 (C), 127.2 (CH), 128.3 (CH), 128.5 (2 CH), 128.9 (CH), 129.0 (2 CH), 130.2 (CH), 139.0 (C), 139.5 (CH), 141.4 (C), 167.9 (C). IR (NaCl) ν 2081, 1691 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{19}H_{21}IN_3O_2$: 450.0673 $[M + H]^+$; found: 450.0686.

**Methyl 4-[*N*-benzyl-*N*-(2-fluorobenzyl)amino]-2-diazobutanoate (4.9b). 4.9b** was obtained from *N*-(2-fluorobenzyl)ethanolamine as a yellow oil following Method A [(a) alkylation; (b) MsCl, $Et_3N$; then NaI; (c) $CH_3COCH_2CO_2CH_3$, NaH, 55% three steps; (d) *p*-ABSA, DBU, 72%]. $^1$H RMN ($CDCl_3$, 400 MHz) δ 2.39 (t, *J* = 6.4 Hz, 2H), 2.65 (t, *J* = 6.4 Hz, 2H), 3.60 (s, 2H), 3.64 (s, 2H), 3.66 (s, 3H), 7.01 (ddd, *J* = 10.4, 7.6 and 1.2 Hz, 1H), 7.10 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.18-7.33 (m, 6H), 7.39 (td, *J* = 7.6 and 1.6 Hz, 1H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 22.2 ($CH_2$), 51.1 (d, *J* = 2.1 Hz, $CH_2$), 51.7 ($CH_2$), 51.9 ($CH_3$), 58.9 ($CH_2$), 115.4 (d, *J* = 22.3 Hz, CH), 124.1 (d, *J* = 3.6 Hz, CH), 125.9 (d, *J* = 14.4 Hz, C), 127.2 (CH), 128.4 (2 CH), 128.7 (d, *J* = 8.2 Hz, CH), 128.9 (2 CH), 131.2 (d, *J* = 4.5 Hz, CH), 139.3 (C), 161.6 (d, *J* = 245.8 Hz, C). Two C were not observed. IR (NaCl) ν 2082, 1692 cm$^{-1}$.

**Methyl 4-(*N*-benzyl-*N*-isopropylamino)-2-diazobutanoate (4.11). 4.11** was obtained from *N*-isopropylethanolamine as a yellow oil following Method A [(a) alkylation, 60%; (b) MsCl, $Et_3N$; then NaI; (c) $CH_3COCH_2CO_2CH_3$, NaH, 58% two steps; (d) *p*-ABSA, DBU, 81%]. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.01 (d, *J* = 6.8 Hz, 2H), 2.25 (t, *J* = 6.4 Hz, 2H), 2.59 (t, *J* = 6.4 Hz, 2H), 2.93 (hept, *J* = 6.8 Hz, 1H), 3.56 (s, 2H), 3.67 (s, 3H), 7.18-7.30 (m, 5H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 17.9 (2 $CH_3$), 23.4 ($CH_2$), 47.9 ($CH_2$), 50.1 (CH), 51.9 ($CH_3$), 54.5 ($CH_2$), 126.8 (CH), 128.3 (2 CH), 128.6 (2 CH), 140.9 (C). Two C were not observed. IR (NaCl) ν 2083, 1694 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{15}H_{22}N_3O_2$: 276.1707 $[M + H]^+$; found: 276.1712.

**Methyl (*E*)-4-[*N*-(2-butenyl)-*N*-*tert*-butylamino]-2-diazobutanoate (4.14). 4.14** was obtained from *E*-2-butenal as a brown oil following Method B [(a) $^t$BuNH$_2$; then $NaBH_4$; (b) $BrCH_2CO_2Me$, 50% two steps; (c) DIBAL-H; (d) MsCl, $Et_3N$; then NaI; (e) $CH_3COCH_2CO_2CH_3$, NaH, 41% three steps; (f) *p*-ABSA, DBU, 60%]. $^1$H RMN ($CDCl_3$,

400 MHz) δ 1.06 (s, 9H), 1.66 (d, *J* = 5.2 Hz, 3H), 2.32 (broad t, *J* = 7.6 Hz, 2H), 2.67 (broad t, *J* = 7.6 Hz, 2H), 3.10 (broad s, 2H), 3.75 (s, 3H), 5.44-5.55 (broad signal, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 17.9 ($CH_3$), 25.1 ($CH_2$), 27.4 (3 $CH_3$), 47.9 ($CH_2$), 51.9 ($CH_3$), 52.5 ($CH_2$), 55.1 (C), 126.4 (CH), 131.7 (CH). Two C were not observed. IR (NaCl) ν 2082, 1696 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{13}H_{24}N_3O_2$: 254.1863 $[M + H]^+$; found: 254.1872.

**Methyl 4-[*N*-*tert*-butyl-*N*-(2-methyl-2-propenyl)amino]-2-diazobutanoate (4.16a). 4.16a** was obtained as a brown oil following Method A [(a) alkylation; (b) MsCl, $Et_3N$; then NaI; (c) $CH_3COCH_2CO_2CH_3$, NaH, 65% three steps; (d) *p*-ABSA, DBU, 67%]. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.05 (s, 9H), 1.70 (dd, *J* = 1.2 and 0.8 Hz, 3H), 2.26 (t, *J* = 7.2 Hz, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.98 (broad s, 2H), 3.73 (s, 3H), 4.74 (q, *J* = 1.2 Hz, 1H), 4.93 (q, *J* = 0.8 Hz, 1H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 20.6 ($CH_3$), 25.4 ($CH_2$), 27.2 (3 $CH_3$), 49.5 ($CH_2$), 51.9 ($CH_3$), 55.1 (C), 57.7 ($CH_2$), 111.4 ($CH_2$), 146.4 (C), 168.4 (C). One C was not observed. IR (NaCl) ν 2082, 1697 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{13}H_{24}N_3O_2$: 254.1863 $[M + H]^+$; found: 254.1866.

**Methyl 4-[*N*-(2-bromo-2-propenyl)-*N*-*tert*-butylamino]-2-diazobutanoate (4.16b). 4.16b** was obtained as a brown oil following Method A [(a) alkylation; (b) MsCl, $Et_3N$; then NaI; (c) $CH_3COCH_2CO_2CH_3$, NaH, 46% three steps; (d) *p*-ABSA, DBU, 74%]. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.08 (s, 9H), 2.34 (t, *J* = 7.2 Hz, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 3.32 (m, 2H), 3.75 (s, 3H), 5.50 (m, 1H), 6.04 (m, 1H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 25.3 ($CH_2$), 27.2 (3 $CH_3$), 49.6 ($CH_2$), 52.0 ($CH_3$), 55.4 (C), 60.0 ($CH_2$), 116.6 ($CH_2$), 136.0 (C), 168.0 (C). One C was not observed. IR (NaCl) ν 2084, 1694 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{12}H_{21}BrN_3O_2$: 310.1945 $[M + H]^+$; found: 310.1953.

**Methyl 4-[*N*-*tert*-butyl-*N*-(2-iodo-2-propenyl)amino]-2-diazobutanoate (4.16c). 4.16c** was obtained as a brown oil following Method A [(a) alkylation; (b) MsCl, $Et_3N$; then NaI; (c) $CH_3COCH_2CO_2CH_3$, NaH, 40% three steps; (d) *p*-ABSA, DBU, 55%]. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.07 (s, 9H), 2.33 (m, 2H), 2.70 (t, *J* = 7.6 Hz, 2H), 3.27 (t, *J* = 1.6 Hz, 2H), 3.74 (s, 3H), 5.79 (m, 1H), 6.50 (m, 1H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 25.3

($CH_2$), 27.3 (3 $CH_3$), 49.4 ($CH_2$), 52.0 ($CH_3$), 55.4 (C), 63.9 ($CH_2$), 124.9 ($CH_2$), 150.5 (C), 173.4 (C). One C was not observed. IR (NaCl) ν 2083, 1693 $cm^{-1}$.

**Methyl (*Z*)-4-(*N*-*tert*-butyl-*N*-propargylamino)-2-diazobutanoate (4.18a). 4.18a** was obtained as a brownish oil following Method A [(a) alkylation; (b) MsCl, $Et_3N$; then NaI; (c) $CH_3COCH_2CO_2CH_3$, NaH, 35% two steps; (d) *p*-ABSA, DBU, 60%]. $^1H$ RMN ($CDCl_3$, 400 MHz) δ 1.12 (s, 9H), 2.15 (t, *J* = 2.4 Hz, 1H), 2.41 (t, *J* = 6.8 Hz, 2H), 2.84 (t, *J* = 6.8 Hz, 2H), 3.47 (broad, 2H), 3.76 (s, 3H). $^{13}C$ RMN ($CDCl_3$, 100.5 MHz) δ 23.4 ($CH_2$), 27.5 (3 $CH_3$), 36.9 ($CH_2$), 45.9 ($CH_2$), 52.0 ($CH_3$), 55.4 (C), 72.2 (CH), 82.7 (C), 168.3 (C). One C was not observed. IR (NaCl) ν 2083, 1693 $cm^{-1}$.

**Methyl 4-[*N*-*tert*-butyl-*N*-(2-butynyl)amino]-2-diazobutanoate (4.18b). 4.18b** was obtained as a yellowish oil following Method A [(a) alkylation; (b) MsCl, $Et_3N$; then NaI; (c) $CH_3COCH_2CO_2CH_3$, NaH, 58% three steps; (d) *p*-ABSA, DBU, 79%]. $^1H$ RMN ($CDCl_3$, 400 MHz) δ 1.10 (s, 9H), 1.78 (t, *J* = 2.4 Hz, 3H), 2.41 (t, *J* = 6.8 Hz, 2H), 2.80 (t, *J* = 6.8 Hz, 2H), 3.39 (q, *J* = 2.4 Hz, 2H), 3.76 (s, 3H). $^{13}C$ RMN ($CDCl_3$, 100.5 MHz) δ 3.7 ($CH_3$), 23.7 ($CH_2$), 27.5 (3 $CH_3$), 37.4 ($CH_2$), 46.1 ($CH_2$), 52.0 ($CH_3$), 55.2 (C), 77.6 (C), 79.4 (C), 168.4 (C). One C was not observed. IR (NaCl) ν 2083, 1694 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{13}H_{22}N_3O_2$: 252.1712 $[M + H]^+$; found: 252.1717.

**Methyl 4-(*N*-*tert*-butyl-*N*-[3-(trimethylsilyl)-2-propynyl]amino)-2-diazobutanoate (4.18c). 4.18c** was obtained as a yellowish oil following Method A [(a) alkylation; (b) MsCl, $Et_3N$; then NaI; (c) $CH_3COCH_2CO_2CH_3$, NaH, 24% three steps; (d) *p*-ABSA, DBU, 74%]. $^1H$ RMN ($CDCl_3$, 400 MHz) δ 0.12 (s, 9H), 1.09 (s, 9H), 2.40 (t, *J* = 6.8 Hz, 2H), 2.81 (t, *J* = 6.8 Hz, 2H), 3.44 (s, 2H), 3.74 (s, 3H). $^{13}C$ RMN ($CDCl_3$, 100.5 MHz) δ 0.02 (3 $CH_3$), 23.4 ($CH_2$), 27.5 (3 $CH_3$), 37.9 ($CH_2$), 45.9 ($CH_2$), 52.0 ($CH_3$), 55.4 (C), 88.9 (C), 105.4 (C). Two C were not observed. IR (NaCl) ν 2084, 1694 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{15}H_{28}N_3O_2Si$: 310.1945 $[M + H]^+$; found: 310.1953.

**Methyl 4-[*N*-allyl-*N*-*tert*-butylamino]-2-diazobutanoate (4.20). 4.20** was obtained as a brownish oil following Method A [(a) alkylation; (b) MsCl, $Et_3N$; then NaI; (c) $CH_3COCH_2CO_2CH_3$, NaH, 43% three steps; (d) *p*-ABSA, DBU, 80%]. $^1H$ RMN ($CDCl_3$, 400 MHz) δ 1.06 (s, 9H), 2.32 (t, *J* = 6.8 Hz, 2H), 2.68 (t, *J* = 6.8 Hz, 2H), 3.18 (d, *J* =

6.4 Hz, 2H), 3.75 (s, 3H), 4.99 (dq, *J* = 11.6 and 1.6 Hz, 1H), 5.13 (dq, *J* = 17.2 and 1.6 Hz, 1H), 5.85 (ddt, *J* = 17.2, 11.6 and 6.4 Hz, 1H),. $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 25.0 ($CH_2$), 27.4 (3 $CH_3$), 48.3 ($CH_2$), 52.0 ($CH_3$), 53.6 ($CH_2$), 55.2 (C), 115.3 ($CH_2$), 139.5 (CH). Two C were not observed. IR (NaCl) ν 2082, 1694 $cm^{-1}$.

**Representative procedure for the C-H insertion reaction (Table 4.1, Entry 1).** A mixture of diazoester **4.1a** (40 mg, 0.14 mmol) and Ru-1 (3.3 mg, 0.004 mmol) in dichloromethane (10 mL) was stirred at reflux under Argon atmosphere for 24 h. The solvent was removed *in vacuo*, and the residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 95:5) to give **4.2a** (32.5 mg, 90%).

**Characterization data for the compounds of Tables 4.1-4.4 and Figure 4.2**

**Methyl *cis*-1-*tert*-butyl-2-phenylpyrrolidine-3-carboxylate (4.2a).** $^1$H NMR ($CDCl_3$, 400 MHz) δ 0.98 (s, 9H), 1.85 (dtd, *J* = 12.4, 6.0 and 0.8 Hz, 1H), 2.29 (dddd, *J* = 13.2, 12.4, 12.0 and 6.8 Hz, 1H), 2.82 (ddd, *J* = 12.0, 9.0 and 6.0 Hz, 1H), 3.09 (ddd, *J* = 13.2, 9.0 and 6.0 Hz, 1H), 3.24 (ddd, *J* = 9.6, 6.8 and 0.8 Hz, 1H), 3.25 (s, 3H), 4.38 (d, *J* = 9.6 Hz, 1H), 7.14 (tt, *J* = 7.2 and 1.6 Hz, 1H), 7.19-7.25 (m, 2H), 7.31-7.35 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 26.3 ($CH_2$), 27.0 (3 $CH_3$), 46.9 ($CH_2$), 51.1 (CH), 51.2 ($CH_3$), 53.8 (C), 62.9 (CH), 126.8 (CH), 127.5 (2 CH), 127.8 (2 CH), 145.5 (C), 172.3 (C). IR (film) 1743 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{16}H_{24}NO_2$: 262.1802 $[M + H]^+$; found: 262.1805.

**Methyl *cis*-1-*tert*-butyl-2-(4-chlorophenyl)pyrrolidine-3-carboxylate (4.2b).** $^1$H NMR ($CDCl_3$, 400 MHz) δ 0.97 (s, 9H), 1.86 (dtd, *J* = 12.4, 5.6 and 0.8 Hz, 1H), 2.24 (dddd, *J* = 12.8, 12.4, 11.6 and 6.8 Hz, 1H), 2.81 (ddd, *J* = 11.6, 9.6 and 5.6 Hz, 1H), 3.08 (ddd, *J* = 12.8, 9.6 and 5.6 Hz, 1H), 3.23 (ddd, *J* = 9.6, 6.8 and 0.8 Hz, 1H), 3.29 (s, 3H), 4.35 (d, *J* = 9.6 Hz, 1H), 7.17-7.21 (m, 2H), 7.26-7.30 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 26.3 ($CH_2$), 27.0 (3 $CH_3$), 46.9 ($CH_2$), 51.0 (CH), 51.4 ($CH_3$), 53.8 (C), 62.2 (CH), 127.8 (2 CH), 129.2 (2 CH), 132.4 (C), 145.2 (C), 172.1 (C). IR (film) 1742 $cm^{-1}$.

**Methyl *cis*-1-*tert*-butyl-2-(2-fluorophenyl)pyrrolidine-3-carboxylate (4.2c).** $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 0.98 (s, 9H), 1.90 (dddd, *J* = 12.0, 6.4, 5.6 and 1.2 Hz, 1H), 2.30 (dddd, *J* = 12.8, 12.0, 11.6 and 7.2 Hz, 1H), 2.83 (ddd, *J* = 11.6, 8.4 and 5.6 Hz, 1H), 3.14 (ddd, *J* = 12.8, 9.6 and 6.4 Hz, 1H), 3.25 (ddd, *J* = 8.4, 6.4 and 1.2 Hz, 1H), 3.31 (s, 3H), 4.79 (d, *J* = 9.6 Hz, 1H), 6.88 (dddd, *J* = 10.0, 7.6, 1.2 and 0.8 Hz, 1H), 7.07 (tdd, *J* = 7.6, 1.2 and 0.4 Hz, 1H), 7.10-7-16 (m, 1H), 7.64 (td, *J* = 7.6 and 2.0 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 26.8 (3 $CH_3$), 27.0 ($CH_2$), 46.8 ($CH_2$), 50.2 (CH), 51.3 ($CH_3$), 53.9 (C), 54.9 (d, *J* = 3.2 Hz, CH), 114.2 (d, *J* = 22.5 Hz, CH), 123.7 (d, *J* = 3.3 Hz, CH), 128.1 (d, *J* = 8.3 Hz, CH), 131.0 (d, *J* = 4.3 Hz, CH), 132.6 (d, *J* = 12.5 Hz, C), 159.6 (d, *J* = 244.3 Hz, C), 172.4 (C). IR (film) 1743 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{16}H_{23}FNO_2$: 280.1713 $[M + H]^+$; found: 280.1715.

