Reactivity and Applications of New Substrates for the Intermolecular Pauson-Khand Reaction: *N*-Boc-propargylamines and trifluoromethyl alkynes

Nuria Aiguabella Font

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Nuria Aiguabella Font

Programa de doctorat de Química Orgànica

Directors de Tesi: Dr. Antoni Riera Escalé i Dr. Xavier Verdaguer Espaulella

Deptartament de Química Orgànica.

Universitat de Barcelona.

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Nuria Aiguabella Font

Revisada per:

Dr. Antoni Riera Escalé

Dr. Xavier Verdaguer Espaulella

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Pero, cuando conseguiste contar exactamente lo que año y medio decidiste que contarías, o lo que resultó de ello, piensas: qué largo camino para llegar a esto. Una felicidad singular, ésa. Es como empezar a navegar, marcar un punto de arribada en la carta, un faro por ejemplo, trazar el rumbo y navegar a ciegas. Al fin, un día, ves la luz de ese faro exactamente donde lo esperabas, a cinco grados por tu amura de babor. Y piensas:

no sé si soy buen marino, pero esta vez he sido buen marino.

Arturo Pérez-Reverte

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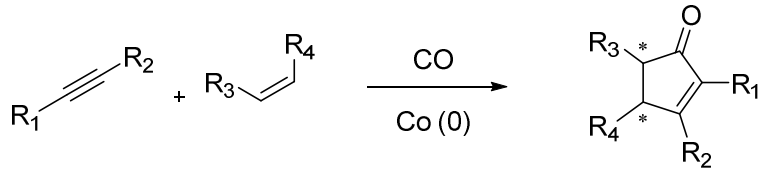
α	alpha
β	beta
°C	Celsius degree
δ	NMR chemical shift
λ	wavelength
acac	acetylacetonate
add.	addition
Bn	benzyl
Boc	*tert*-butoxycarbonyl
cat.	catalytic
COX	cyclooxygenase
DABCO	1,4-diazabicyclo [2.2.2] octane
DBU	1,8-diazabicyclo [5.4.0.] undec-7-ene
DCM	dichloromethane
DFT	Density Functional Theory
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMP	Dess-Martin periodinane
dr	diastereomeric ratio
eq.	equivalent
ee	enantiomeric excess
EDG	electron-donating group
ESI	electrospray ionization
Et_2O	diethylether
EWG	electron-withdrawing group
h	hour(s)
HMPA	hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
hυ	ultraviolet radiation
IPA	2-propanol
IR	infrared
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LUMO	Lowest Unoccupied Molecular Orbital

MA	maleic anhydride
min	minute(s)
Mol. sieves	molecular sieves
MW	microwaves
NBD	norbornadiene
nd	not determined
NMO	*N*-methylmorpholine-*N*-oxide
NOESY	nuclear Overhauser effect spectroscopy
NMR	Nuclear Magnetic Resonance
Nu	nucleophile
o	orto
p	para
PDA	phytodienoic acid
PKR	Pauson-Khand reaction
PNSO	*N*-phosphino sulfinamide
ppm	parts per million
rac	racemic
rt	room temperature
s	second(s)
SM	starting material
t_R	retention time
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
TMANO	trimethylamine-*N*-oxide
TMS	trimethylsilyl
Tr	triphenylmethyl
TS	transition state
W	watt(s)

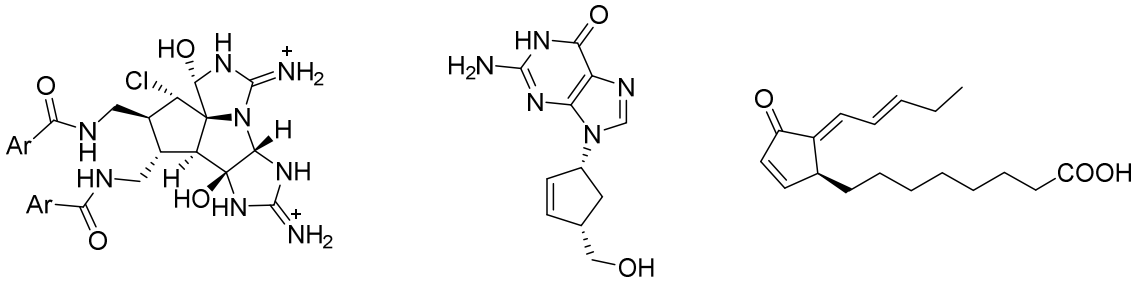
1. Introduction and objectives

The Pauson-Khand reaction (PKR) is, formally, a [2+2+1] cycloaddition where an alkene, an alkyne and a carbon monoxide molecule form a cyclopentenone. In this reaction, typically mediated or catalyzed by a cobalt (0) complex[1], three new carbon-carbon bonds and up to two stereogenic centers, depending on the substitution pattern of the alkene, are formed (Scheme 1)[2].



Scheme 1: **G**eneral scheme for the Pauson-Khand reaction.

Since its discovery in 1971 by P. L. Pauson and I. U. Khand[1a] the PKR has been one of the most used methods for the construction of five-membered ring compounds like natural or biologically interesting products. Some examples of this would be Axinellamines A and B[3], (-)-Carbovir[4] and Deoxy-J1-phytoprostanes, $dPPJ_1$-I and $dPPJ_1$-II[5] (Figure 1).



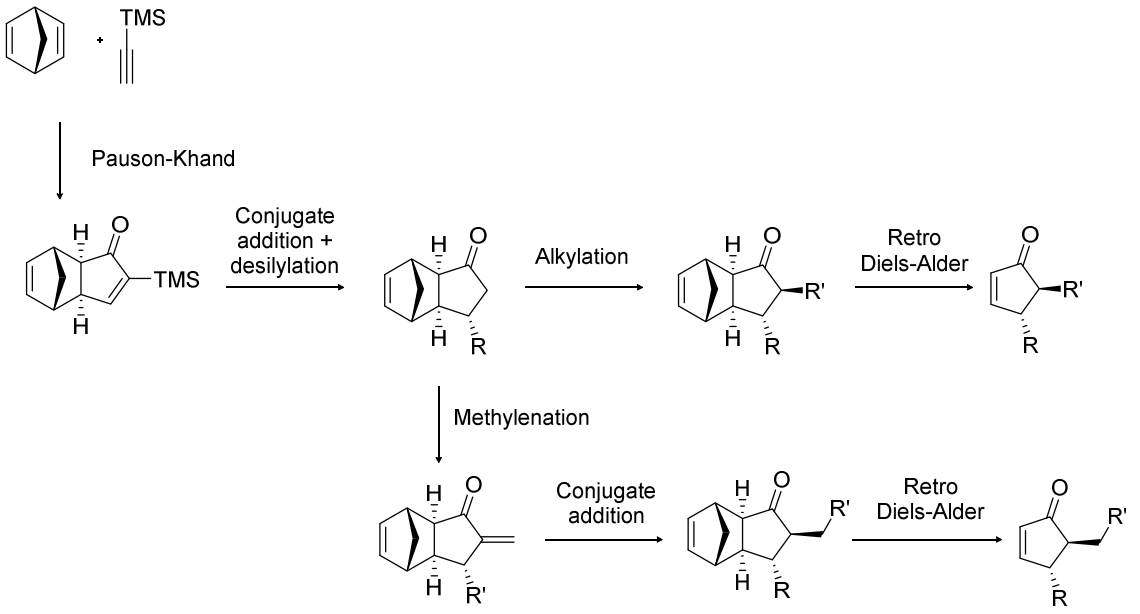
Axinellamine A (-)-Carbovir $dPPJ_1$-I

Figure 1: Some products of biological interest synthesized by the PKR.