**Methyl *cis*-2-(2-bromophenyl)-1-*tert*-butylpyrrolidine-3-carboxylate (4.2d).** $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 0.97 (s, 9H), 1.91 (dddd, *J* = 12.0, 6.8, 5.6 and 1.6 Hz, 1H), 2.33 (qd, *J* = 12.0 and 6.8 Hz, 1H), 2.84 (ddd, *J* = 12.0, 8.8 and 5.6 Hz, 1H), 3.19 (ddd, *J* = 12.0, 9.6 and 6.8 Hz, 1H), 3.28 (ddd, *J* = 8.8, 6.8 and 1.6 Hz, 1H), 3.26 (s, 3H), 4.83 (d, *J* = 9.6 Hz, 1H), 7.02 (ddd, *J* = 8.0, 7.6 and 1.6 Hz, 1H), 7.25 (ddd, *J* = 8.0, 7.6 and 1.2 Hz, 1H), 7.39 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.69 (dd, *J* = 8.0 and 1.6 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 26.9 (3 $CH_3$), 27.5 ($CH_2$), 47.1 ($CH_2$), 49.9 (CH), 51.2 ($CH_3$), 54.0 (C), 61.6 (CH), 123.0 (C), 127.0 (CH), 128.3 (CH), 131.6 (CH), 131.9 (CH), 144.4 (C), 172.4 (C). IR (film) 1740 $cm^{-1}$.

**Methyl *cis*-1-*tert*-butyl-2-(2-methoxyphenyl)pyrrolidine-3-carboxylate (4.2e).** $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 0.97 (s, 9H), 1.87 (dddd, *J* = 12.0, 6.8, 5.6 and 1.6 Hz, 1H), 2.23 (qd, *J* = 12.0 and 6.8 Hz, 1H), 2.81 (ddd, *J* = 12.0, 8.8 and 5.6 Hz, 1H), 3.07 (ddd, *J* = 12.0, 9.6 and 6.8 Hz, 1H), 3.23 (ddd, *J* = 8.8, 6.8 and 1.2 Hz, 1H), 3.26 (s, 3H), 3.79 (s, 3H), 4.87 (d, *J* = 9.6 Hz, 1H), 6.73 (dd, *J* = 8.0 and 1.2 Hz, 1H), 6.91 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.6 and 1.6 Hz, 1H), 7.64 (dd, *J* = 7.6 and 1.6 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 26.8 (3 $CH_3$), 27.8 ($CH_2$), 46.9 ($CH_2$), 50.0 (CH), 51.2 ($CH_3$), 53.8 (C), 55.3 (CH), 55.6 ($CH_3$), 109.2 (CH), 120.2 (CH), 127.4 (CH), 130.2 (CH), 133.8 (C), 155.9 (C), 172.9 (C). IR (film) 1737 $cm^{-1}$.

**Methyl *cis*-2-[(2-bromophenyl)methyl]-1-*tert*-butylpyrrolidine-3-carboxylate (*cis*-4.4).** $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 0.72 (s, 9H), 2.02 (dddd, *J* = 12.4, 8.0, 6.0 and 1.6 Hz, 1H), 2.33 (qd, *J* = 12.0 and 8.0 Hz, 1H), 2.50 (dd, *J* = 13.2 and 9.6 Hz, 1H), 2.76 (dd, *J* = 13.2 and 4.8 Hz, 1H), 2.78-2.86 (m, 2H), 3.10 (ddd, *J* = 10.0, 8.4 and 1.6 Hz, 1H), 3.54 (s, 3H), 3.78 (ddd, *J* = 9.6, 8.0 and 4.8 Hz, 1H), 7.01 (ddd, *J* = 8.0, 6.8 and 2.4 Hz, 1H), 7.16-7.22 (m, 2H), 7.48 (d, *J* = 8.0 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 26.7 (3 $CH_3$), 27.0 ($CH_2$), 40.1 ($CH_2$), 46.0 ($CH_2$), 48.3 (CH), 51.6 ($CH_3$), 53.9 (C), 58.3 (CH), 125.7 (C), 126.6 (CH), 127.7 (CH), 132.4 (CH), 133.0 (CH), 139.3 (C), 173.2 (C). IR (film) 1736 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{17}H_{25}BrNO_2$: 354.1063 $[M + H]^+$; found: 354.1070.

**Methyl *trans*-2-[(2-bromophenyl)methyl]-1-*tert*-butylpyrrolidine-3-carboxylate (*trans*-4.4).** $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 1.14 (s, 9H), 2.03 (broad, 1H), 2.13 (dddd, *J* = 8.8, 6.8, 5.6 and 2.4 Hz, 1H), 2.67 (d, *J* = 6.8 Hz, 1H), 2.83-2.90 (m, 2H), 3.01-3.08 (m, 2H), 3.53 (s, 3H), 3.83 (broad, 1H), 7.07 (td, *J* = 7.6 and 1.6 Hz, 1H), 7.24 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.30 (dd, *J* = 7.6 and 1.6 Hz, 1H), 7.53 (dd, *J* = 7.6 and 1.2 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 27.4 ($CH_2$), 27.6 (3 $CH_3$), 29.9 ($CH_2$), 45.1 (C), 47.5 (CH), 47.6 ($CH_2$), 51.9 ($CH_3$), 61.3 (CH), 125.2 (C), 127.5 (CH), 128.1 (CH), 131.8 (CH), 133.0 (CH), 139.2 (C), 175.0 (C). IR (film) 1736 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{17}H_{25}BrNO_2$: 354.1063 $[M + H]^+$; found: 354.1069.

**Methyl *cis*-2-(benzyloxymethyl)-1-*tert*-butylpyrrolidine-3-carboxylate (*cis*-4.6).** $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9H), 1.91 (dt, *J* = 12.0 and 6.0 Hz, 1H), 2.23 (qd, *J* = 12.4 and 7.2 Hz, 1H), 2.59-2.68 (m, 1H), 2.69-2.80 (m, 1H), 2.94 (t, *J* = 8.0 Hz, 1H), 3.29 (dd, *J* = 8.8 and 3.2 Hz, 1H), 3.38 (ddd, *J* = 9.6, 6.4 and 3.2 Hz, 1H), 3.43-3.48 (masked, 1H), 3.47 (s, 3H), 4.34 (d, *J* = 11.6 Hz, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 7.29-7.34 (m, 5H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 26.5 (3 $CH_3$), 27.3 ($CH_2$), 46.0 (CH), 46.6 ($CH_2$), 51.6 ($CH_3$), 53.6 (C), 58.7 (CH), 73.2 (2 $CH_2$), 127.6 (CH), 128.0 (2 CH), 128.4 (2 CH), 138.3 (C), 173.0 (C). IR (film) 1737 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{18}H_{28}NO_3$: 306.2069 $[M + H]^+$; found: 306.2060.

**Methyl *trans*-2-(benzyloxymethyl)-1-*tert*-butylpyrrolidine-3-carboxylate (*trans*-4.6).** $^{1}$H NMR ($CDCl_3$, 400 MHz, signals from a ≈ 5:1 mixture of ***trans*-4.6** and ***cis*-4.6**) δ 1.06 (s, 9H), 1.96 (broad, 1H), 2.14 (dd, *J* = 12.8 and 5.6 Hz, 1H), 2.83 (td, *J* = 10.0 and 6.0 Hz, 1H), 2.90-3.00 (m, 1H), 2.99 (d, *J* = 7.2 Hz, 1H), 3.22 (broad, 1H), 3.42-3.50 (m, 1H), 3.41-3.56 (m, 1H), 3.69 (s, 3H), 4.52 (d, *J* = 12.4 Hz, 1H), 4.58 (d, *J* = 12.4 Hz, 1H), 7.26-7.34 (m, 5H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 5:1 mixture of ***trans*-4.6** and ***cis*-4.6**) δ 27.0 (3 $CH_3$), 27.2 ($CH_2$), 47.0 (CH), 47.4 ($CH_2$), 52.0 ($CH_3$), 54.2 (C), 60.5 (CH), 73.2 ($CH_2$), 74.8 ($CH_2$), 127.8 (CH), 127.9 (2 CH), 128.5 (2 CH), 138.4 (C), 175.2 (C). IR (film) 1736 $cm^{-1}$.

**Methyl *cis*-1-*tert*-butyl-2-(2-phenylethyl)pyrrolidine-3-carboxylate (4.8).** $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 1.02 (s, 9H), 1.59 (broad, 1H), 1.75-1.85 (m, 1H), 1.93 (dt, *J* = 12.0 and 6.4 Hz, 1H), 2.22 (qd, *J* = 12.0 and 7.6 Hz, 1H), 2.43-2.57 (m, 2H), 2.68 (ddd, *J* = 11.2, 9.6 and 6.4 Hz, 1H), 2.79 (ddd, *J* = 12.4, 8.0 and 6.8 Hz, 1H), 3.00 (t, *J* = 8.8 Hz, 1H), 3.27-3.35 (m, 1H), 3.72 (s, 3H), 7.13-7.17 (m, 3H), 7.23-7.27 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 26.8 (3 $CH_3$), 27.6 ($CH_2$), 33.2 ($CH_2$), 38.0 ($CH_2$), 46.5 ($CH_2$), 47.9 (CH), 51.7 ($CH_3$), 54.2 (C), 58.7 (CH), 125.8 (CH), 128.4 (2 CH), 128.6 (2 CH), 142.7 (C), 173.5 (C). IR (film) 1737 $cm^{-1}$.

**Methyl *cis*-1-(2-iodobenzyl)-2-phenylpyrrolidine-3-carboxylate (*cis*-4.10a).** $^{1}$H NMR ($CDCl_3$, 400 MHz, signals from a ≈ 12:1 mixture of ***cis*-4.10a** and ***trans*-4.10a**) δ 1.98 (dddd, *J* = 12.4, 8.4, 6.4 and 1.6 Hz, 1H), 2.28-2.48 (m, 2H), 3.10 (s, 3H), 3.27-3.39 (m, 2H), 3.38 (d, *J* = 14.8 Hz, 1H), 3.72 (d, *J* = 14.8 Hz, 1H), 3.98 (d, *J* = 9.6 Hz, 1H), 6.88-6.93 (m, 1H), 7.19-7.41 (m, 6H), 7.59 (dt, *J* = 7.6 and 1.2 Hz, 1H), 7.76 (dd, *J* = 7.6 and 1.6 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 5:1 mixture of ***cis*-4.10a** and ***trans*-4.10a**) δ 26.5 ($CH_2$), 49.7 (CH), 51.3 ($CH_3$), 52.9 ($CH_2$), 62.1 ($CH_2$), 71.4 (CH), 99.6 (C), 127.7 (CH), 128.1 (2 CH), 128.4 (CH), 128.5 (2 CH), 128.6 (CH), 130.0 (CH), 139.2 (CH), 139.5 (C), 141.4 (C), 173.6 (C). IR (film) 1736 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{19}H_{21}INO_2$: 422.0611 $[M + H]^+$; found: 422.0620.

**Methyl *trans*-1-(2-iodobenzyl)-2-phenylpyrrolidine-3-carboxylate (*trans*-4.10a).** $^{1}$H NMR ($CDCl_3$, 400 MHz, significant signals from a ≈ 5:1 mixture of ***cis*-4.10a** and ***trans*-**

**4.10a**) δ 2.05-2.15 (m, 1H), 2.15-2.27 (m, 1H), 2.94 (ddd, *J* = 10.8, 8.4 and 5.6 Hz, 1H), 3.16 (ddd, *J* = 9.6, 8.4 and 2.0 Hz, 1H), 3.65 (s, 3H), 3.80 (d, *J* = 8.4 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 5:1 mixture of ***cis*-4.10a** and ***trans*-4.10a**) δ 27.7 ($CH_2$), 52.0 ($CH_3$), 52.4 ($CH_2$), 52.8 (CH), 62.0 ($CH_2$), 72.7 (CH), 99.8 (C), 139.4 (CH), 141.5 (C), 141.6 (C), 175.2 (C).

**Methyl *cis*-1-(2-fluorobenzyl)-2-phenylpyrrolidine-3-carboxylate (*cis*-4.10b).** $^1$H NMR ($CDCl_3$, 400 MHz, signals from a ≈ 5:1 mixture of ***cis*-4.10b** and ***trans*-4.10b**) δ 1.90-1.97 (m, 1H), 2.29-2.48 (m, 2H), 3.08 (s, 3H), 3.20-3.32 (m, 2H), 3.37 (dd, *J* = 13.6 and 1.2 Hz, 1H), 3.78 (dt, *J* = 13.6 and 0.8 Hz, 1H), 3.84 (d, *J* = 10.0 Hz, 1H), 6.98 (m, 1H), 7.09 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.17-7.42 (m, 7H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 5:1 mixture of ***cis*-4.10b** and ***trans*-4.10b**) δ 26.4 ($CH_2$), 49.7 (CH), 49.9 (d, *J* = 2.2 Hz, $CH_2$), 51.3 ($CH_3$), 52.6 ($CH_2$), 70.9 (CH), 115.2 (d, *J* = 22.1 Hz, CH), 124.0 (d, *J* = 3.5 Hz, CH), 125.6 (d, *J* = 14.9 Hz, C), 127.7 (CH), 128.1 (2 CH), 128.6 (2 CH), 128.7 (d, *J* = 5.5 Hz, CH), 131.4 (d, *J* = 4.8 Hz, CH), 139.5 (C), 161.3 (d, *J* = 245.5 Hz, C), 173.7 (C). IR (film) 1738 $cm^{-1}$.

**Methyl *trans*-1-(2-fluorobenzyl)-2-phenylpyrrolidine-3-carboxylate (*trans*-4.10b).** $^1$H NMR ($CDCl_3$, 400 MHz, significant signals from a ≈ 5:1 mixture of ***cis*-4.10b** and ***trans*-4.10b**) δ 1.99-2.08 (m, 1H), 2.15-2.31 (m, 2H), 2.87-2.94 (m, 1H), 3.11-3.17 (m, 1H), 3.63 (s, 3H), 3.66-3.74 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, significant signals from a ≈ 5:1 mixture of ***cis*-4.10b** and ***trans*-4.10b**) δ 27.4 ($CH_2$), 50.3 (d, *J* = 2.2 Hz, $CH_2$), 51.9 ($CH_3$), 52.4 ($CH_2$), 52.5 (CH), 72.4 (CH), 115.3 (d, *J* = 21.8 Hz, CH), 141.5 (C), 175.2 (C).

**Methyl *cis*-1-(benzyl)-2-(2-fluorophenyl)pyrrolidine-3-carboxylate (*cis*-4.10b').** $^1$H NMR ($CDCl_3$, 400 MHz, signals from a ≈ 3:1 mixture of ***cis*-4.10b'** and ***cis*-4.10b**) δ 1.90-2.01 (m, 1H), 2.22-2.41 (m, 2H), 3.10 (s, 3H), 3.12 (d, *J* = 13.6 Hz, 1H), 3.19-3.25 (m, 1H), 3.34-3.41 (m, 1H), 3.88 (d, *J* = 13.6 Hz, 1H), 4.19 (d, *J* = 9.6 Hz, 1H), 7.01 (m, 1H), 7.06-7.42 (m, 7H), 7.66 (td, *J* = 7.6 and 2.0 Hz, 1H).

**Methyl *cis*-1-isopropyl-2-phenylpyrrolidine-3-carboxylate (*cis*-4.12).** $^1$H NMR ($CDCl_3$, 400 MHz, signals from a ≈ 5.8:1 mixture of ***cis*-4.12** and ***trans*-4.12**) δ 0.89 (d, *J*

= 6.4 Hz, 3H), 1.02 (d, *J* = 6.4 Hz, 3H), 1.82 (dddd, *J* = 12.4, 8.4, 6.4 and 1.6 Hz, 1H), 2.35 (dddd, *J* = 12.4, 10.0, 9.6 and 7.6 Hz, 1H), 2.64 (ddd, *J* = 10.0, 8.4 and 6.4 Hz, 1H), 2.79 (hept, *J* = 6.4 Hz, 1H), 3.11 (s, 3H), 3.18-3.23 (m, 2H), 4.09 (d, *J* = 9.6 Hz, 1H), 7.16-7.40 (m, 5H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 5.8:1 mixture of ***cis*-4.12** and ***trans*-4.12**) δ 15.8 ($CH_3$), 22.2 ($CH_3$), 26.2 ($CH_2$), 46.3 ($CH_2$), 49.2 (CH), 49.9 (CH), 50.9 ($CH_3$), 66.7 (CH), 127.0 (CH), 127.6 (2 CH), 128.2 (2 CH), 141.5 (C), 173.1 (C). IR (film) 1737 $cm^{-1}$.

**Methyl *trans*-1-isopropyl-2-phenylpyrrolidine-3-carboxylate (*trans*-4.12).** $^1$H NMR ($CDCl_3$, 400 MHz, significant signals from a ≈ 5.8:1 mixture of ***cis*-4.12** and ***trans*-4.12**) δ 0.91 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 1.99-2.06 (m, 1H), 2.14-2.15 (m, 1H), 3.63 (s, 3H), 3.87 (d, *J* = 7.6 Hz, 1H).

**Methyl 1-benzyl-2,2-dimethylpyrrolidine-3-carboxylate (4.13).** $^1$H NMR ($CDCl_3$, 400 MHz) δ 0.90 (s, 3H), 1.35 (s, 3H), 1.88 (dddd, *J* = 13.2, 9.6, 9.2 and 5.6 Hz, 1H), 2.18 (dddd, *J* = 13.2, 10.0, 9.2 and 4.8 Hz, 1H), 2.49 (ddd, *J* = 10.0, 9.6 and 5.6 Hz, 1H), 2.79 (td, *J* = 9.2 and 4.8 Hz, 1H), 2.81 (t, *J* = 9.2 Hz, 1H), 3.25 (d, *J* = 13.0 Hz, 1H), 3.71 (s, 3H), 3.80 (d, *J* = 13.0 Hz, 1H), 7.19-7.33 (m, 5H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 15.9 ($CH_3$), 23.9 ($CH_2$), 26.3 ($CH_3$), 49.5 ($CH_2$), 51.7 ($CH_3$), 52.8 ($CH_2$), 54.5 (CH), 62.8 (C), 126.9 (CH), 128.4 (2 CH), 128.6 (2 CH), 140.5 (C), 174.2 (C). IR (film) 1736 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{15}H_{22}NO_2$: 248.1645 $[M + H]^+$; found: 248.1650.

**Methyl (*E*)-*cis*-1-*tert*-butyl-2-(1-propenyl)pyrrolidine-3-carboxylate (*cis*-4.15).** $^1$H NMR ($CDCl_3$, 400 MHz, signals from a ≈ 8:1 mixture of ***cis*-4.15** and ***trans*-4.15**) δ 1.06 (s, 9H), 1.61 (ddd, *J* = 6.0, 1.6 and 0.4 Hz, 3H), 1.89 (dtd, *J* = 12.4, 6.4 and 1.2 Hz, 1H), 2.20 (tdd, *J* = 12.4, 10.8 and 7.6 Hz, 1H), 2.70 (ddd, *J* = 11.2, 8.8 and 6.0 Hz, 1H), 2.89 (ddd, *J* = 12.4, 8.8 and 6.8 Hz, 1H), 3.02 (t, *J* = 8.8 Hz, 1H), 3.61 (s, 3H), 3.74 (d, *J* = 8.4 Hz, 1H), 5.35-5.52 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 8:1 mixture of ***cis*-4.15** and ***trans*-4.15**) δ 17.8 ($CH_3$), 26.4 ($CH_2$), 27.0 (3 $CH_3$), 46.4 ($CH_2$), 49.5 (CH), 51.5 ($CH_3$), 54.2 (C), 61.5 (CH), 125.8 (CH), 133.1 (CH), 172.8 (C). IR (film) 1742 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{13}H_{24}NO_2$: 226.1802 $[M + H]^+$; found: 226.1810.

**Methyl *cis*-1-*tert*-butyl-2-(1-methylvinyl)pyrrolidine-3-carboxylate (*cis*-4.17a).** $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 1.03 (s, 9H), 1.72 (dd, *J* = 1.6 and 1.2 Hz, 3H), 1.85 (dddd, *J* = 12.0, 6.4, 5.6 and 0.8 Hz, 1H), 2.22 (dtd, *J* = 13.2, 12.0 and 7.2 Hz, 1H), 2.71 (ddd, *J* = 12.0, 8.4 and 5.6 Hz, 1H), 2.93 (ddd, *J* = 13.2, 9.6 and 6.4 Hz, 1H), 3.08 (ddd, *J* = 8.4, 7.2 and 0.8 Hz, 1H), 3.61 (s, 3H), 3.81 (d, *J* = 9.6 Hz, 1H), 4.74 (dd, *J* = 1.2 and 0.8 Hz, 1H), 4.83 (dd, *J* = 1.6 and 0.8 Hz, H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 20.2 ($CH_3$), 26.6 (3 $CH_3$), 27.7 ($CH_2$), 46.8 ($CH_2$), 50.3 (CH), 51.5 ($CH_3$), 53.9 (C), 64.6 (CH), 111.9 ($CH_2$), 150.0 (C), 173.0 (C). IR (film) 1743 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{13}H_{24}NO_2$: 226.1802 $[M + H]^+$; found: 226.1808.

**Methyl *trans*-1-*tert*-butyl-2-(1-methylvinyl)pyrrolidine-3-carboxylate (*trans*-4.17a).** $^{1}$H NMR ($CDCl_3$, 400 MHz, signals from a ≈ 4:1 mixture of ***trans*-4.17**a and ***cis*-4.17a**) δ 1.02 (s, 9H), 1.75 (dd, *J* = 1.6 and 0.8 Hz, 3H), 1.90-2.00 (m, 2H), 2.59 (dt, *J* = 7.6 and 4.0 Hz, 1H), 2.86 (dddd, *J* = 10.0, 8.8, 6.4 and 0.8 Hz, 1H), 2.99 (ddd, *J* = 9.2, 6.4 and 2.8 Hz, 1H), 3.63 (dd, *J* = 4.0 and 0.8 Hz, 1H), 3.69 (s, 3H), 4.73 (m, 1H), 5.10 (dt, *J* = 2.4 and 0.8 Hz, H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 4:1 mixture of ***trans*-4.17a** and ***cis*-4.17a**) δ 19.1 ($CH_3$), 27.1 (3 $CH_3$), 27.8 ($CH_2$), 47.5 ($CH_2$), 50.0 (CH), 51.9 ($CH_3$), 53.7 (C), 66.5 (CH), 110.7 ($CH_2$), 150.7 (C), 177.7 (C).

**Methyl *cis*-2-(1-bromovinyl)-1-*tert*-butylpyrrolidine-3-carboxylate (*cis*-4.17b).** $^{1}$H NMR ($CDCl_3$, 400 MHz, signals from a ≈ 11:1 mixture of ***cis*-4.17b** and ***trans*-4.17b**) δ 1.05 (s, 9H), 1.87 (dddd, *J* = 12.0, 6.0, 5.6 and 0.8 Hz, 1H), 2.26 (dtdd, *J* = 13.2, 12.0, 7.2 and 0.4 Hz, 1H), 2.71 (ddd, *J* = 12.0, 8.4 and 5.6 Hz, 1H), 2.86 (ddd, *J* = 13.2, 8.8 and 6.0 Hz, 1H), 3.10 (ddd, *J* = 8.4, 7.2 and 0.8 Hz, 1H), 3.69 (s, 3H), 3.95 (dd, *J* = 8.8 and 0.8 Hz, 1H), 5.63 (d, *J* = 1.2 Hz, 1H), 6.14 (t, *J* = 1.2 Hz, H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 11:1 mixture of ***cis*-4.17b** and ***trans*-4.17b**) δ 26.7 (3 $CH_3$), 26.8 ($CH_2$), 46.3 ($CH_2$), 48.9 (CH), 51.9 ($CH_3$), 53.9 (C), 66.5 (CH), 119.1 ($CH_2$), 137.8 (C), 172.0 (C). IR (film) 1743 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{12}H_{21}BrNO_2$: 290.0750 $[M + H]^+$; found: 290.0758.

**Methyl *trans*-2-(1-bromovinyl)-1-*tert*-butylpyrrolidine-3-carboxylate (*trans*-4.17b).** $^{1}$H NMR ($CDCl_3$, 400 MHz, significant signals from a ≈ 11:1 mixture of ***cis*-4.17b** and

***trans*-4.17b**) δ 1.04 (s, 9H), 1.95-2.08 (m, 2H), 2.82-2.92 (m, 1H), 3.03 (ddd, *J* = 8.8, 6.8 and 2.0 Hz, 1H), 3.71 (s, 3H), 5.51 (t, *J* = 1.2 Hz, 1H), 6.22 (t, *J* = 1.2 Hz, H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 11:1 mixture of ***cis*-4.17b** and ***trans*-4.17b**) δ 27.2 (3 $CH_3$), 29.9 ($CH_2$), 47.3 ($CH_2$), 49.6 (CH), 52.1 ($CH_3$), 53.6 (C), 68.0 (CH), 116.6 ($CH_2$), 140.2 (C). One C was not observed.

**Methyl 1-bromo-3-(*tert*-butyl)-3-azabicyclo[4.1.0]heptane-6-carboxylate.** $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.01 (s, 9H), 1.58 (d, *J* = 5.6 Hz, 1H), 1.70 (ddd, *J* = 13.6, 12.0 and 6.4 Hz, 1H), 1.90 (d, *J* = 5.6 Hz, 1H), 2.08 (td, *J* = 12.0 and 4.8 Hz, 1H), 2.62 (ddd, *J* = 13.6, 4.8 and 2.0 Hz, 1H), 2.74 (d, *J* = 11.2 Hz, 1H), 2.85 (ddt, *J* = 12.0, 6.4 and 2.0 Hz, 1H), 3.47 (dd, *J* = 11.2 and 2.0 Hz, 1H), 3.74 (s, 3H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 24.2 ($CH_2$), 26.4 (3 $CH_3$), 28.7 ($CH_2$), 30.1 (C), 40.6 (C), 44.2 ($CH_2$), 52.4 ($CH_3$), 53.8 (C), 54.5 ($CH_2$), 172.2 (C). IR (film) 1739 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{12}H_{21}BrNO_2$: 290.0750 $[M + H]^+$; found: 290.0753.

**Methyl *cis*-1-*tert*-butyl-2-(1-iodovinyl)pyrrolidine-3-carboxylate (*cis*-4.17c).** $^1$H NMR ($CDCl_3$, 400 MHz, signals from a ≈ 14:1 mixture of ***cis*-4.17c** and ***trans*-4.17c**) δ 1.06 (s, 9H), 1.87 (dtd, *J* = 12.0, 6.0 and 0.8 Hz, 1H), 2.39 (dtd, *J* = 13.2, 12.0 and 7.2 Hz, 1H), 2.73 (ddd, *J* = 12.0, 8.4 and 6.0 Hz, 1H), 2.92 (ddd, *J* = 13.2, 9.2 and 6.0 Hz, 1H), 3.13 (ddd, *J* = 8.4, 7.2 and 0.8 Hz, 1H), 3.69 (s, 3H), 3.77 (dd, *J* = 9.2 and 0.8 Hz, 1H), 5.92 (d, *J* = 1.2 Hz, 1H), 6.50 (t, *J* = 1.2 Hz, H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 14:1 mixture of ***cis*-4.17c** and ***trans*-4.17c**) δ 26.7 ($CH_2$), 27.0 (3 $CH_3$), 46.5 ($CH_2$), 49.8 (CH), 51.9 ($CH_3$), 53.7 (C), 67.9 (CH), 120.3 (C), 126.7 ($CH_2$), 172.0 (C). IR (film) 1742 $cm^{-1}$.

**Methyl *trans*-1-*tert*-butyl-2-(1-iodovinyl)pyrrolidine-3-carboxylate (*trans*-4.17c).** $^1$H NMR ($CDCl_3$, 400 MHz, significant signals from a ≈ 14:1 mixture of ***cis*-4.17c** and ***trans*-4.17c**) δ 1.04 (s, 9H), 1.98-2.05 (m, 2H), 2.63-2.68 (m, 1H), 2.80-2.86 (m, 1H), 3.03-3.08 (m, 1H), 3.71 (s, 3H), 5.79 (t, *J* = 0.8 Hz, 1H), 6.63 (t, *J* = 1.2 Hz, H).

**Methyl *cis*-1-*tert*-butyl-2-ethynylpyrrolidine-3-carboxylate (*cis*-4.19a).** $^1$H NMR ($CDCl_3$, 400 MHz, signals from a ≈ 6:1 mixture of ***cis*-4.19a** and ***trans*-4.19a**) δ 1.16 (s, 9H), 1.99 (dtddd, *J* = 12.8, 7.2, 6.8 and 3.2 Hz, 1H), 2.27 (d, *J* = 2.0 Hz, 1H), 2.34 (ddt, *J*

= 12.8, 11.6 and 8.4 Hz, 1H), 2.79 (td, *J* = 8.4 and 6.8 Hz, 1H), 3.01-3.09 (m, 2H), 3.72 (s, 3H), 4.13 (dd, *J* = 8.4 and 2.0 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 6:1 mixture of ***cis*-4.19a** and ***trans*-4.19a**) δ 25.7 ($CH_2$), 26.9 (3 $CH_3$), 44.9 ($CH_2$), 49.4 (CH), 50.6 (CH), 52.0 ($CH_3$), 53.8 (C), 73.0 (CH), 84.2 (C), 171.9 (C). IR (film) 1744 $cm^{-1}$.

**Methyl *trans*-1-*tert*-butyl-2-ethynylpyrrolidine-3-carboxylate (*trans*-4.19a).** $^1$H NMR ($CDCl_3$, 400 MHz, significant signals from a ≈ 6:1 mixture of ***cis*-4.19a** and ***trans*-4.19a**) δ 1.16 (s, 9H), 2.08 (ddt, *J* = 12.4, 6.8 and 3.6 Hz, 1H), 2.16-2.24 (m, 1H), 2.29 (d, *J* = 2.4 Hz, 1H), 2.74-2.81 (masked, 1H), 2.96-3.12 (m, 2H), 3.72 (s, 3H), 4.07 (dd, *J* = 3.6 and 2.4 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 6:1 mixture of ***cis*-4.19a** and ***trans*-4.19a**) δ 27.2 (3 $CH_3$), 28.0 ($CH_2$), 45.8 ($CH_2$), 51.1 (CH), 51.7 (CH), 52.3 ($CH_3$), 53.9 (C), 71.2 (CH), 174.1 (C). One C was not observed.

**Methyl *cis*-1-*tert*-butyl-2-(1-propynyl)pyrrolidine-3-carboxylate (*cis*-4.19b).** $^1$H NMR ($CDCl_3$, 400 MHz, signals from a ≈ 4:1 mixture of ***cis*-4.19b** and ***trans*-4.19b**) δ 1.14 (s, 9H), 1.75 (d, *J* = 2.4 Hz, 3H), 1.87 (dtd, *J* = 12.8, 6.8 and 3.2 Hz, 1H), 2.32 (dddd, *J* = 12.8, 11.2, 8.4 and 8.0 Hz, 1H), 2.74 (td, *J* = 8.4 and 6.8 Hz, 1H), 2.95-3.06 (m, 2H), 3.70 (s, 3H), 4.08 (ddt, *J* = 8.4, 2.4 and 2.0 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 4:1 mixture of ***cis*-4.19b** and ***trans*-4.19b**) δ 3.8 ($CH_3$), 25.8 ($CH_2$), 26.9 (3 $CH_3$), 45.0 ($CH_2$), 49.6 (CH), 50.9 (CH), 51.9 ($CH_3$), 53.6 (C), 79.0 (C), 80.5 (C), 172.3 (C). IR (film) 1744 $cm^{-1}$.

**Methyl *trans*-1-*tert*-butyl-2-(1-propynyl)pyrrolidine-3-carboxylate (*trans*-4.19b).** $^1$H NMR ($CDCl_3$, 400 MHz, significant signals from a ≈ 4:1 mixture of ***cis*-4.19b** and ***trans*-4.19b**) δ 1.15 (s, 9H), 1.78 (d, *J* = 2.4 Hz, 3H), 2.03 (ddt, *J* = 12.4, 7.2 and 4.0 Hz, 1H), 2.17 (dtd, *J* = 12.4, 8.8 and 7.6 Hz, 1H), 3.70 (s, 3H), 3.97 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 4:1 mixture of ***cis*-4.19b** and ***trans*-4.19b**) δ 4.0 ($CH_3$), 27.2 (3 $CH_3$), 28.0 ($CH_2$), 46.1 ($CH_2$), 51.5 (CH), 52.0 ($CH_3$), 52.2 (CH), 53.9 (C), 78.7 (C), 82.4 (C), 174.5 (C).

**Methyl *cis*-1-*tert*-butyl-2-[2-(trimethylsilyl)ethynyl]pyrrolidine-3-carboxylate (*cis*-4.19c).** $^1$H NMR ($CDCl_3$, 400 MHz) δ 0.11 (s, 9H), 1.16 (s, 9H), 1.96 (m, 1H), 2.32

(dddd, *J* = 12.0, 10.4, 9.2, and 8.0 Hz, 1H), 2.78 (q, *J* = 9.2 Hz, 1H), 2.98-3.08 (m, 2H), 3.69 (s, 3H), 4.13 (d, *J* = 8.0 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 0.1 (9 $CH_3$), 25.4 ($CH_2$), 27.0 (3 $CH_3$), 44.6 ($CH_2$), 49.5 (CH), 51.5 (CH), 51.9 ($CH_3$), 53.7 (C), 89.6 (C), 106.1 (C), 171.9 (C). IR (film) 1747 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{15}H_{28}NO_2Si$: 282.1884 $[M + H]^+$; found: 282.1887.

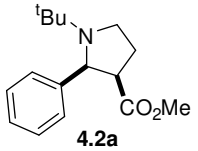
**Methyl *trans*-1-*tert*-butyl-2-[2-(trimethylsilyl)ethynyl]pyrrolidine-3-carboxylate (*trans*-4.19c).** $^1$H NMR ($CDCl_3$, 400 MHz, significant signals from a ≈ 3:1 mixture of ***cis*-4.19c** and ***trans*-4.19c**) δ 0.10 (s, 9H), 1.15 (s, 9H), 3.69 (s, 3H), 4.05 (d, *J* = 3.2 Hz, 1H).

**Methyl *cis*-5-(*tert*-butyl)-3,3a,4,5,6,7-hexahydro-7aH-pyrazolo[4,3-*c*]pyridine-7a-carboxylate (4.21).** $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.00 (s, 9H), 1.90-1.98 (m, 1H), 2.35-2.64 (m, 6H), 3.78 (s, 3H), 4.43 (dd, *J* = 17.2 and 6.4 Hz, 1H), 4.63 (dd, *J* = 17.2 and 7.6 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 26.2 (3 $CH_3$), 30.0 ($CH_2$), 36.3 (CH), 42.0 ($CH_2$), 44.6 ($CH_2$), 52.9 ($CH_3$), 53.7 (C), 80.5 ($CH_2$), 91.9 (C), 171.2 (C). HRMS (ESI-TOF) cald for $C_{12}H_{22}N_3O_2$: 240.1707 $[M + H]^+$; found: 240.1705.

**Methyl *cis*-5-(*tert*-butyl)-1,3a,4,5,6,7-hexahydro-7aH-pyrazolo[4,3-*c*]pyridine-7a-carboxylate (4.22). 4.22** was isolated as a brown oil (35%) from the crude reaction mixture of the reaction of **4.20** with **Ru-1** (Figure 4.2). $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 9H), 1.87 (ddd, *J* = 14.0, 4.8 and 3.2 Hz, 1H), 2.02 (dtd, *J* = 14.0, 10.0 and 4.4 Hz, 1H), 2.13 (dd, *J* = 11.6 and 9.2 Hz, 1H), 2.45 (ddd, *J* = 12.0, 10.0 and 3.2 Hz, 1H), 2.67 (ddd, *J* = 12.0, 4.8 and 4.4 Hz, 1H), 2.95 (ddd, *J* = 11.6, 6.0 and 1.6 Hz, 1H), 3.31 (dd, *J* = 9.2 and 6.0 Hz, 1H), 3.73 (s, 3H), 6.16 (s, 1H), 6.79 (dd, *J* = 1.6 and 0.8 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 26.3 (3 $CH_3$), 30.9 ($CH_2$), 42.1 ($CH_2$), 45.4 ($CH_2$), 47.2 (CH), 52.8 ($CH_3$), 54.2 (C), 68.3 (C), 147.8 (CH), 175.7 (C). IR (film) 1732 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{12}H_{22}N_3O_2$: 240.1707 $[M + H]^+$; found: 240.1709.