Given that the intramolecular PKR leads to complex polycyclic structures in very few synthetic steps and that it shows minor reactivity requirements traditionally it has been the most used version of this reaction. On the other hand and in spite of its great synthetic potential, the intermolecular PKR has been less studied and exploited. One of the main reasons for this is that the intermolecular PKR shows a small range of applicability regarding the alkene. Only tensioned alkenes such as norbornadiene, norbornene or cyclopropene react with acceptable yields, ethylene being an exception to this rule. Another issue to take into account is the PKR regiochemical outcome when dealing with internal alkynes. Whereas terminal alkynes afford a single cyclopentenone with the substituent α to the carbonyl group, internal non-symmetric alkynes can lead to a mixture of regioisomers[6]. Finally, the fact that asymmetric versions of the PKR have

been developed during the past few years adds value to this version of the reaction, although the impossibility of accessing the optically active PK adducts by a catalytic method is still a problem to overcome[7].

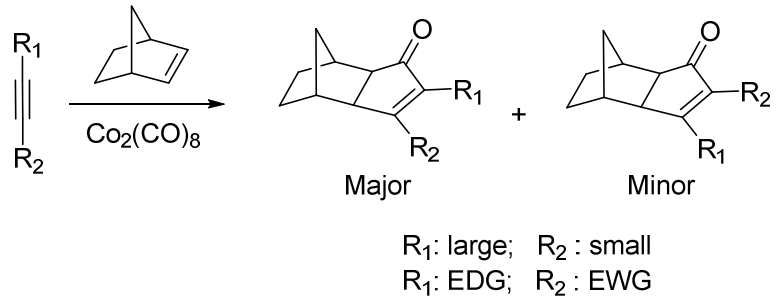
Two of the most prominent families of cyclopentanic compounds in nature are prostaglandins and phytoprostanes. Prostaglandins are generated by the action of cyclooxygenase (COX) on the fatty acids that come from the phospholipid bilayer. The most common substrate for this reaction cascade in the human body is arachidonic acid[8]. In plants, a similar process occurs with linolenic acid as substrate and the family of phytoprostanes as product[9]. The extremely interesting properties of these compounds, such as antitumor activity[10], along with the difficulty to isolate them from natural sources, has led to an increasing interest on finding simple and efficient methods to access them. The fact that these products share a cyclopentenone ring (or a derivative) as a structural feature makes them a perfect synthetic target for the PKR. Our group has been successful in synthesizing chiral 4-substituted cyclopentenones or 5-alkylidenecyclopen-2-enones starting from the PK adduct of norbornadiene and trimethylsilylacetylene[4,5], although the introduction of a saturated α side chain to the carbonyl has always been troublesome. The first approach to the introduction of saturated substituents in this position was developed by Agustí Lledó during his Doctoral Thesis. He envisaged that α,β-disubstituted cyclopentenones could be synthesized from the PK adduct of norbornadiene and trimethylsilylacetylene after a conjugate addition/desylilation tandem process. The alkylation of the resulting ketone would yield the desired products after a retro Diels-Alder reaction. An alternative method would be to methylenate the ketone in order to reach an exocyclic enone which, after a second conjugate addition and a retro Diels-Alder reaction, would also unveil the desired α,β-disubstituted cyclopentenone (Scheme 2). However, although the conjugate addition/desilylation works well[11], the alkylation of these compounds produced mixtures of starting material and alkylated and dialkylated products, and the methylenation reaction was generally low yielding and provided complex crudes.



Scheme2: A. Lledó's approaches to 4, 5-disubstituted cyclopentenones.

It was clear that we needed to **develop a new approach to access α, β-disubstituted cyclopentenones from a PK adduct** that solved the problem of the introduction of a saturated substituent in the α position. This would be one of our objectives during this Thesis and will be discussed in **Chapter 3**. Once this methodology was available, we envisaged to apply it to the **synthesis of a natural occurring phytoprostane: 13-*epi*-12-oxo phytodienoic acid.** The synthesis of this product will be addressed in **Chapter 4**.