**Methyl (*E*)-*cis*-1-*tert*-butyl-2-vinylpyrrolidine-3-carboxylate (4.23). 4.23** was isolated as a brown oil (15%) from the crude reaction mixture of the reaction of **4.20** with **Ru-1** (Figure 4.2). $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.09 (s, 9H), 1.90 (dtd, *J* = 12.4, 6.0 and 1.2 Hz, 1H), 2.18 (tdd, *J* = 12.4, 11.2 and 7.6 Hz, 1H), 2.72 (ddd, *J* = 11.2, 8.8 and 6.0 Hz,

1H), 2.92 (ddd, *J* = 12.4, 8.8 and 6.0 Hz, 1H), 3.04 (ddd, *J* = 8.8, 7.6 and 1.2 Hz, 1H), 3.63 (s, 3H), 3.78 (t, *J* = 8.8 Hz, 1H), 4.98 (ddd, *J* = 10.0, 2.0 and 1.2 Hz, 1H), 5.12 (ddd, *J* = 17.2, 2.0 and 1.2 Hz, 1H), 5.76 (ddd, *J* = 17.2, 10.0 and 8.8 Hz, 1H). IR (film) 1744 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{12}H_{22}NO_2$: 212.1651 $[M + H]^+$; found: 212.1649.




**4.2a**

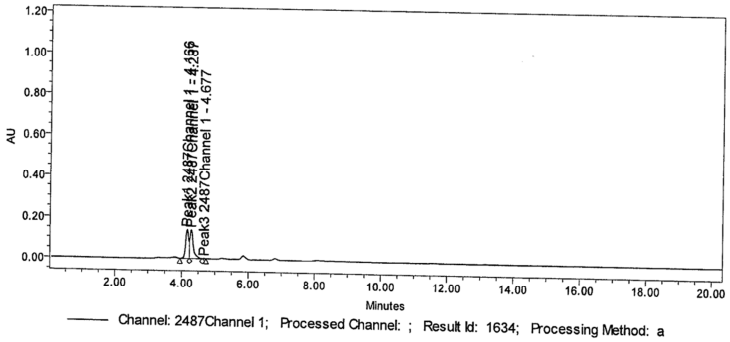
HPLC of a racemic mixture of **4.2a**

Empower 2 software

## Injection Summary Report

### SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | | Acquired By: | System |
| Sample Type: | Unknown | Sample Set Name: | |
| Vial: | 1:A,1 | Acq. Method Set: | IC_254_Hex_iPrOH_80_20_1 |
| Injection #: | 3 | Processing Method: | a |
| Injection Volume: | 10.00 ul | Channel Name: | 2487Channel 1 |
| Run Time: | 45.0 Minutes | Proc. Chnl. Descr.: | |
| Date Acquired: | 6/8/2018 3:15:29 PM CEST | | |
| Date Processed: | 6/8/2018 3:47:35 PM CEST | | |

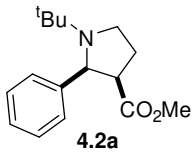



**Processed Channel Descr.:**

| | Peak Name | RT | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | Peak1 2487Channel 1 | 4.166 | 878505 | 47.28 | 140835 |
| 2 | Peak2 2487Channel 1 | 4.287 | 977798 | 52.63 | 139115 |
| 3 | Peak3 2487Channel 1 | 4.677 | 1667 | 0.09 | 376 |

Reported by User: System
Report Method: Injection Summary Report
Report Method ID: 1392
Page: 1 of 1

Project Name: BEN
Date Printed:
6/8/2018
3:49:06 PM Europe/Madrid




**4.2a** e.e. = 33%

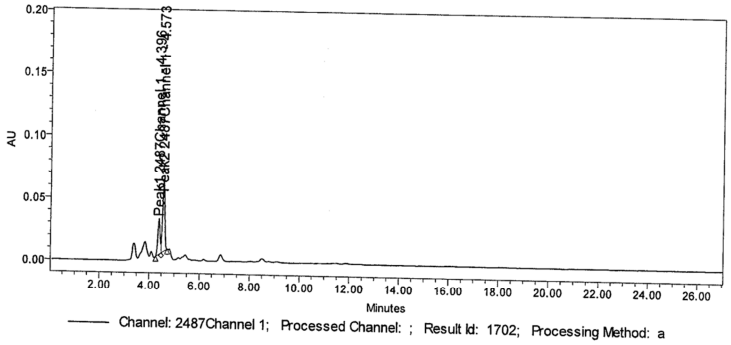
HPLC of **4.2a** from Entry 7, Table 4.5

Empower 2 software

Injection Summary Report

SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | | Acquired By: | System |
| Sample Type: | Unknown | Sample Set Name: | |
| Vial: | 1:A,1 | Acq. Method Set: | IC_254_Hex_iPrOH_90_10_1 |
| Injection #: | 8 | Processing Method: | a |
| Injection Volume: | 10.00 ul | Channel Name: | 2487Channel 1 |
| Run Time: | 45.0 Minutes | Proc. Chnl. Descr.: | |
| Date Acquired: | 6/12/2018 3:25:56 PM CEST | | |
| Date Processed: | 6/12/2018 5:03:35 PM CEST | | |



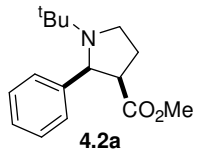

Channel: 2487Channel 1; Processed Channel: ; Result Id: 1702; Processing Method: a

**Processed Channel Descr.:**

| | Peak Name | RT | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | Peak1 2487Channel 1 | 4.396 | 175860 | 33.53 | 28384 |
| 2 | Peak2 2487Channel 1 | 4.573 | 348663 | 66.47 | 55356 |

Reported by User: System
Report Method: Injection Summary Report
Report Method ID: 1392
Page: 1 of 1

Project Name: BEN
Date Printed:
6/12/2018
5:07:10 PM Europe/Madrid




**4.2a** e.e. = 25%

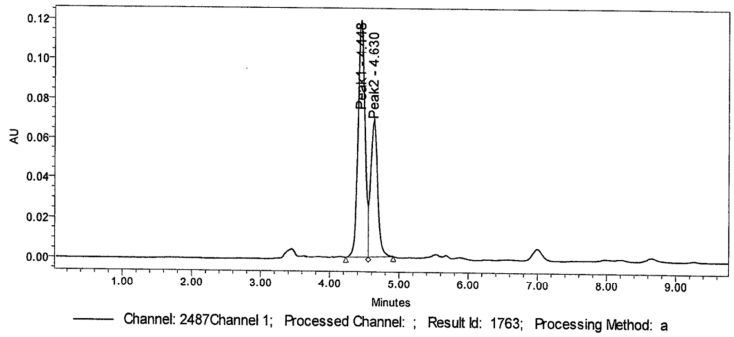
HPLC of **4.2a** from Entry 9, Table 4.5

Empower2

Injection Summary Report

SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | ~~AA-EXO #1~~ | Acquired By: | System |
| Sample Type: | Unknown | Sample Set Name: | |
| Vial: | 1:A,1 | Acq. Method Set: | IC_254_Hex_iPrOH_90_10_1 |
| Injection #: | 4 | Processing Method: | a |
| Injection Volume: | 10.00 ul | Channel Name: | 2487Channel 1 |
| Run Time: | 30.0 Minutes | Proc. Chnl. Descr.: | |
| Date Acquired: | 7/16/2018 3:44:41 PM CEST | | |
| Date Processed: | 7/16/2018 4:00:00 PM CEST | | |



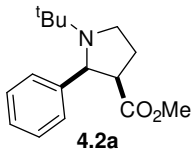

Channel: 2487Channel 1; Processed Channel: ; Result Id: 1763; Processing Method: a

**Processed Channel Descr.:**

| | Peak Name | RT | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | Peak1 | 4.448 | 800217 | 62.26 | 118387 |
| 2 | Peak2 | 4.630 | 485043 | 37.74 | 68237 |

Reported by User: System
Report Method: Injection Summary Report
Report Method ID: 1392
Page: 1 of 1

Project Name: BEN
Date Printed:
7/16/2018
4:04:26 PM Europe/Madrid




**4.2a** e.e. = 39%

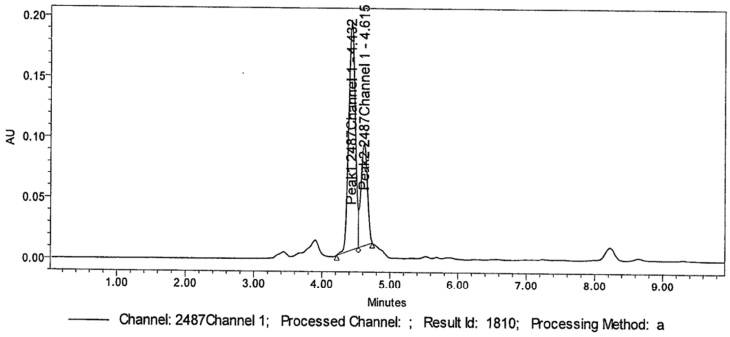
HPLC of **4.2a** from Entry 10, Table 4.5

Empower 2 software

Injection Summary Report

SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | IC_AA517F1_Hex_iPrOH_90_10_1 | Acquired By: | System |
| Sample Type: | Unknown | Sample Set Name: | |
| Vial: | 1:A,1 | Acq. Method Set: | IC_254_Hex_iPrOH_90_10_1 |
| Injection #: | 1 | Processing Method: | a |
| Injection Volume: | 10.00 ul | Channel Name: | 2487Channel 1 |
| Run Time: | 30.0 Minutes | Proc. Chnl. Descr.: | |
| Date Acquired: | 7/20/2018 11:02:03 AM CEST | | |
| Date Processed: | 7/20/2018 11:21:07 AM CEST | | |




Channel: 2487Channel 1; Processed Channel: ; Result Id: 1810; Processing Method: a

**Processed Channel Descr.:**

| | Peak Name | RT | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | Peak1 2487Channel 1 | 4.432 | 1234578 | 69.36 | 188423 |
| 2 | Peak2 2487Channel 1 | 4.615 | 545373 | 30.64 | 84110 |

e.e. 39 %

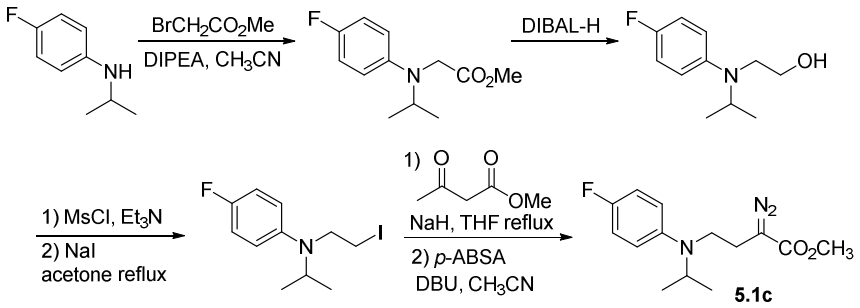
Reported by User: System
Report Method: Injection Summary Report
Report Method ID: 1392
Page: 1 of 1

Project Name: BEN
Date Printed:
7/20/2018
11:24:45 AM Europe/Madrid

## 8.4. Experimental Part of Chapter 5

**Experimental procedures and characterization data for the starting materials**

**PROCEDURE A: Methyl 2-diazo-4-[*N*-(4-fluorophenyl)-*N*-isopropylamino]butanoate (5.1c).**




A solution of 4-fluoro-*N*-isopropylaniline (1.63 g, 10.64 mmol), methyl 2-bromoacetate (5.0 mL, 53.0 mmol) and DIPEA (5.6 mL, 32.5 mmol) in $CH_3CN$ (70 mL) was stirred at reflux for 24 h. The resulting mixture was concentrated *in vacuo* and the residue was partitioned between $CH_2Cl_2$ and a saturated $NaHCO_3$ aqueous solution. The organic extracts were dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 75:25) to give methyl 2-[*N*-(4-fluorophenyl)-*N*-isopropylamino]acetate (2.06 g, 86%) as a yellow oil.

To a cooled (-30ºC) solution of methyl 2-[*N*-(4-fluorophenyl)-*N*-isopropylamino]acetate (2.06 g, 9.14 mmol) in $CH_2Cl_2$ (175 mL), DIBAL-H (21 mL of a 1M solution in $CH_2Cl_2$, 21 mmol) was added dropwise. After being stirred at room temperature for 3 hours, the reaction mixture was poured into a saturated $NH_4Cl$ aqueous solution, and the stirring was maintained for an additional 1.5 hours. The organic layer was washed with a saturated $NaHCO_3$ aqueous solution, dried, filtered and concentrated to give crude 2-[*N*-(4-fluorophenyl)-*N*-isopropylamino]ethanol (1.68 g), which was used in the next step without purification.

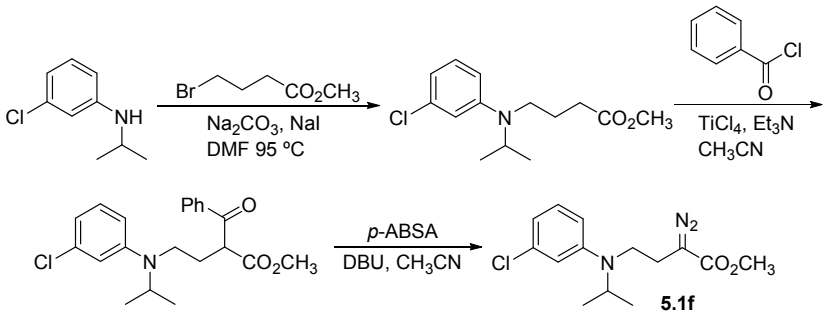
2-[*N*-(4-Fluorophenyl)-*N*-isopropylamino]ethanol (1.68 g) and triethylamine (1.5 mL, 11.1 mmols) were dissolved in $CH_2Cl_2$ (11 mL), and methanesulfonyl chloride (0.7 mL, 9.4 mmols) was added dropwise at 0 ºC. The resulting solution was stirred at room

temperature for 1 h. The mixture was poured into water and ice, basified with a saturated $NaHCO_3$ aqueous solution, and extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried, filtered and concentrated. The residue was dissolved in acetone (64 mL), NaI (12.8 g, 85 mmols) was added, and the mixture was stirred at reflux overnight. The resulting mixture was concentrated *in vacuo* and the residue was partitioned between water and $Et_2O$. The organic extracts were washed with water, dried, filtered and concentrated to give crude 4-fluoro-*N*-(2-iodoethyl)-*N*-isopropylaniline (1.89 g), which was used in the next step without purification.

A solution of methyl 3-oxobutanoate (4.0 mL, 36.8 mmols) in dry THF (31 mL) was added dropwise, under an argon atmosphere, to a stirred suspension of NaH (0.84 g, 36.8 mmols) in dry THF (31 mL) at room temperature. After the mixture became clear (5 min), a solution of 4-fluoro-*N*-(2-iodoethyl)-*N*-isopropylaniline (1.89 g) in dry THF (31 mL) was added dropwise, and the mixture was stirred at 80 ºC for 96 h. The reaction mixture was poured into a saturated ammonium chloride aqueous solution and ice, and then extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 95:5) to give methyl 2-acetyl-4-[*N*-(4-fluorophenyl)-*N*-isopropylamino]butanoate (1.17 g, 43% for three steps) as a yellow oil.

To a solution of methyl 2-acetyl-4-[*N*-(4-fluorophenyl)-*N*-isopropylamino]butanoate (0.74 g, 2.5 mmols) and DBU (0.56 mL, 3.7 mmols) in dry acetonitrile (13 mL) was added dropwise a solution of *p*-ABSA (0.78 g, 3.2 mmols) in dry acetonitrile (11 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was purified by chromatography ($SiO_2$, $CH_2Cl_2$) to give **5.1c** (0.55 g, 78%) as a yellow oil. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.11 (d, *J* = 6.8 Hz, 6H), 2.43 (t, *J* = 6.8 Hz, 2H), 3.26 (t, *J* = 6.8 Hz, 2H), 3.77 (s, 3H), 3.79 (septuplet, *J* = 6.8 Hz, 1H), 6.78-6.84 (m, 2H), 6.90-6.97 (m, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 19.9 (2 $CH_3$), 23.1 ($CH_2$), 42.9 ($CH_2$), 52.1 ($CH_3$), 52.4 (CH), 115.7 (d, *J* = 22.0 Hz, 2 CH), 118.3 (d, *J* = 7.3 Hz, 2 CH), 144.9 (d, *J* = 2.2 Hz, C), 156.6 (d, *J* = 237.5 Hz, C), 168.1 (C). C=$N_2$ was not observed. IR (NaCl) ν 2083, 1692 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{14}H_{19}FN_3O_2$: 280.1456 $[M + H]^+$; found: 280.1457.

**PROCEDURE B: Methyl 4-[*N*-(3-chlorophenyl)-*N*-isopropylamino]-2-diazobutanoate (5.1f).**




A mixture of 3-chloro-*N*-isopropylaniline (0.53 g, 3.12 mmol), methyl 4-bromobutyrate (1.6 mL, 12.5 mmol), $Na_2CO_3$ (0.66 g, 6.23 mmol) and NaI (1.87 g, 12.5 mmol) in DMF (3 mL) was stirred at 95ºC for 24 h. The reaction mixture was partitioned between $Et_2O$ and brine. The organic extracts were washed with brine, dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 97:3) to give methyl 4-[*N*-(3-chlorophenyl)-*N*-isopropylamino]butanoate (0.52 g, 61%) as a yellow oil.

Titanium tetrachloride (0.31 mL, 2.88 mmol) was added dropwise to a solution of benzoyl chloride (0.67 mL, 5.76 mmol) and methyl 4-[*N*-(3-chlorophenyl)-*N*-isopropylamino]butanoate (0.52 g, 1.92 mmol) in $CH_3CN$ (5 mL) at 0ºC. After 15 min, $Et_3N$ (1.6 mL, 11.5 mmol) was added dropwise. The mixture was stirred at reflux for 15 min, cooled to room temperature, poured into a saturated $NaHCO_3$ aqueous solution, and partitioned between water and EtOAc. The organic extracts were dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 95:5) to give methyl 2-benzoyl-4-[*N*-(3-chlorophenyl)-*N*-isopropylamino]butanoate (0.22 g, 31%) as a yellow oil.

To a solution of methyl 2-benzoyl-4-[*N*-(3-chlorophenyl)-*N*-isopropylamino]butanoate (0.32 g, 0.86 mmols) and DBU (0.2 g, 1,29 mmols) in dry acetonitrile (4 mL) was added dropwise a solution of *p*-ABSA (0.27 g, 1,11 mmols) in dry acetonitrile (4 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was purified by chromatography ($SiO_2$, $CH_2Cl_2$) to give methyl

4-[*N*-(3-chlorophenyl)-*N*-isopropylamino]-2-diazobutanoate **5.1f** (0.24 g, 93%) as a yellow oil. $^{1}$H RMN ($CDCl_3$, 400 MHz) δ 1.17 (d, *J* = 6.8 Hz, 6H), 2.50 (m, 2H), 3.32 (m, 2H), 3.80 (s, 3H), 3.99 (septuplet, *J* = 6.8 Hz, 1H), 6.68 (dd, *J* = 8.0 and 2.0 Hz, 2H), 6.78 (t, *J* = 2.0 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 20.1 (2 $CH_3$), 23.5 ($CH_2$), 42.1 ($CH_2$), 50.1 (CH), 52.2 ($CH_3$), 112.3 (CH), 114.0 (CH), 117.2 (CH), 130.3 (CH), 135.3 (C), 149.6 (C), 168.0 (C). C=$N_2$ was not observed. IR (NaCl) ν 2082, 1692 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{14}H_{19}ClN_3O_2$: 296.1160 $[M + H]^+$; found: 296.1159.

**Methyl 2-diazo-4-[*N*-isopropyl-*N*-(4-methylphenyl)amino]butanoate (5.1b). 5.1b** was obtained as a yellow oil following Procedure A [(a) alkylation, 93%; (b) DIBAL-H; (c) MsCl, $Et_3N$; then NaI; (d) $CH_3COCH_2CO_2CH_3$, NaH, 50% three steps; (d) *p*-ABSA, DBU, 64%]. $^{1}$H RMN ($CDCl_3$, 400 MHz) δ 1.14 (d, *J* = 6.8 Hz, 6H), 2.27 (s, 3H), 2.47 (t, *J* = 6.8 Hz, 2H), 3.29 (t, *J* = 6.8 Hz, 2H), 3.78 (s, 3H), 3.91 (septuplet, *J* = 6.8 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 19.9 (2 $CH_3$), 20.4 ($CH_3$), 23.2 ($CH_2$), 42.4 ($CH_2$), 51.4 (CH), 52.0 ($CH_3$), 66.6 (C), 116.3 (2 CH), 127.6 (C), 129.9 (2 CH), 146.2 (C), 168.2 (C). IR (NaCl) ν 2082, 1694 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{15}H_{22}N_3O_2$: 276.1707 $[M + H]^+$; found: 276.1706.

**Methyl 2-diazo-4-[*N*-isopropyl-*N*-(4-methoxyphenyl)amino]butanoate (5.1d). 5.1d** was obtained as a yellow oil following Procedure A [(a) alkylation, 93%; (b) DIBAL-H, 96%; (c) MsCl, $Et_3N$; then NaI; (d) $CH_3COCH_2CO_2CH_3$, NaH, 56% two steps; (d) *p*-ABSA, DBU, 77%]. $^{1}$H RMN ($CDCl_3$, 400 MHz) δ 1.08 (d, *J* = 6.8 Hz, 6H), 2.39 (t, *J* = 6.8 Hz, 2H), 3.23 (t, *J* = 6.8 Hz, 2H), 3.68 (septuplet, *J* = 6.8 Hz, 1H), 3.76 (s, 3H), 3.77 (s, 3H), 6.80-6.89 (m, 4H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 19.9 (2 $CH_3$), 23.0 ($CH_2$), 43.7 ($CH_2$), 52.0 ($CH_3$), 53.2 (CH), 55.7 ($CH_3$), 114.6 (2 CH), 120.3 (2 CH), 142.4 (C), 153.6 (C), 168.2 (C). C=$N_2$ was not observed. IR (NaCl) ν 2083, 1693 cm$^{-1}$.

**Methyl 2-diazo-4-[*N*-isopropyl-*N*-(3-methoxyphenyl)amino]butanoate (5.1e). 5.1e** was obtained as a yellow oil following Procedure A [(a) alkylation, 89%; (b) DIBAL-H; (c) MsCl, $Et_3N$; then NaI; (d) $CH_3COCH_2CO_2CH_3$, NaH, 40% three steps; (d) *p*-ABSA, DBU, 80%]. $^{1}$H RMN ($CDCl_3$, 400 MHz) δ 1.17 (d, *J* = 6.8 Hz, 6H), 2.52 (t, *J* = 7.2 Hz, 2H), 3.33 (t, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 4.02 (septuplet, *J* = 6.8 Hz, 1H),

6.32 (ddd, *J* = 8.4, 2.4 and 0.8 Hz, 1H), 6.39 (t, *J* = 2.4 Hz, 1H), 6.45 (ddd, *J* = 8.4, 2.4 and 0.8 Hz, 1H), 7.15 (t, *J* = 8.4 Hz, 1H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 20.1 (2 $CH_3$), 23.5 ($CH_2$), 42.2 ($CH_2$), 50.2 (CH), 52.0 ($CH_3$), 55.2 ($CH_3$), 101.1 (CH), 102.2 (CH), 107.5 (CH), 130.0 (CH), 149.8 (C), 160.9 (C), 168.0 (C). C=$N_2$ was not observed. IR (NaCl) ν 2082, 1694 $cm^{-1}$.

**Methyl 2-diazo-4-[*N*-(3-iodophenyl)-*N*-isopropylamino]butanoate (5.1g). 5.1g** was obtained as a yellow oil following Procedure B [(a) alkylation, 75%; (b) benzoylation, 37%; (c) *p*-ABSA, DBU, 75%]. $^{1}$H RMN ($CDCl_3$, 400 MHz) δ 1.16 (d, *J* = 6.4 Hz, 6H), 2.48 (t, *J* = 7.6 Hz, 2H), 3.31 (t, *J* = 7.6 Hz, 2H), 3.80 (s, 3H), 3.97 (septuplet, *J* = 6.4 Hz, 1H), 6.77 (dd, *J* = 8.4, 2.8 and 0.8 Hz, 1H), 6.92 (dd, *J* = 8.4 and 7.6 Hz, 1H), 7.04 (ddd, *J* = 7.6, 1.6 and 0.8 Hz, 1H), 7.13 (dd, *J* = 2.8 and 1.6 Hz, 1H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 20.1 (2 $CH_3$), 23.4 ($CH_2$), 42.0 ($CH_2$), 50.1 (CH), 52.2 ($CH_3$), 95.8 (C), 113.5 (CH), 123.0 (CH), 126.3 (CH), 130.8 (CH), 149.7 (C), 168.0 (C). C=$N_2$ was not observed. IR (NaCl) ν 2082, 1691 $cm^{-1}$.

**Methyl 2-diazo-4-{*N*-isopropyl-*N*-[3-(methoxycarbonyl)phenyl]amino}butanoate (5.1h). 5.1h** was obtained as a yellow oil following Procedure B [(a) alkylation, 90%; (b) benzoylation, 29%; (c) *p*-ABSA, DBU, 74%]. $^{1}$H RMN ($CDCl_3$, 400 MHz) δ 1.18 (d, *J* = 6.8 Hz, 6H), 2.51 (m, 2H), 3.38 (m, 2H), 3.79 (s, 3H), 3.90 (s, 3H), 4.08 (septuplet, *J* = 6.8 Hz, 1H), 7.01 (dd, *J* = 8.0 and 1.6 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.40 (ddd, *J* = 8.0, 2.4 and 0.8 Hz, 1H), 7.49 (dd, *J* = 2.4 and 1.6 Hz, 1H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 20.1 (2 $CH_3$), 23.4 ($CH_2$), 42.0 ($CH_2$), 50.5 (CH), 52.2 ($CH_3$), 115.3 (CH), 118.6 (CH), 118.9 (CH), 129.4 (CH), 131.2 (C), 148.4 (C), 167.8 (C), 168.0 (C). 2 C were not observed. IR (NaCl) ν 2083, 1721, 1693 $cm^{-1}$.

**Methyl 2-diazo-4-[*N*-isopropyl-*N*-(3-nitrophenyl)amino]butanoate (5.1i). 5.1i** was obtained as a pale orange oil following Procedure B [(a) alkylation, 90%; (b) benzoylation, 29%; (c) *p*-ABSA, DBU, 74%]. $^{1}$H RMN ($CDCl_3$, 400 MHz) δ 1.23 (d, *J* = 6.8 Hz, 6H), 2.54 (m, 2H), 3.43 (m, 2H), 3.82 (s, 3H), 4.11 (septuplet, *J* = 6.8 Hz, 1H), 7.11 (dd, *J* = 8.4 and 2.4 Hz, 1H), 7.35 (t, *J* = 8.4 Hz, 1H), 7.52 (ddd, *J* = 8.4, 2.4 and 0.8 Hz, 1H), 7.62 (t, *J* = 2.4 Hz, 1H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 20.1 (2 $CH_3$), 23.5 ($CH_2$), 42.2 ($CH_2$), 49.9 (CH), 52.3 ($CH_3$), 107.6 (CH), 111.5 (CH), 119.2 (CH), 130.0

(CH), 149.1 (C), 149.7 (C), 167.9 (C). One C was not observed. IR (NaCl) ν 2082, 1691, 1526, 1356 $cm^{-1}$.

**Methyl 2-diazo-4-[*N*-(3,5-dimethylphenyl)-*N*-isopropylamino]butanoate (5.1j). 5.1j** was obtained as a yellow oil following Procedure B [(a) alkylation, 51%; (b) benzoylation, 42%; (c) *p*-ABSA, DBU, 81%]. $^{1}H$ RMN ($CDCl_3$, 400 MHz) δ 1.15 (d, *J* = 6.8 Hz, 6H), 2.27 (s, 6H), 2.49 (m, 2H), 3.31 (m, 2H), 3.79 (s, 3H), 4.00 (septuplet, *J* = 6.8 Hz, 1H), 6.42 (m, 1H), 6.46 (m, 2H). $^{13}C$ RMN ($CDCl_3$, 100.5 MHz) δ 20.1 (2 $CH_3$), 22.0 (2 $CH_3$), 23.5 ($CH_2$), 42.2 ($CH_2$), 50.4 (CH), 52.1 ($CH_3$), 112.9 (2 CH), 119.7 (CH), 138.8 (C), 148.6 (C), 168.2 (C). C=$N_2$ was not observed. IR (NaCl) ν 2082, 1694 $cm^{-1}$.

**Methyl 2-diazo-4-[*N*-(2-fluorophenyl)-*N*-isopropylamino]butanoate (5.1k). 5.1k** was obtained as an orange oil following Procedure B [(a) alkylation, 57%; (b) benzoylation, 45%; (c) *p*-ABSA, DBU, 84%]. $^{1}H$ RMN ($CDCl_3$, 400 MHz) δ 1.09 (d, *J* = 6.4 Hz, 6H), 2.34 (t, *J* = 6.4 Hz, 2H), 3.26 (t, *J* = 6.4 Hz, 2H), 3.53 (septuplet, *J* = 6.4 Hz, 1H), 3.74 (s, 3H), 6.90-7.08 (m, 4H). $^{13}C$ RMN ($CDCl_3$, 100.5 MHz) δ 19.8 (2 $CH_3$), 22.9 ($CH_2$), 43.0 ($CH_2$), 52.0 ($CH_3$), 52.4 (d, *J* = 3.9 Hz, CH), 116.7 (d, *J* = 21.3 Hz, CH), 123.2 (d, *J* = 7.9 Hz, CH), 124.0 (d, *J* = 3.3 Hz, CH), 124.1 (d, *J* = 3.6 Hz, CH), 136.9 (d, *J* = 9.2 Hz, C), 157.9 (d, *J* = 245.9 Hz, C), 168.2 (C). C=$N_2$ was not observed. IR (NaCl) ν 2084, 1693 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{14}H_{19}FN_3O_2$: 280.1456 $[M + H]^+$; found: 280.1460.

**Methyl 4-(*N*-benzhydryl-*N*-phenylamino)-2-diazobutanoate (5.1l). 5.1l** was obtained as a yellow oil following Procedure B [(a) alkylation, 41%; (b) benzoylation, 50%; (c) *p*-ABSA, DBU, 77%]. $^{1}H$ RMN ($CDCl_3$, 400 MHz) δ 1.98 (m, 2H), 3.50 (m, 2H), 3.70 (s, 3H), 6.16 (s, 1H), 6.74 (t, *J* = 7.2 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 7.17-7.33 (m, 12H). $^{13}C$ RMN ($CDCl_3$, 100.5 MHz) δ 23.0 ($CH_2$), 46.6 ($CH_2$), 52.0 ($CH_3$), 66.7 (CH), 113.9 (2 CH), 117.8 (CH), 127.5 (2 CH), 128.6 (4 CH), 129.3 (4 CH), 129.5 (2 CH), 140.7 (2 C), 148.7 (C), 167.8 (C). C=$N_2$ was not observed. IR (NaCl) ν 2084, 1694 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{24}H_{24}N_3O_2$: 386.1863 $[M + H]^+$; found: 386.1862.

**Methyl 2-diazo-4-[*N*-phenyl-*N*-(1-phenylethyl)amino]butanoate (5.1m). 5.1m** was obtained as a yellow oil following Procedure B [(a) alkylation, 69%; (b) benzoylation, 55%; (c) *p*-ABSA, DBU, 65%]. $^{1}H$ RMN ($CDCl_3$, 400 MHz) δ 1.52 (d, *J* = 7.2 Hz, 3H),

2.25 (ddd, *J* = 15.2, 8.0 and 6.0 Hz, 1H), 2.38 (ddd, *J* = 15.2, 8.0 and 6.0 Hz, 1H), 3.17 (ddd, *J* = 14.4, 8.0 and 6.0 Hz, 1H), 3.27 (ddd, *J* = 14.4, 8.0 and 6.0 Hz, 1H), 3.68 (s, 3H), 5.02 (q, *J* = 7.2 Hz, 1H), 6.80 (tt, *J* = 7.6 and 1.2 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 2H), 7.22-7.33 (m, 7H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 16.6 ($CH_3$), 22.9 ($CH_2$), 43.9 ($CH_2$), 52.0 ($CH_3$), 58.7 (CH), 115.8 (2 CH), 118.5 (CH), 127.2 (CH), 127.4 (2 CH), 128.5 (2 CH), 129.5 (2 CH), 142.5 (C), 148.5 (C), 167.9 (C). C=$N_2$ was not observed. IR (NaCl) ν 2082, 1693 $cm^{-1}$.

**Methyl 4-(*N*-cyclohexyl-*N*-phenylamino)-2-diazobutanoate (5.1n). 5.1n** was obtained as a yellow oil following Procedure B [(a) alkylation, 69%; (b) benzoylation, 34%; (c) *p*-ABSA, DBU, 92%]. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.07-1.45 (m, 5H), 1.58-1.97 (m, 5H), 2.48 (m, 2H), 3.37 (m, 2H), 3.50 (m, 1H), 3.78 (s, 3H), 6.72 (tt, *J* = 7.6 and 0.8 Hz, 1H), 6.81 (dd, *J* = 8.8 and 0.8Hz, 2H), 7.20-7.25 (m, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 23.6 ($CH_2$), 26.0 ($CH_2$), 26.4 (2 $CH_2$), 30.8 (2 $CH_2$), 43.2 ($CH_2$), 52.1 ($CH_3$), 59.3 (CH), 114.6 (2 CH), 117.5 (CH), 129.4 (2 CH), 148.4 (C), 168.2 (C). C=$N_2$ was not observed. IR (NaCl) ν 2081, 1694 $cm^{-1}$.

**Methyl 4-(*N*-cyclopentyl-*N*-phenylamino)-2-diazobutanoate (5.1o). 5.1o** was obtained as a yellow oil following Procedure B [(a) alkylation, 64%; (b) benzoylation, 40%; (c) *p*-ABSA, DBU, 85%]. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.44-1.96 (m, 8H), 2.48 (t, *J* = 7.6 Hz, 2H), 3.37 (t, *J* = 7.6 Hz, 2H), 3.77 (s, 3H), 3.98 (m, 1H), 6.76 (t, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 7.23 (dd, *J* = 8.8 and 7.2 Hz, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 23.1 ($CH_2$), 23.6 (2 $CH_2$), 29.6 (2 $CH_2$), 45.1 ($CH_2$), 52.1 ($CH_3$), 61.3 (CH), 115.8 (2 CH), 118.1 (CH), 129.3 (2 CH), 149.3 (C), 168.1 (C). C=$N_2$ was not observed. IR (NaCl) ν 2081, 1693 $cm^{-1}$.

**Methyl 4-(*N*-*tert*-butyl-*N*-phenylamino)-2-diazobutanoate (5.1p). 5.1p** was obtained as a yellow oil starting from *N*-*tert*-butylaniline[102] following Procedure B [(a) alkylation, 37%; (b) benzoylation, 79%; (c) *p*-ABSA, DBU, 67%]. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.07 (s, 9H), 2.13 (t, *J* = 6.4 Hz, 2H), 3.28 (t, *J* = 6.4 Hz, 2H), 3.73 (s, 3H), 7.10-7.29 (m, 5H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 23.6 ($CH_2$), 28.3 (3 $CH_3$), 46.7 ($CH_2$), 51.9 ($CH_3$),

[102] Seo, H.; Roberts, B. P.; Abboud, K. A.; Merz Jr., K. M.; Hong, S. *Org. Lett.* **2010**, *12*, 4860.

55.5 (C), 125.4 (CH), 128.4 (2 CH), 130.0 (2 CH), 148.2 (C), 168.5 (C). C=$N_2$ was not observed. IR (NaCl) ν 2084, 1694 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{15}H_{22}N_3O_2$: 276.1707 $[M + H]^+$; found: 276.1707.