One of the main issues of the intermolecular PKR is the regiochemical outcome of the reaction. Many efforts have been devoted to the understanding of the intermolecular PKR regioselectivity of internal dissymmetric alkynes. Its first rationalization came in 2001 in the hands of Greene and co-workers[6a]. They proposed that, when dealing with this kind of substrates, there were two factors to take into account: the size of the substituents and their electronic properties. Regarding the size, the bulkiest substituent would tend to end up α to the newly formed ketone, whereas the smaller one would prefer the β position. Concerning the electronic properties of the alkyne they stated that, among sterically similar substituents, the more electron-donating group is prone to be α to the ketone while the more electron-withdrawing group will be in the β position (Scheme 3).



Scheme 3: General regiochemical outcome of the PKR.

Even though this theory has been widely accepted for the past decade, more recent studies showed that this approach is far from general and can't explain many of the results observed. Recently, Helaja and co-workers[12] proposed a different approach to the explanation of the PKR regioselectivity of alkynes with sterically equivalent but electronically unsymmetrical substituents. In their report, they studied the charge densities of the carbon atoms at the α alkyne-position instead of the substituents as a whole unit. The reason of this was the fact that these carbon atoms are directly associated to p-type orbitals, which are essentially involved in the PKR. Helaja and co-workers confirmed the general trend proposed by Greene, although with nuances and better correlation between theoretical and experimental results.

The intermolecular PKR has proved to be a very tolerant reaction in what refers to alkynes. Probably this feature of the PKR has made that not many studies have been devoted to the range of applicability of alkynes. Several alkyne substitution patterns remain unstudied, one of the most interesting being fluorinated alkynes. At the beginning of this work, only a few examples of intramolecular PKR with fluorinated substrates had been described[13], but there were no precedents of intermolecular PKR of fluorinated alkynes. Our initial results of the PKR of fluorinated alkynes and norbornadiene showed that the reaction was extremely regioselective and always led to the α fluorinated cyclopentenones. These results were striking, since we expected that the more electron-withdrawing group should end up β to the ketone. At sight of this, we decided to perform a deeper **study on the intermolecular PKR of fluorinated alkynes, and explore how the presence of fluorine and electronically different substituents would affect the regioselectivity of the PKR** to shed some light into the regioselectivity of the PKR. Our results will be shown in **Chapter 5**.

One of main research lines of our research group over the past decade has been the study of the introduction of chirality in the PKR. These studies began with the use of chiral auxiliaries attached either to the alkene or the alkyne[14]. This approach evolved to

the much more efficient use of chiral ligands bond to the metal cluster. Among these, the hemilabile chiral bidentate *N*-phosphino sulfinamides (PNSO) ligands[7b, c] are the ones that stand out the most for the asymmetric PKR of terminal alkynes (Figure 2).

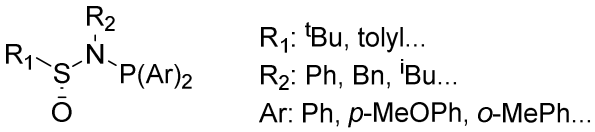


Figure 2: **G**eneral structure of a PNSO ligand.

The use of this family of ligands was recently expanded to the enantioselective PKR of symmetrically substituted internal alkynes[7d], but unsymmetrical disubstituted alkynes remain unexplored. For this reason, in **Chapter 6** we will discuss the **development of an intermolecular asymmetric PKR for our dissymmetrical fluorinated alkynes**.

In summary, the main objectives of this Doctoral Thesis were:

I. To develop a new methodology to access α, β-disubstituted cyclopentenones from a PK adduct (Chapter 3).

II. To apply this methodology to the synthesis of a naturally occurring phytoprostane (Chapter 4).

III. To study the intermolecular PKR of fluorinated alkynes and to evaluate how the presence of fluorine affects the PKR regioselectivity (Chapter 5).