**Methyl 2-diazo-4-(diphenylamino)butanoate (5.1q). 5.1q** was obtained as a yellow oil starting from 2-(diphenylamino)ethanol[103] and following Procedure A [(a) MsCl, $Et_3N$; then NaI; (b) $CH_3COCH_2CO_2CH_3$, NaH, 18% two steps; (c) *p*-ABSA, DBU, 68%]. $^1H$ RMN ($CDCl_3$, 400 MHz) δ 2.63 (t, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 3.96 (t, *J* = 7.2 Hz, 2H), 6.97 (tt, *J* = 7.2 and 1.2 Hz, 1H), 7.01-7.05 (m, 2H), 7.25-7.31 (m, 2H). $^{13}C$ RMN ($CDCl_3$, 100.5 MHz) δ 22.6 ($CH_2$), 50.4 ($CH_2$), 52.1 ($CH_3$), 71.1 (C), 121.0 (2 CH), 121.8 (CH), 129.5 (2 CH), 147.6 (C), 168.0 (C). IR (NaCl) ν 2082, 1694 $cm^{-1}$.

**Methyl 2-diazo-4-[*N*-(4-methylphenyl)sulfonyl-*N*-phenylamino]butanoate (5.1r). 5.1r** was obtained as a yellow oil starting from *N*-(2-bromoethyl)-4-methyl-*N*-phenylbenzenesulfonamide and following Procedure A [(a) NaI; (b) $CH_3COCH_2CO_2CH_3$, NaH, 43% two steps; (c) *p*-ABSA, DBU, 96%]. $^1H$ RMN ($CDCl_3$, 400 MHz) δ 2.42 (s, 3H), 2.46 (t, *J* = 6.4 Hz, 2H), 3.69 (s, 3H), 3.72 (t, *J* = 6.4 Hz, 2H), 7.03-7.06 (m, 2H), 7.21-7.25 (m, 2H), 7.28-7.34 (m, 3H), 7.43-7.46 (m, 2H). $^{13}C$ RMN ($CDCl_3$, 100.5 MHz) δ 21.7 ($CH_3$), 24.1 ($CH_2$), 49.1 ($CH_2$), 52.1 ($CH_3$), 127.9 (2 CH), 128.2 (CH), 128.5 (2 CH), 129.3 (2 CH), 129.6 (2 CH), 135.0 (C), 139.2 (C), 143.8 (C), 167.6 (C). C=$N_2$ was not observed. IR (NaCl) ν 2085, 1690 $cm^{-1}$.

**Methyl 2-diazo-4-[*N*-isopropyl-*N*-(1-naphthyl)amino]butanoate (5.1s). 5.1s** was obtained as a yellow oil following Procedure B [(a) alkylation, 84%; (b) benzoylation, 31%; (c) *p*-ABSA, DBU, 81%]. $^1H$ RMN ($CDCl_3$, 400 MHz) δ 1.14 (broad, 6H), 2.33 (t, *J* = 6.4 Hz, 2H), 3.36 (broad, 2H), 3.48 (septuplet, *J* = 6.4 Hz, 1H), 3.79 (broad, 3H), 7.20 (dd, *J* = 7.6 and 1.2 Hz, 1H), 7.39 (dd, *J* = 8.0 and 7.2 Hz, 1H), 7.41-7.49 (m, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.77-7.82 (m, 1H), 8.13-8.18 (m, 1H). $^{13}C$ RMN ($CDCl_3$, 100.5 MHz) δ 19.1 (broad, 2 $CH_3$), 22.9 ($CH_2$), 42.1 ($CH_2$), 51.9 ($CH_3$), 55.1 (CH), 118.7 (CH), 123.9 (CH), 124.3 (CH), 125.4 (CH), 125.5 (CH), 125.9 (CH), 128.4 (CH), 131.5 (C),

[103] Sun, W.; Blanton, M. P.; Gabriel, J. L.; Canney, D. J. *Med. Chem. Res.* **2005**, *14*, 241.

135.3 (C), 146.2 (C), 168.4 (C). C=$N_2$ was not observed. IR (NaCl) ν 2083, 1693 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{18}H_{22}N_3O_2$: 312.1707 $[M + H]^+$; found: 312.1705.

**Representative procedure for the C–H insertion reaction (Table 5.1, Entry 3).** A mixture of diazoester **5.1a** (50 mg, 0.19 mmol) and **Ru-1** (4.7 mg, 0.0057 mmol) in dichloromethane (10 mL) was stirred at reflux under an Argon atmosphere for 24 h. The solvent was removed *in vacuo*, and the residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 97:3) to give **5.2a** (44.6 mg, 82%).

**Characterization data for the compounds of Tables 5.1 and 5.2**

**Methyl 1-isopropyl-6-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2b).** $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.14 (d, *J* = 6.4 Hz, 3H), 1.18 (d, *J* = 6.4 Hz, 3H), 1.94 (ddt, *J* = 14.0, 8.8 and 5.6 Hz, 1H), 2.21 (s, 3H), 2.25 (dq, *J* = 14.0 and 4.0 Hz, 1H), 3.14-3.19 (m, 2H), 3.70 (s, 3H), 3.72 (dd, *J* = 5.6 and 4.0 Hz, 1H), 4.10 (septuplet, *J* = 6.4 Hz, 1H), 6.68 (d, *J* = 8.8 Hz, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 6.93 (dd, *J* = 8.8 and 2.4 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 18.6 ($CH_3$), 19.5 ($CH_3$), 20.3 ($CH_3$), 25.2 ($CH_2$), 37.1 ($CH_2$), 43.1 (CH), 47.2 (CH), 52.2 ($CH_3$), 111.9 (CH), 119.0 (C), 124.6 (C), 129.2 (CH), 130.9 (CH), 143.1 (C), 175.1 (C). IR (NaCl) ν 1736 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{15}H_{22}NO_2$: 248.1645 $[M + H]^+$; found: 248.1647.

**Methyl 6-fluoro-1-isopropyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2c).** Brownish oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.14 (d, *J* = 6.4 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.94 (ddt, *J* = 13.6, 8.4 and 6.0 Hz, 1H), 2.27 (dq, *J* = 13.6 and 4.4 Hz, 1H), 3.11-3.19 (m, 2H), 3.71 (dd, *J* = 6.0 and 4.4 Hz, 1H), 3.72 (s, 3H), 4.06 (septuplet, *J* = 6.4 Hz, 1H), 6.64-6.69 (m, 1H), 6.80-6.86 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 18.5 (s, $CH_3$), 19.5 (s, $CH_3$), 25.0 (s, $CH_2$), 37.1 (s, $CH_2$), 43.0 (s, CH), 47.7 (s, CH), 52.3 (s, $CH_3$), 112.6 (d, *J* = 7.3 Hz, CH), 114.9 (d, *J* = 26.2 Hz, CH), 116.6 (d, *J* = 22.2 Hz, CH), 120.1 (d, *J* = 6.4 Hz, C), 141.9 (d, *J* = 1.8 Hz, C), 154.3 (d, *J* = 234.0 Hz, C), 174.4 (s,

C). IR (NaCl) ν 1739 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{14}H_{19}FNO_2$: 252.1394 $[M + H]^+$; found: 252.1397.

**Methyl 6-fluoro-1-isopropyl-2,3-dihydrocyclohepta[b]pyrrole-3a(1H)-carboxylate (5.4c).** $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.04 (d, *J* = 6.4 Hz, 3H), 1.21 (d, *J* = 6.4 Hz, 3H), 2.22 (dt, *J* = 12.8 and 7.2 Hz, 1H), 2.44 (ddd, *J* = 12.8, 7.2 and 5.2 Hz, 1H), 3.10 (ddd, *J* = 8.8, 7.2 and 5.2 Hz, 1H), 3.42 (dt, *J* = 8.8 and 7.2 Hz, 1H), 3.57 (s, 3H), 3.75 (m, 1H), 5.02 (dd, *J* = 8.4 and 4.0 Hz, 1H), 5.15 (dd, *J* = 10.0 and 5.6 Hz, 1H), 6.27 (ddd, *J* = 18.8, 8.4 and 1.6 Hz, 1H), 6.36 (ddd, *J* = 10.0, 8.0 and 1.6 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) δ 18.2 (s, $CH_3$), 18.3 (s, $CH_3$), 36.3 (s, $CH_2$), 44.1 (s, $CH_2$), 46.8 (s, CH), 52.5 (s, $CH_3$), 56.9 (s, C), 87.6 (d, *J* = 10.8 Hz, CH), 112.0 (d, *J* = 27.4 Hz, CH), 120.6 (d, *J* = 12.8 Hz, CH), 122.7 (d, *J* = 34.4 Hz, CH), 143.0 (s, C), 154.3 (d, *J* = 227.9 Hz, C), 174.2 (s, C). IR (NaCl) ν 1735 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{14}H_{19}FNO_2$: 252.1394 $[M + H]^+$; found: 252.1395.

**Methyl 1-isopropyl-6-methoxy-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2d).** Brownish oil. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.13 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.96 (ddt, *J* = 13.2, 8.4 and 6.0 Hz, 1H), 2.27 (dt, *J* = 13.2, and 4.4 Hz, 1H), 3.11-3.18 (m, 2H), 3.70 (s, 3H), 3.73 (dd, *J* = 6.0 and 4.4 Hz, 1H), 3.73 (s, 3H), 4.06 (septuplet, *J* = 6.8 Hz, 1H), 6.68-6.77 (m, 3H). $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) δ 18.4 ($CH_3$), 19.6 ($CH_3$), 25.4 ($CH_2$), 37.2 ($CH_2$), 43.2 (CH), 47.7 (CH), 52.3 ($CH_3$), 56.0 ($CH_3$), 113.1 (CH), 114.4 (CH), 116.1 (CH), 120.4 (C), 140.0 (C), 150.5 (C), 174.8 (C). IR (NaCl) ν 1736 $cm^{-1}$.

**Methyl 1-isopropyl-7-methoxy-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2e).** Brownish oil. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.16 (d, *J* = 6.4 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.91 (ddt, *J* = 13.6, 8.8 and 6.0 Hz, 1H), 2.25 (dq, *J* = 13.6 and 4.4 Hz, 1H), 3.16-3.21 (m, 2H), 3.70 (s, 3H), 3.71 (dd, *J* = 6.0 and 4.4 Hz, 1H), 3.77 (s, 3H), 4.08 (septuplet, *J* = 6.4 Hz, 1H), 6.18 (dd, *J* = 8.4 and 2.4 Hz, 1H), 6.29 (dd, *J* = 2.4 and 0.8 Hz, 1H), 6.99 (dd, *J* = 8.4 and 0.8 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) δ 18.8 ($CH_3$), 19.5 ($CH_3$), 25.0 ($CH_2$), 37.0 ($CH_2$), 42.3 (CH), 47.3 (CH), 52.2 ($CH_3$), 55.3 ($CH_3$), 98.0

(CH), 100.2 (CH), 111.9 (C), 131.0 (CH), 146.2 (C), 160.3 (C), 175.1 (C). IR (NaCl) ν 1737 $cm^{-1}$.

**Methyl 1-isopropyl-5-methoxy-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2e').** $^{1}H$ NMR ($CDCl_3$, 400 MHz, signals from a 1.5:1 mixture of **5.2e** and **5.2e'**) δ 1.15 (d, *J* = 6.4 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 2.00 (tdd, *J* = 10.8, 6.8 and 4.0 Hz, 1H), 2.12-2.19 (m, 1H), 3.03 (ddd, *J* = 12.0, 10.8 and 2.8 Hz, 1H ), 3.13 (dt, *J* = 12.0 and 4.4 Hz, 1H), 3.67 (s, 3H), 3.75 (s, 3H), 3.91 (dd, *J* = 6.8 and 4.4 Hz, 1H), 4.15 (septuplet, *J* = 6.4 Hz, 1H), 6.22 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 7.09 (t, *J* = 8.4 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100.6 MHz, signals from a 1.5:1 mixture of **2e** and **2e'**) δ 19.0 ($CH_3$), 19.7 ($CH_3$), 25.9 ($CH_2$), 36.8 ($CH_2$), 38.3 (CH), 47.5 (CH), 52.0 ($CH_3$), 55.6 ($CH_3$), 98.5 (CH), 105.1 (CH), 108.4 (C), 128.5 (CH), 146.6 (C), 158.3 (C), 176.2 (C).

**Methyl 7-chloro-1-isopropyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2f).** Brownish oil. $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 1.17 (d, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.89 (m, 1H), 2.27 (dq, *J* = 12.4 and 4.4 Hz, 1H), 3.18-3.22 (m, 2H), 3.70 (s, 3H), 3.70 (masked, 1H), 4.05 (septuplet, *J* = 6.8 Hz, 1H), 6.54 (dd, *J* = 8.4 and 2.0 Hz, 1H), 6.70 (d, *J* = 2.0 Hz, 1H), 6.98 (dd, *J* = 8.4 and 0.8 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) δ 18.8 ($CH_3$), 19.4 ($CH_3$), 25.5 ($CH_2$), 37.0 ($CH_2$), 42.5 (CH), 47.5 (CH), 52.3 ($CH_3$), 111.2 (CH), 115.1 (CH), 117.1 (C), 131.4 (CH), 134.3 (C), 146.1 (C), 174.5 (C). IR (NaCl) ν 1736$cm^{-1}$.

**Methyl 5-chloro-1-isopropyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2f').** $^{1}H$ NMR ($CDCl_3$, 400 MHz, signals from a 2:1 mixture of **5.2f** and **5.2f'**) δ 1.16 (d, *J* = 6.4 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.89-1.98 (m, 1H), 2.28-2.35 (m, 1H), 3.00 (td, *J* = 12.0 and 3.2 Hz, 1H), 3.21-3.27 (m, 1H), 3.70 (s, 3H), 4.07-4.10 (maked, 1H), 4.13 (septuplet, *J* = 6.4 Hz, 1H), 6.66 (dd, *J* = 8.8 and 1.2 Hz, 1H), 6.69 (dd, *J* = 8.4 and 1.2 Hz, 1H), 7.04 (dd, *J* = 8.4 and 8.0 Hz, 1H).

**Methyl 7-iodo-1-isopropyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2g).** Violet oil. $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 1.16 (d, *J* = 6.4 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.88 (ddt, *J* = 13.2, 9.2 and 6.0 Hz, 1H), 2.27 (dq, *J* = 13.2 and 4.0 Hz, 1H), 3.14-3.21 (m, 2H), 3.68 (t, *J* = 4.8 Hz, 1H), 3.69 (s, 3H), 4.04 (septuplet, *J* = 6.4 Hz, 1H), 6.78 (dd, *J* =

8.0 and 0.8 Hz, 1H), 6.89 (dd, *J* = 8.0 and 1.6 Hz, 1H), 7.03 (dd, *J* = 1.6 and 0.8 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 1:0.13 mixture of **5.2g** and **5.2g'**) δ 18.9 ($CH_3$), 19.4 ($CH_3$), 24.4 ($CH_2$), 36.9 ($CH_2$), 42.7 (CH), 47.4 (CH), 52.3 ($CH_3$), 94.6 (C), 118.3 (C), 120.0 (CH), 124.2 (CH), 131.9 (CH), 146.3 (C), 174.3 (C). IR (NaCl) ν 1734 $cm^{-1}$.

**Methyl 5-iodo-1-isopropyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2g').** $^1$H NMR ($CDCl_3$, 400 MHz, signals from a ≈ 1:0.13 mixture of **5.2g** and **5.2g'**) δ 1.16 (d, *J* = 6.4 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.87-1.95 (m, 1H), 2.35 (dq, *J* = 13.2 and 3.2 Hz, 1H), 2.98 (ddd, *J* = 13.2, 12.0 and 3.2 Hz, 1H), 3.24 (dddd, *J* = 12.0, 4.8, 2.8 and 1.6 Hz, 1H), 3.69 (maked, 1H), 3.71 (s, 3H), 4.12 (septuplet, *J* = 6.4 Hz, 1H), 6.74 (dd, *J* = 8.4 and 1.2 Hz, 1H), 6.80 (dd, *J* = 8.4 and 7.6 Hz, 1H), 7.13 (dd, *J* = 7.6 and 1.2 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, significant signals from a ≈ 1:0.13 mixture of **5.2g** and **5.2g'**) δ 19.1 ($CH_3$), 19.5 ($CH_3$), 25.7 ($CH_2$), 37.1 ($CH_2$), 49.6 (CH), 52.4 ($CH_3$), 104.4 (C), 111.8 (C), 126.5 (CH), 129.9 (CH), 174.1 (C).

**Methyl 1-isopropyl-7-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2h).** Brownish oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.18 (d, *J* = 6.4 Hz, 3H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.93 (ddt, *J* = 13.2, 9.2 and 5.6 Hz, 1H), 2.30 (dq, *J* = 13.2 and 4.4 Hz, 1H), 3.17-3.27 (m, 2H), 3.70 (s, 3H), 3.78 (dd, *J* = 6.0 and 4.4 Hz, 1H), 3.88 (s, 3H), 4.23 (septuplet, *J* = 6.4 Hz, 1H), 7.12 (dd, *J* = 8.0 and 0.8 Hz, 1H), 7.23 (dd, *J* = 8.0 and 1.6 Hz, 1H), 7.43 (dd, *J* = 1.6 and 0.8 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 18.8 ($CH_3$), 19.5 ($CH_3$), 24.5 ($CH_2$), 37.1 ($CH_2$), 43.1 (CH), 47.3 (CH), 52.1 ($CH_3$), 52.3 ($CH_3$), 112.5 (CH), 116.4 (CH), 123.6 (C), 130.2 (C), 130.4 (CH), 145.1 (C), 167.8 (C), 174.3 (C). IR (NaCl) ν 1735, 1716 $cm^{-1}$.