IV. To develop an intermolecular asymmetric PKR for our dissymmetrical fluorinated alkynes (Chapter 6).

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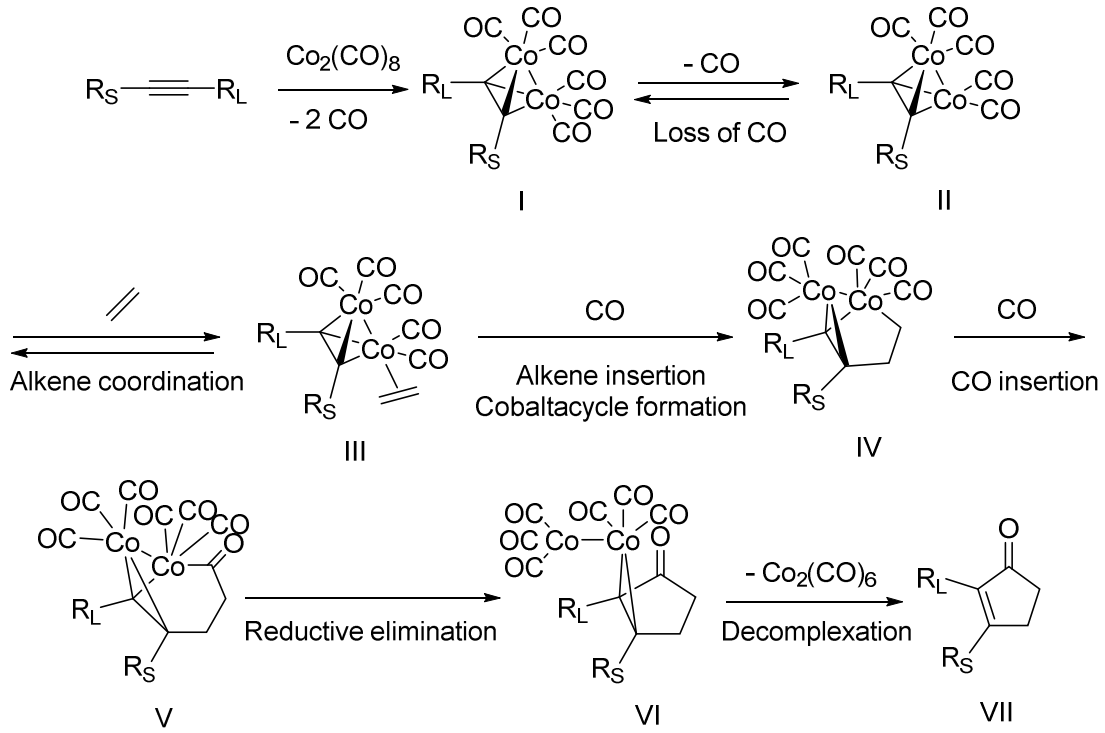
2. Background

2.1 The intermolecular Pauson-Khand Reaction

2.1.1 Mechanism

Fourteen years after it was discovered, Magnus and Principe proposed the first rationalization of the regio and stereochemical outcome of the PKR[1]. This mechanistic proposal has been widely accepted ever since, being further confirmed more recently by theoretical studies carried out by Nakamura[2] and Pericàs[3]. Magnus's mechanism for the stoichiometric PKR is shown in Scheme 1.



Scheme 1: Magnus's mechanism for the stoichiometric PKR.

The first step of this mechanism corresponds to the coordination of the alkyne with $Co_2(CO)_8$, with the subsequent loss of two CO molecules. This complex (**I**), generally stable and isolable, suffers the loss of another CO molecule in order to generate a coordination vacant, where the alkene will coordinate to yield complex **III**. Calculations show that the dissociative loss of CO is strongly endothermic. Practical rate increase in the PKR can be achieved through facilitation of this dissociation process with the use of promoters such as amine *N*-oxides. Alkene insertion into the less hindered Co-C bond leads to cobaltacycle **IV**. This step is the product determining step, since both the stereo and the regiochemistry of the final product will be established in it. CO insertion followed by reductive elimination and decomplexation of the metal complex leads to the final cyclopentenone **VII**.

2.1.2 Scope of the reaction

The PKR is generally a very tolerant reaction in which refers to alkynes, but more demanding when dealing with the alkenes. The intermolecular PKR is restricted to strained cyclic alkenes such as norbornadiene, norbornene or cyclopropene. Ethylene is one of the few examples were a non-strained acyclic olefin is reactive enough for the PKR.

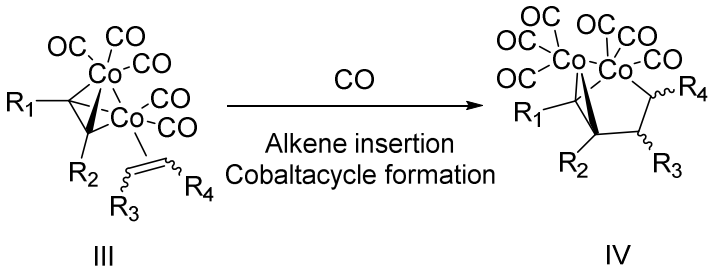
A possible explanation for this could be found in the formation of cobaltacycle **IV**, since most of the olefin strain is released at this point with the change of hybridization of the double bond sp^2 carbons to sp^3. Pericàs and co-workers were the first to explore this possibility[3]. More recently, these results were confirmed and further explored by our group[4]. In all these studies, a clear correlation between the exothermic character of the cobaltacycle formation step and the olefin strain was observed.

A thorough theoretical study carried out by Gimbert and co-workers[5] shed some light into the alkenes' reactivity from the point of view of molecular orbitals. According to their study, the reactivity of the alkenes is directly related to the back donation of the cobalt atoms into the π^* orbitals of the alkene. The larger this back donation is, the more reactive the alkene will be. The magnitude of the back donation depends directly on the LUMO energy of the alkene. In general, the back donation is more effective when the LUMO orbital is of lower energy. The LUMO energy of the alkene can be directly related to the C=C-C angle; as this angle becomes smaller, the LUMO orbital energy descends. That is to say, the more tensioned the alkene is, the lower the C=C-C angle will be. This will directly imply that the LUMO orbital energy will be lower and the back donation from the cobalt atoms into the π^* orbitals of the alkene more intense, making the alkene more reactive in the PKR.

It must also be taken into account that the PKR is sensitive to steric and electronic effects both of the alkene and the alkyne. Sterically hindered substrates tend to be low yielding, and terminal alkynes are known to react easier than internal alkynes.

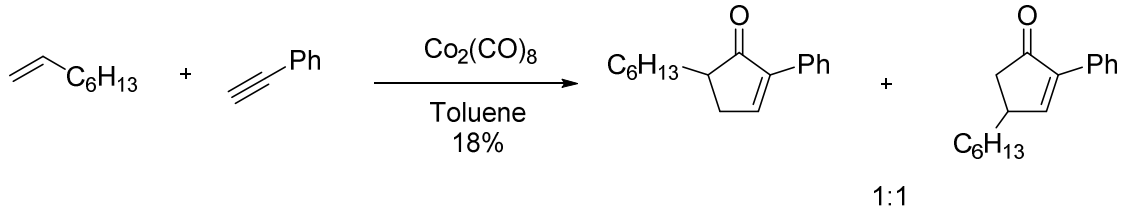
2.1.3 Regioselectivity

The regiochemical outcome of the PKR is determined in the formation of cobaltacycle **IV** (Scheme 2). We will discuss the regioselectivity of the intermolecular PKR with respect to the alkene and the alkyne.



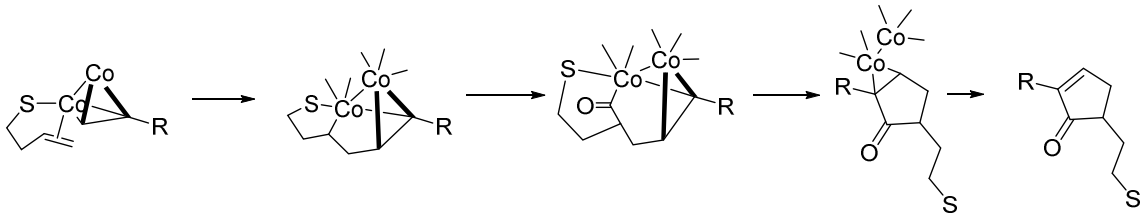
Scheme 2: Regiochemistry determining step.