**Methyl 1-isopropyl-7-nitro-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2i).** Brownish oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.22 (d, *J* = 6.8 Hz, 3H), 1.24 (d, *J* = 6.8 Hz, 3H), 1.91 (ddt, *J* = 13.6, 10.4 and 5.2 Hz, 1H), 2.33 (dq, *J* = 13.6 and 4.0 Hz, 1H), 3.20-3.33 (m, 2H), 3.72 (s, 3H), 3.80 (dd, *J* = 5.6 and 4.0 Hz, 1H), 4.18 (septuplet, *J* = 6.8 Hz, 1H), 7.18 (dd, *J* = 8.0 and 0.8 Hz, 1H), 7.39 (dd, *J* = 8.0 and 2.4 Hz, 1H), 7.55 (dd, *J* = 2.4 and 0.8 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 18.8 ($CH_3$), 19.3 ($CH_3$), 24.0

($CH_2$), 37.0 ($CH_2$), 43.0 (CH), 47.8 (CH), 52.5 ($CH_3$), 105.6 (CH), 109.8 (CH), 125.2 (C), 130.9 (CH), 145.6 (C), 148.8 (C), 173.5 (C). IR (NaCl) ν 1736, 1522, 1345 $cm^{-1}$.

**Methyl 1-isopropyl-5,7-dimethyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2j).** Brownish oil. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.14 (d, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.90 (dddd, *J* = 13.2, 12.4, 5.6 and 4.8 Hz, 1H), 2.14 (s, 3H), 2.24 (s, 3H), 2.29 (dq, *J* = 13.2 and 3.2 Hz, 1H), 3.06 (td, *J* = 12.4 and 3.2 Hz, 1H), 3.20 (dddd, *J* = 12.4, 4.8, 3.2 and 1.2 Hz, 1H), 3.67 (s, 3H), 3.81 (ddd, *J* = 5.6, 3.2 and 1.2 Hz, 1H), 4.16 (septuplet, *J* = 6.8 Hz, 1H), 6.33 (s, 1H), 6.49 (s, 1H). $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) δ 18.9 ($CH_3$), 19.6 ($CH_3$), 20.0 ($CH_3$), 22.0 ($CH_3$), 25.6 ($CH_2$), 36.4 ($CH_2$), 40.4 (CH), 47.5 (CH), 52.2 ($CH_3$), 110.4 (CH), 115.5 (C), 118.9 (CH), 137.4 (C), 137.6 (C), 145.4 (C), 175.3 (C). IR (NaCl) ν 1728 $cm^{-1}$.

**Methyl *N*-(3,5-dimethylphenyl)-2,2-dimethylpyrrolidine-3-carboxylate (5.3j).** Significant signals from a 3:1 mixture of **5.2j** and **5.3j**. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.28 (s, 3H), 1.62 (s, 3H), 2.06 (dtd, *J* = 13.4, 6.4 and 2.8 Hz, 1H), 2.26 (s, 6H), 2.26-2.32 (m, 1H), 2.89 (dd, *J* = 11.2 and 6.8 Hz, 1H), 3.32-3.44 (m, 2H), 3.74 (s, 3H), 6.39 (s, 1H), 6.42 (s, 2H).

**Methyl 8-fluoro-1-isopropyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2k).** $^1H$ NMR ($CDCl_3$, 400 MHz, signals from a ≈ 1:1.4 mixture of **5.3k** and **5.2k**) δ 1.13 (dd, *J* = 6.8 and 1.2 Hz, 3H), 1.19 (dd, *J* = 6.8 and 1.2 Hz, 3H), 1.92 (dddd, *J* = 13.6, 9.6, 5.6 and 5.2 Hz, 1H), 2.24 (dq, *J* = 13.6 and 4.8 Hz, 1H), 3.13-3.25 (m, 2H), 3.70 (s, 3H), 3.75 (t, *J* = 5.6 Hz, 1H), 4.14 (septuplet of doublets, *J* = 6.8 and 1.6 Hz, 1H), 6.66 (td, *J* = 8.0 and 4.8 Hz, 1H), 6.84-6.91 (m, 2H). $^{13}C$ NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 1:1.4 mixture of **5.3k** and **5.2k**) δ 20.0 (s, $CH_3$), 20.6 (s, $CH_3$), 25.3 (s, $CH_2$), 38.2 (s, $CH_2$), 43.0 (d, *J* = 3.0 Hz, CH), 52.1 (d, *J* = 12.5 Hz, CH), 52.3 (s, $CH_3$), 115.6 (d, *J* = 22.5 Hz, CH), 118.2 (d, *J* = 8.5 Hz, CH), 125.2 (d, *J* = 2.8 Hz, CH), 125.8 (d, *J* = 3.8 Hz, C), 135.3 (d, *J* = 7.7 Hz, C), 154.1 (d, *J* = 242.3 Hz, C), 174.5 (C).

**Methyl *N*-(2-fluorophenyl)-2,2-dimethylpyrrolidine-3-carboxylate (5.3k).** $^1H$ NMR ($CDCl_3$, 400 MHz, signals from a ≈ 11:1 mixture of **5.3k** and **5.2k**) δ 1.05 (d, *J* = 1.2 Hz, 3H), 1.31 (d, *J* = 1.6 Hz, 3H), 2.12 (dtd, *J* = 12.8, 8.4 and 4.4 Hz, 1H), 2.37 (dtd, *J* =

12.8, 9.2 and 7.2 Hz, 1H), 2.90 (dd, *J* = 9.2 and 8.4 Hz, 1H), 3.42 (q, *J* = 8.4 Hz, 1H), 3.51 (dt, *J* = 8.4 and 4.4 Hz, 1H), 3.72 (s, 3H), 6.97-7.07 (m, 3H), 7.16 (td, *J* = 8.0 and 1.6 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 11:1 mixture of **5.3k** and **5.2k**) δ 21.1 (d, *J* = 3.9 Hz, $CH_3$), 25.3 (d, *J* = 2.3 Hz, $CH_2$), 27.1 (d, *J* = 3.2 Hz, $CH_3$), 49.1 (d, *J* = 4.1 Hz, $CH_2$), 51.8 (s, $CH_3$), 55.3 (s, CH), 64.4 (s, C), 116.7 (d, *J* = 22.4 Hz, CH), 124.0 (d, *J* = 3.4 Hz, CH), 124.3 (d, *J* = 8.2 Hz, CH), 127.2 (d, *J* = 3.5 Hz, CH), 134.2 (d, *J* = 9.9 Hz, C), 158.8 (d, *J* = 246.6 Hz, C), 173.6 (C).

**Methyl 1-benzhydryl-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2l).** Yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.93 (dddd, *J* = 13.6, 10.0, 5.6 and 4.4 Hz, 1H), 2.17 (dddd, *J* = 13.6, 5.6, 4.4 and 3.6 Hz, 1H), 3.05 (dtd, *J* = 12.4, 4.4 and 1.2 Hz, 1H), 3.14 (ddd, *J* = 12.4, 10.0 and 3.6 Hz, 1H), 3.70 (s, 3H), 3.80 (t, *J* = 5.6 Hz, 1H), 6.17 (s, 1H), 6.60-6.64 (m, 2H), 7.04 (ddd, *J* = 8.4, 7.6 and 1.6 Hz, 1H), 7.11 (ddd, *J* = 7.6, 1.6 and 0.8 Hz, 1H), 7.16-7.36 (m, 10H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 25.0 ($CH_2$), 42.1 (CH), 43.2 ($CH_2$), 52.2 ($CH_3$), 66.0 (CH), 112.2 (CH), 116.1 (CH), 118.7 (C), 127.4 (CH), 127.5 (CH), 128.6 (2 CH), 128.7 (2 CH), 128.7 (CH), 129.0 (2 CH), 129.3 (2 CH), 130.0 (CH), 140.4 (C), 140.5 (C), 145.3 (C), 174.8 (C). IR (NaCl) ν 1732 cm$^{-1}$. HRMS (ESI-TOF) cald for $C_{24}H_{24}NO_2$: 358.1802 $[M + H]^+$; found: 358.1802.

**Methyl 1-(1-phenylethyl)-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2m).** Yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz, 2:1 mixture of diastereomers) δ 1.57 (d, *J* = 6.8 Hz, 3H major diastereomer), 1.58 (d, *J* = 6.8 Hz, 3H minor diastereomer), 1.88 (dddd, *J* = 13.2, 11.6, 5.6 and 4.4 Hz, 1H major diastereomer), 1.97 (dddd, *J* = 13.2, 9.6, 5.6 and 4.4 Hz, 1H minor diastereomer), 2.16-2.26 (m, 1H major and 1H minor diastereomer), 3.01 (dtd, *J* = 12.0, 4.4 and 1.2 Hz, 1H major diastereomer), 3.07-3.20 (m, 2H minor diastereomer), 3.28 (td, *J* = 12.0 and 3.2 Hz, 1H major diastereomer), 3.69 (s, 3H minor diastereomer), 3.70 (s, 3H major diastereomer), 3.76 (dd, *J* = 6.0 and 3.2 Hz, 1H major diastereomer), 3.81 (t, *J* = 5.6 Hz, 1H minor diastereomer), 5.13 (q, *J* = 6.8 Hz, 1H minor diastereomer), 5.16 (q, *J* = 6.8 Hz, 1H major diastereomer), 6.58-6.64 (m, 1H major and 1H minor diastereomer), 6.73-6.79 (m, 1H major and 1H minor diastereomer), 7.05-7.35 (m, 7H major and 7H minor diastereomer). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, 2:1 mixture of diastereomers) δ 16.1 ($CH_3$ major), 16.4 ($CH_3$ minor), 24.4 ($CH_2$ major), 25.3 ($CH_2$

minor), 38.9 ($CH_2$ major), 40.2 ($CH_2$ minor), 42.7 (CH major), 43.5 (CH minor), 52.1 ($CH_3$ minor), 52.2 ($CH_3$ major), 54.9 (CH major), 55.2 (CH minor), 111.4 (CH major), 111.8 (CH minor), 115.7 (CH major), 115.9 (CH minor), 118.5 (C major), 119.0 (C minor), 127.0 (CH minor), 127.0 (2 CH major), 127.1 (2 CH minor), 127.1 (CH major), 128.5 (CH minor), 128.6 (2 CH minor), 128.6 (2 CH major), 128.7 (CH major), 130.0 (CH minor), 130.8 (CH major), 142.4 (C minor), 142.7 (C major), 145.2 (C minor), 145.4 (C major), 174.8 (C major), 174.9 (C minor). IR (NaCl) ν 1732 $cm^{-1}$.

**Methyl 1-cyclohexyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2n).** Brownish oil. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.14 (qt, *J* = 12.8 and 3.6 Hz, 1H), 1.25-1.55 (m, 4H), 1.69 (m, 1H), 1.75-1.97 (m, 5H), 2.26 (dq, *J* = 13.2 and 4.4 Hz, 1H), 3.23-3.27 (m, 2H), 3.61 (tt, *J* = 11.6 and 3.6 Hz, 1H), 3.70 (s, 3H), 3.75 (t, *J* = 4.8 Hz, 1H), 6.57 (t, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 7.07-7.12 (m, 2H). $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) δ 25.0 ($CH_2$), 26.2 ($CH_2$), 26.4 ($CH_2$), 29.5 ($CH_2$), 29.9 ($CH_2$), 30.0 ($CH_2$), 38.6 ($CH_2$), 43.0 (CH), 52.2 ($CH_3$), 56.6 (CH), 111.4 (CH), 115.2 (CH), 118.8 (C), 128.5 (CH), 130.4 (CH), 145.1 (C), 174.9 (C). IR (NaCl) ν 1732 $cm^{-1}$.

**Methyl 1-cyclopentyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2o).** Brownish oil. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.55-1.75 (m, 6H), 1.83-2.00 (m, 3H), 2.28 (dq, *J* = 13.2 and 4.4 Hz, 1H), 3.17-3.30 (m, 2H), 3.70 (s, 3H), 3.76 (t, *J* = 4.4 Hz, 1H), 4.21 (m, 1H), 6.59 (t, *J* = 7.2 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 7.07-7.14 (m, 2H). $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) δ 24.3 ($CH_2$), 28.0 ($CH_2$), 28.7 ($CH_2$), 39.0 ($CH_2$), 43.0 (CH), 52.2 ($CH_3$), 48.7 (CH), 111.9 (CH), 115.5 (CH), 119.0 (C), 128.5 (CH), 130.2 (CH), 145.9 (C), 174.9 (C). IR (NaCl) ν 1735 $cm^{-1}$.

**Methyl 1-phenyl-1-azaspiro[4.4]nonane-4-carboxylate (5.3o).** $^1H$ NMR ($CDCl_3$, 400 MHz, signals from a ≈ 1:8 mixture of **5.2o** and **5.3o**) δ 1.42 (m, 1H), 1.58-2.00 (m, 5H), 2.05-2.30 (m, 3H), 2.48 (m, 1H), 2.95 (dd, *J* = 8.4 and 6.4 Hz, 1H), 3.40 (q, *J* = 8.4 Hz, 1H), 3.52 (td, *J* = 8.4 and 4.4 Hz, 1H), 3.71 (s, 3H), 6.65 (d, *J* = 8.0 Hz, 2H), 6.66 (t, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 2H). $^{13}C$ NMR ($CDCl_3$, 100.6 MHz, signals from a ≈ 1:8 mixture of **5.2o** and **5.3o**) δ 25.0 ($CH_2$), 25.7 ($CH_2$), 26.0 ($CH_2$), 30.2 ($CH_2$), 34.1 ($CH_2$),

48.8 (CH), 51.9 ($CH_3$), 57.6 ($CH_2$), 73.9 (C), 113.8 (2 CH), 116.0 (CH), 129.0 (2 CH), 145.1 (C), 173.4 (C).

**Methyl 1-*tert*-butyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2p).** Colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9H), 1.90 (dddd, *J* = 13.2, 8.0, 6.8 and 5.2 Hz, 1H), 2.40 (dddd, *J* = 10.8, 7.6, 6.8 and 5.2 Hz, 1H), 3.10 (ddd, *J* = 11.2, 6.8 and 5.6 Hz, 1H), 3.37 (ddd, *J* = 11.2, 8.0 and 6.8 Hz, 1H), 3.67 (s, 3H), 3.63 (t, *J* = 5.2 Hz, 1H), 6.74 (ddd, *J* = 7.6, 6.8 and 1.6 Hz, 1H), 7.04-7.13 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 ($CH_2$), 29.1 (3 $CH_3$), 41.3 (CH), 43.8 ($CH_2$), 52.1 ($CH_3$), 55.2 (C), 118.2 (CH), 119.5 (CH), 126.8 (CH), 128.3 (CH), 128.6 (C), 145.9 (C), 174.8 (C). IR (NaCl) ν 1732 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{15}H_{22}NO_2$: 248.1645 $[M + H]^+$; found: 248.1644.

**Methyl 1-phenyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (5.2q).** Brownish oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.16 (dddd, *J* = 13.6, 10.0, 5.6 and 4.0 Hz, 1H), 2.36 (dddd, *J* = 13.6, 5.6, 4.0 and 3.6 Hz, 1H), 3.60 (dddd, *J* = 11.6, 5.6, 4.0 and 0.8 Hz, 1H), 3.74 (s, 3H), 3.76 (ddd, *J* = 11.6, 10.0 and 4.0 Hz, 1H), 3.88 (t, *J* = 5.6 Hz, 1H), 6.69-6.74 (m, 2H), 6.95-7.01 (m, 1H), 7.13 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.18 (ddd, *J* = 7.6, 1.6 and 0.8 Hz, 1H), 7.22-7.27 (m, 2H), 7.33-7.38 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 25.3 ($CH_2$), 42.6 (CH), 48.1 ($CH_2$), 52.4 ($CH_3$), 116.0 (CH), 118.3 (CH), 120.1 (C), 124.5 (CH), 125.6 (2 CH), 127.9 (CH), 129.7 (2 CH), 130.2 (CH), 144.6 (C), 148.1 (C), 174.8 (C). IR (NaCl) ν 1734 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{17}H_{18}NO_2$: 268.1332 $[M + H]^+$; found: 268.1334.

**Methyl 1-isopropyl-1,2,3,4-tetrahydrobenzo[*h*]quinoline-4-carboxylate (5.2s).** $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.18 (d, *J* = 6.8 Hz, 3H), 1.23 (d, *J* = 6.8 Hz, 3H), 2.04 (dddd, *J* = 13.2, 9.6, 6.8 and 4.4 Hz, 1H), 2.26 (dddd, *J* = 13.2, 6.0, 4.8 and 4.0 Hz, 1H), 3.31 (ddd, *J* = 13.2, 6.0 and 4.4 Hz, 1H), 3.40 (ddd, *J* = 13.2, 9.6 and 4.0 Hz, 1H), 3.70 (s, 3H), 3.91 (dd, *J* = 6.8 and 4.8 Hz, 1H), 4.06 (septuplet, *J* = 6.8 Hz, 1H), 7.22 (dd, *J* = 8.4 and 0.8 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.37-7.42 (m, 2H), 7.72-7.76 (m, 1H), 7.93-7.98 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 20.6 ($CH_3$), 20.8 ($CH_3$), 24.9 ($CH_2$), 39.6 ($CH_2$), 43.0 (CH), 52.3 ($CH_3$), 55.1 (CH), 120.8 (CH), 124.6 (CH), 124.9 (CH), 125.5 (CH), 127.5 (CH), 128.5 (CH), 128.7 (C), 134.7 (C), 144.0 (C), 147.5 (C), 175.3 (C). IR

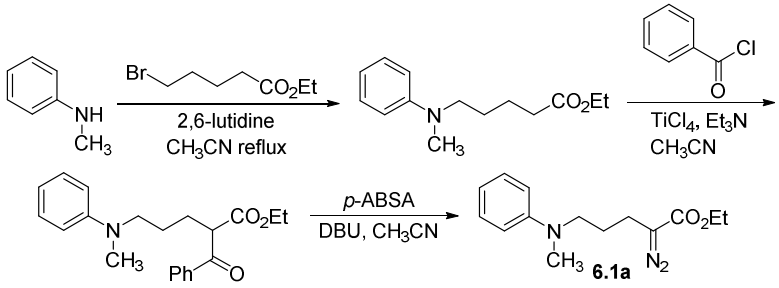
(NaCl) ν 1734 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{18}H_{22}NO_2$: 284.1645 $[M + H]^+$; found: 284.1646.