The regiochemistry regarding the alkene is not an issue as long as we deal with symmetric alkenes. Nevertheless, it becomes critical when terminal or non-symmetric alkenes are required. In general, these substrates are low yielding and exhibit a poor selectivity (Scheme 3). However, the use of a coordinating heteroatom tethered to the alkene by a carbon chain can dramatically improve both yield and selectivity.



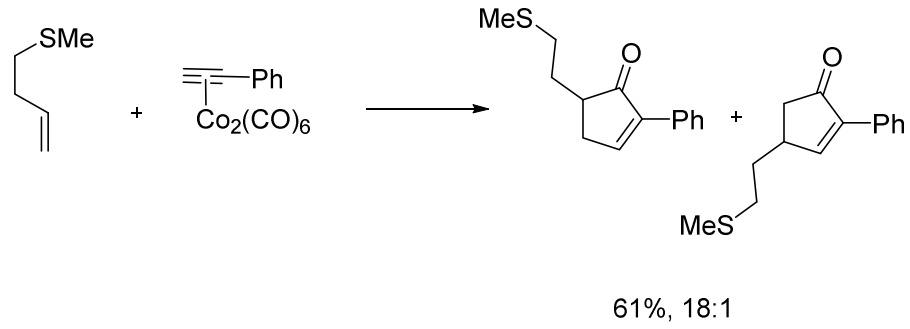
Scheme 3: Example of a PKR with terminal alkene.

Krafft[6] reported that an heteroatom such as nitrogen or sulfur could coordinate cobalt and orient the alkene to react preferentially on one side only (Scheme 4), although the alkyne substitution had also an influence on the selectivity[7]. The yield and chelation efficiency was strongly influenced by the substitution on the chelating atom.



Scheme 4: Alkene insertion directed by chelation to the cobalt center. CO ligands have been omitted for simplicity.

Krafft succeeded in improving the PKR yields and selectivity (up to 40:1) when dealing when nitrogen and sulfur-substituted homoallylic alkenes (Scheme 5). Oxygen didn't provide ligand-directed regioselectivity, and the PKR could only be carried out stoichiometric.



Scheme 5: Example of chelation-directed PKR.

The regiochemical outcome with respect to the alkyne is determined in the same reaction step. Once the complex **III** is formed, the alkene must insert into one of the Co-C bonds in order to form **IV**. The insertion takes places preferentially into the Co-C bond bearing the smaller substituent (R_S in Scheme 1; Figure 1). Consequently, the largest substituent (R_L in Scheme 1) will end up α to the ketone in the final cyclopentenone **VII**.

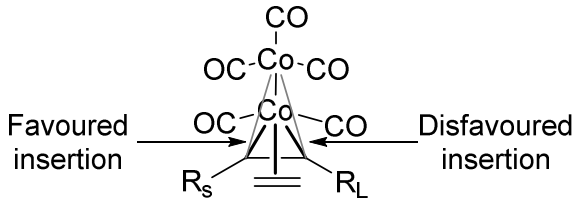
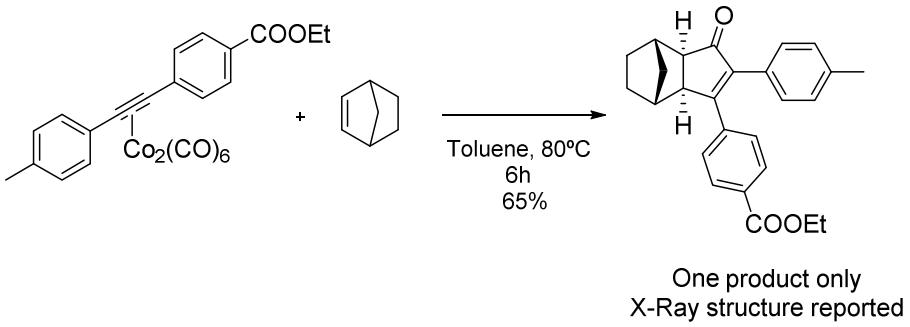


Figure 1: Possible insertion sites for the alkene.