**Methyl 2,2-dimethyl-1-(1-naphthyl)pyrrolidine-3-carboxylate (5.3s).** $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 3H), 1.15 (s, 3H), 2.21 (dtd, *J* = 13.2, 8.8 and 5.2 Hz, 1H), 2.47 (dddd, *J* = 13.2, 9.2, 8.8 and 6.0 Hz, 1H), 3.07 (t, *J* = 8.8 Hz, 1H), 3.41 (td, *J* = 8.8 and 6.0 Hz, 1H), 3.53 (td, *J* = 9.2 and 5.2 Hz, 1H), 3.74 (s, 3H), 7.39-7.47 (m, 4H), 7.68 (dd, *J* = 7.2 and 1.6 Hz, 1H), 7.78-7.82 (m, 1H), 8.47-8.51 (m, 1H). $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) δ 14.3 ($CH_3$), 25.4 ($CH_2$), 26.9 ($CH_3$), 51.5 ($CH_2$), 51.8 ($CH_3$), 55.3 (CH), 64.9 (C), 124.9 (CH), 125.3 (CH), 125.4 (2 CH), 125.7 (CH), 126.0 (CH), 127.9 (CH), 134.7 (C), 134.8 (C), 143.9 (C), 174.4 (C). IR (NaCl) ν 1734 $cm^{-1}$. HRMS (ESI-TOF) cald for $C_{18}H_{22}NO_2$: 284.1645 $[M + H]^+$; found: 284.1648.

## 8.5. Experimental Part of Chapter 6

### Experimental procedures and characterization data for the starting materials

**Ethyl 2-diazo-5-(*N*-methyl-*N*-phenylamino)pentanoate (6.1a).**




A mixture of *N*-methylaniline (0.25 mL, 2.33 mmol), ethyl 5-bromovalerate (0.39 mL, 2.45 mmol) and 2,6-lutidine (0.28 mL, 2.45 mmol) in acetonitrile (10 mL) was stirred at reflux for 48 h. The solvent was removed *in vacuo* and the resulting residue was partitioned between $Et_2O$ and water. The organic extracts were washed with brine, dried, filtered and concentrated to give ethyl 5-(*N*-methyl-*N*-phenylamino)pentanoate (0.4 g), which was used in the next step without further purification.

Titanium tetrachloride (0.27 mL, 2.50 mmol) was added dropwise to a solution of benzoyl chloride (0.57 mL, 4.91 mmol) and ethyl 4-[*N*-methyl-*N*-phenylamino]pentanoate (0.4 g) in $CH_3CN$ (10 mL) at 0ºC. After 15 min, $Et_3N$ (1.4 mL, 10.0 mmol) was added dropwise. The mixture was stirred at reflux for 15 min and then cooled to 0 ºC. 7.9M Aqueous solution of dimethylamine (4.2 mL, 33 mmol) was added, and the resulting mixture was stirred at room temperature for 10 min. The reaction mixture was poured into a saturated $NaHCO_3$ aqueous solution, and partitioned between water and EtOAc. The organic extracts were dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, from hexanes to hexanes-EtOAc 95:5) to give ethyl 2-benzoyl-5-(*N*-methyl-*N*-phenylamino)pentanoate (0.41 g, 52%) as a yellow oil.

To a solution of ethyl 2-benzoyl-5-(*N*-methyl-*N*-phenylamino)pentanoate (0.41 g, 1.20 mmols) and DBU (0.27 mL, 1,80 mmols) in dry acetonitrile (4 mL) was added dropwise a solution of *p*-ABSA (0.38 g, 1,56 mmols) in dry acetonitrile (4 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was purified by chromatography ($SiO_2$, $CH_2Cl_2$) to give ethyl 2-diazo-5-(*N*-methyl-*N*-phenylamino)pentanoate **6.1a** (0.28 g, 89%) as a yellow oil. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.27 (t, *J* = 7.2 Hz, 3H), 1.80 (quint, *J* = 7.6 Hz, 2H), 2.35 (t, *J* = 7.6 Hz, 2H), 2.93 (s, 3H), 3.37 (t, *J* = 7.6 Hz, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 6.68-6.72 (m, 3H), 7.20-7.25 (m, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 14.7 ($CH_3$), 21.0 ($CH_2$), 25.0 ($CH_2$), 38.6 ($CH_3$), 51.9 ($CH_2$), 60.9 ($CH_2$), 112.5 (2 CH), 116.5 (CH), 129.3 (2 CH), 149.3 (C), 167.6 (C). C=$N_2$ was not observed.

**Methyl 2-diazo-5-(*N*-methyl-*N*-phenylamino)pentanoate (6.1b)** was prepared following the procedure described above. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.80 (quint, *J* = 7.6 Hz, 2H), 2.35 (t, *J* = 7.6 Hz, 2H), 2.93 (s, 3H), 3.37 (t, *J* = 7.6 Hz, 2H), 3.76 (s, 3H), 6.69-6.72 (m, 3H), 7.20-7.25 (m, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 21.0 ($CH_2$), 25.0 ($CH_2$), 38.5 ($CH_3$), 51.8 ($CH_2$), 52.1 ($CH_3$), 112.5 (2 CH), 116.6 (CH), 129.3 (2 CH), 149.3 (C), 168.0 (C). C=$N_2$ was not observed.

**Methyl 2-diazo-5-[*N*-methyl-*N*-(4-methylphenyl)amino]pentanoate (6.1c)** was prepared following the procedure described above. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.78

(quint, *J* = 7.6 Hz, 2H), 2.25 (s, 3H), 2.34 (t, *J* = 7.6 Hz, 2H), 2.88 (s, 3H), 3.32 (t, *J* = 7.6 Hz, 2H), 3.76 (s, 3H), 6.64 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 20.4 ($CH_3$), 21.1 ($CH_2$), 24.9 ($CH_2$), 38.8 ($CH_3$), 52.1 ($CH_3$), 52.3 ($CH_2$), 113.1 (2 CH), 126.0 (C), 129.9 (2 CH), 147.5 (C), 168.0 (C). C=$N_2$ was not observed.

**Methyl 2-diazo-5-[*N*-methyl-*N*-(4-methoxyphenyl)amino]pentanoate (6.1d)** was prepared following the procedure described above. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.76 (quint, *J* = 7.6 Hz, 2H), 2.34 (t, *J* = 7.6 Hz, 2H), 2.84 (s, 3H), 3.26 (t, *J* = 7.6 Hz, 2H), 3.76 (s, 6H), 6.69-6.73 (m, 2H), 6.80-6.85 (m, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 21.1 ($CH_2$), 24.9 ($CH_2$), 39.5 ($CH_3$), 52.1 ($CH_3$), 53.1 ($CH_2$), 55.9 ($CH_3$), 114.9 (2 CH), 115.2 (2 CH), 144.5 (C), 152.1 (C), 168.0 (C). C=$N_2$ was not observed.

**Methyl 2-diazo-5-(*N*-benzyl-*N*-phenylamino)pentanoate (6.5)** was prepared following the procedure described above. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.86 (quint, *J* = 7.6 Hz, 2H), 2.35 (t, *J* = 7.6 Hz, 2H), 3.44 (t, *J* = 7.6 Hz, 2H), 3.75 (s, 3H), 4.54 (s, 2H), 6.68-6.70 (m, 3H), 7.17-7.32 (m, 7H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 21.1 ($CH_2$), 25.4 ($CH_2$), 50.3 ($CH_2$), 52.1 ($CH_3$), 54.8 ($CH_2$), 112.6 (2 CH), 116.7 (CH), 126.7 (2 CH), 127.0 (CH), 128.7 (2 CH), 129.4 (2 CH), 138.9 (C), 148.5 (C), 167.9 (C). C=$N_2$ was not observed.

**Methyl 2-diazo-5-(*N*-allyl-*N*-phenylamino)pentanoate (6.8)** was prepared following the procedure described above. $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.83 (quint, *J* = 7.6 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 3.36 (t, *J* = 7.6 Hz, 2H), 3.77 (s, 3H), 3.91 (m, 2H), 5.12-5.19 (m, 2H), 5.79-5.89 (m, 1H), 6.67-6.71 (m, 3H), 7.17-7.23 (m, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 21.1 ($CH_2$), 25.6 ($CH_2$), 49.8 ($CH_2$), 52.1 ($CH_3$), 53.6 ($CH_2$), 112.6 (2 CH), 116.3 ($CH_2$), 116.5 (CH), 129.4 (2 CH), 134.2 (CH), 148.3 (C), 168.0 (C). C=$N_2$ was not observed.

**Ethyl 2-diazo-3-(*N*-methyl-*N*-phenylamino)propanoate (6.2)** was prepared following the procedure reported in the literature.[104] $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.27 (t, *J* = 7.2

[104] Xiao, T.; Li, L.; Lin, G.; Mao, Z.-W.; Zhou, L. *Org. Lett.* **2014**, *16*, 4232.

Hz, 3H), 2.98 (s, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.37 (s, 2H), 6.76-6.84 (m, 3H), 7.22-7.28 (m, 2H).

**Representative procedure for the iron-promoted decomposition reaction (Table 6.1, Entry 7).** A mixture of diazoester **6.1b** (44 mg, 0.178 mmol), DBU (26 μL, 0.178 mmol) and $FeSO_4 \cdot 7H_2O$ (74 mg, 0.27 mmol) in dichloroethane (10 mL) was stirred at reflux under an Argon atmosphere for 24 h. The reaction mixture was diluted with $CH_2Cl_2$ and washed with water. The organic extracts were dried, filtered and concentrated. The resulting residue was purified by chromatography ($SiO_2$, $CH_2Cl_2$) to give **6.3b** (30.5 mg, 83%) as a yellow oil.

**Characterization data for the compounds of Tables 6.1, 6.2, 6.3 and 6.4 and Figure 6.6**

**Ethyl *N*-phenylprolinate (6.3a).** $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.21-1.26 (m, 3H), 2.00-2.09 (m, 1H), 2.10-2.21 (m, 2H), 2.21-2.32 (m, 1H), 3.32-3.40 (m, 1H), 3.53-3.61 (m, 1H), 4.10-4.26 (m, 3H), 6.52-6.57 (m, 2H), 6.68-6.73 (m, 1H), 7.18-7.26 (m, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 14.4 ($CH_3$), 24.0 ($CH_2$), 31.0 ($CH_2$), 48.4 ($CH_2$), 61.0 (CH), 61.1 ($CH_2$), 112.1 (2 CH), 116.7 (CH), 129.3 (2 CH), 146.9 (C), 174.6 (C).

**Methyl *N*-phenylprolinate (6.3b).** $^1$H RMN ($CDCl_3$, 400 MHz) δ 2.00-2.09 (m, 1H), 2.10-2.21 (m, 2H), 2.21-2.32 (m, 1H), 3.35 (q, *J* = 8.0 Hz, 1H), 3.57 (td, *J* = 8.0 and 3.2 Hz, 1H), 3.70 (s, 3H), 4.24 (dd, *J* = 8.0 and 1.6 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 2H), 6.70 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 24.0 ($CH_2$), 31.0 ($CH_2$), 48.4 ($CH_2$), 52.3 ($CH_3$), 60.9 (CH), 112.1 (2 CH), 116.8 (CH), 129.4 (2 CH), 146.8 (C), 175.2 (C).

**Methyl *N*-(4-methylphenyl)prolinate (6.3c).** $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.99-2.33 (m, 4H), 2.25 (s, 3H), 3.34 (q, *J* = 8.0 Hz, 1H), 3.57 (td, *J* = 8.4 and 3.2 Hz, 1H), 3.71 (s, 3H), 4.23 (dd, *J* = 8.4 and 2.0 Hz, 1H), 6.47 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H).

$^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 20.4 ($CH_3$), 24.1 ($CH_2$), 31.1 ($CH_2$), 48.6 ($CH_2$), 52.2 ($CH_3$), 61.1 (CH), 112.1 (2 CH), 125.9 (C), 129.9 (2 CH), 144.8 (C), 175.4 (C).

**Methyl *N*-(4-methyoxyphenyl)prolinate (6.3d).** $^1$H RMN ($CDCl_3$, 400 MHz) δ 2.00-2.33 (m, 4H), 3.31 (q, *J* = 7.6 Hz, 1H), 3.55 (td, *J* = 8.0 and 3.6 Hz, 1H), 3.71 (s, 3H), 3.75 (s, 3H), 4.19 (dd, *J* = 8.4 and 2.4 Hz, 1H), 6.50 (d, *J* = 9.2 Hz, 2H), 6.83 (d, *J* = 9.2 Hz, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 24.2 ($CH_2$), 31.1 ($CH_2$), 49.0 ($CH_2$), 52.2 ($CH_3$), 56.0 ($CH_3$), 61.4 (CH), 112.9 (2 CH), 115.2 (2 CH), 141.7 (C), 151.6 (C), 175.4 (C).

**Methyl (*Z*)-5-(*N*-methyl-*N*-phenylamino)-2-pentenoate (*Z*-6.4b).** $^1$H RMN ($CDCl_3$, 400 MHz) δ 2.89-2.95 (m, 2H), 2.95 (s, 3H), 3.46 (t, *J* = 7.6 Hz, 2H), 3.71 (s, 3H), 5.85 (d, *J* = 11.6 Hz, 1H), 6.28 (dt, *J* = 11.6 and 7.6 Hz, 1H), 6.70 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 8.0 Hz, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 26.9 ($CH_2$), 38.3 ($CH_3$), 51.3 ($CH_2$), 51.8 ($CH_3$), 112.6 (2 CH), 116.6 (CH), 121.2 (CH), 129.4 (2 CH), 147.0 (CH), 149.5 (C), 166.8 (C).

**Methyl (*E*)-5-(*N*-methyl-*N*-phenylamino)-2-pentenoate (*E*-6.4b).** $^1$H RMN ($CDCl_3$, 400 MHz) δ 2.45-2.51 (m, 2H), 2.94 (s, 3H), 3.47 (t, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 5.88 (d, *J* = 15.6 Hz, 1H), 6.69-6.74 (m, 3H), 6.98 (dt, *J* = 15.6 and 7.6 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 2H).

**Methyl 2-benzyl-1-phenylpyrrolidine-2-carboxylate (6.6).** $^1$H RMN ($CDCl_3$, 400 MHz) δ 0.99-1.10 (m, 1H), 1.69-1.79 (m, 1H), 2.11-2.24 (m, 2H), 3.15-3.20 (m, 1H), 3.16 (d, *J* = 14.0 Hz, 1H), 3.33 (q, *J* = 7.6 Hz, 1H), 3.68 (s, 3H), 3.77 (d, *J* = 14.0 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 2H), 6.74 (t, *J* = 7.6 Hz, 1H), 6.97-7.00 (m, 2H), 7.16-7.19 (m, 3H), 7.25 (t, *J* = 8.0 Hz, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 22.6 ($CH_2$), 37.7 ($CH_2$), 37.8 ($CH_2$), 50.7 ($CH_2$), 52.6 ($CH_3$), 69.3 (C), 113.0 (2 CH), 116.5 (CH), 126.6 (CH), 128.1 (2 CH), 129.4 (2 CH), 131.0 (2 CH), 137.3 (C), 145.9 (C), 177.5 (C).

**Methyl 2-allyl-1-phenylpyrrolidine-2-carboxylate (6.9).** $^1$H RMN ($CDCl_3$, 400 MHz) δ 1.92-2.01 (m, 1H), 2.03-2.10 (m, 1H), 2.12-2.19 (m, 1H), 2.23-2.31 (m, 1H), 2.70 (dd, *J* = 14.8 and 8.8 Hz, 1H), 3.10 (dd, *J* = 14.8 and 6.0 Hz, 1H), 3.47-3.52 (m, 2H), 3.68 (s, 3H), 5.01-5.06 (m, 2H), 5.51-5.62 (m, 1H), 6.53 (d, *J* = 8.0 Hz, 2H), 6.69 (t, *J* = 7.2 Hz,

1H), 7.18 (t, *J* = 8.0 Hz, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 23.1 ($CH_2$), 37.8 ($CH_2$), 37.9 ($CH_2$), 51.0 ($CH_2$), 52.5 ($CH_3$), 67.9 (C), 113.3 (2 CH), 116.7 (CH), 118.9 ($CH_2$), 129.2 (2 CH), 133.5 (CH), 145.8 (C), 177.2 (C).

**Ethyl 3-(*N*-methyl-*N*-phenylamino)propenoate (6.10).** $^{1}$H RMN ($CDCl_3$, 400 MHz) δ 1.28 (t, *J* = 7.2 Hz, 3H), 3.23 (s, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.93 (d, *J* = 13.2 Hz, 1H), 7.08-7.14 (m, 3H), 7.32-7.37 (m, 2H), 7.93 (d, *J* = 13.2 Hz, 1H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 14.7 ($CH_3$), 36.7 ($CH_3$), 59.5 ($CH_2$), 90.6 (CH), 120.0 (2 CH), 124.3 (CH), 129.6 (2 CH), 146.7 (C), 148.6 (CH), 169.3 (C).

**Ethyl *N*-methylindole-3-carboxylate (6.12).** $^{1}$H RMN ($CDCl_3$, 400 MHz) δ 1.42 (t, *J* = 7.2 Hz, 3H), 3.84 (s, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 7.28-7.36 (m, 3H), 7.79 (s, 1H), 7.16-7.19 (m, 2H).

**Ethyl 2-chloro-3-(*N*-methyl-*N*-phenylamino)propanoate (6.13).** $^{1}$H RMN ($CDCl_3$, 400 MHz) δ 1.26 (t, *J* = 7.2 Hz, 3H), 3.01 (s, 3H), 3.73 (dd, *J* = 15.2 and 6.0 Hz, 1H), 4.02 (dd, *J* = 15.2 and 8.0 Hz, 1H), 4.12-4.26 (m, 2H), 4.49 (dd, *J* = 8.0 and 6.0 Hz, 1H), 6.71-6.79 (m, 3H), 7.23-7.28 (m, 2H). $^{13}$C RMN ($CDCl_3$, 100.5 MHz) δ 14.1 ($CH_3$), 39.6 ($CH_3$), 53.5 (CH), 56.9 ($CH_2$), 62.5 ($CH_2$), 112.4 (2 CH), 117.6 (CH), 129.6 (2 CH), 148.1 (C), 169.2 (C).