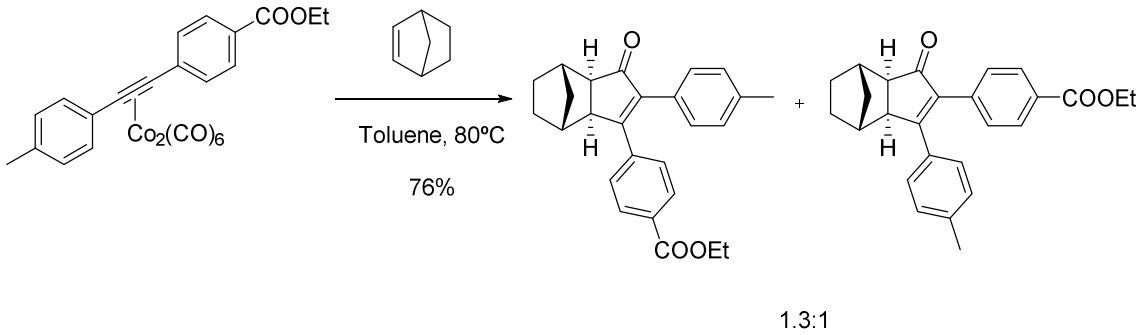
The regioselectivity of the PKR is complete when dealing with terminal alkynes, but when the reaction takes place with internal, non-symmetrical alkynes, mixtures of regioisomeric products may be obtained in variable proportions. In general, the largest the difference in size of the substituents, the larger the selectivity is.

The electronic properties of the substituents present in the alkyne also have an influence in the regiochemistry of the PRK. Greene and co-workers[8] proposed that electron-donating groups would prefer the α position of the enone, whereas electron withdrawing groups would be more prone to the β position. They supported their theoretical studies with some experimental results, one of which is depicted in Scheme 6.



Scheme 6: Greene's experimental result.

However, recent studies carried out by Helaja and co-workers[9] proved that, in fact, this illustrative example was not accurate. When repeating the reaction under similar conditions, they found out that the selectivity of the reaction was far from total (Scheme 7).



Scheme 7: Helaja's result for Greene's reaction.

At sight of this result, a suitable and renovated explanation for the PKR's regioselectivity was needed. As a model for their study, Helaja and co-workers focused on the study of the PKR of norbornene and dissymmetric diarylalkynes. Following a very elegant and new approach, they related the regioselectivity to the relative charge densities of the aryl carbons at the α-alkyne positions. Their study confirms that the alkyne bond polarization dictates the α/β-regioselectivity of the final cyclopentenones, but they uncovered that the electronic effects of the alkyne substituents on the regioselectivity of the PKR are much weaker than expected. They could quantify the α/β-regioselectivity trend for the first time by the use of the Hammett values of each substituent and, in general, their predictions fit well with the experimental results, even though the regioselectivities are, for most of the cases, low.

2.1.4 Stereoselectivity

The PKR is stereospecific regarding to the alkene; that is to say, the enone resulting from the cycloaddition will keep intact the original alkene stereochemistry.

For bicyclic alkenes, two products can be further obtained from the PKR: the *endo* and the *exo* fused polycycles. The fact that we obtain one or the other depends on the face the alkene inserts the Co-C bond to yield complex **IV** (Scheme 1). Generally, the insertion reaction will take place by the less hindered face of the alkene, yielding the *exo* PK adducts (Figure 2). The stoichiometric PKR is extremely stereoselective, and most of the times the *endo* adduct can't be observed. However, the catalytic PKR is less stereoselective and small amounts of *endo* adduct can be detected.

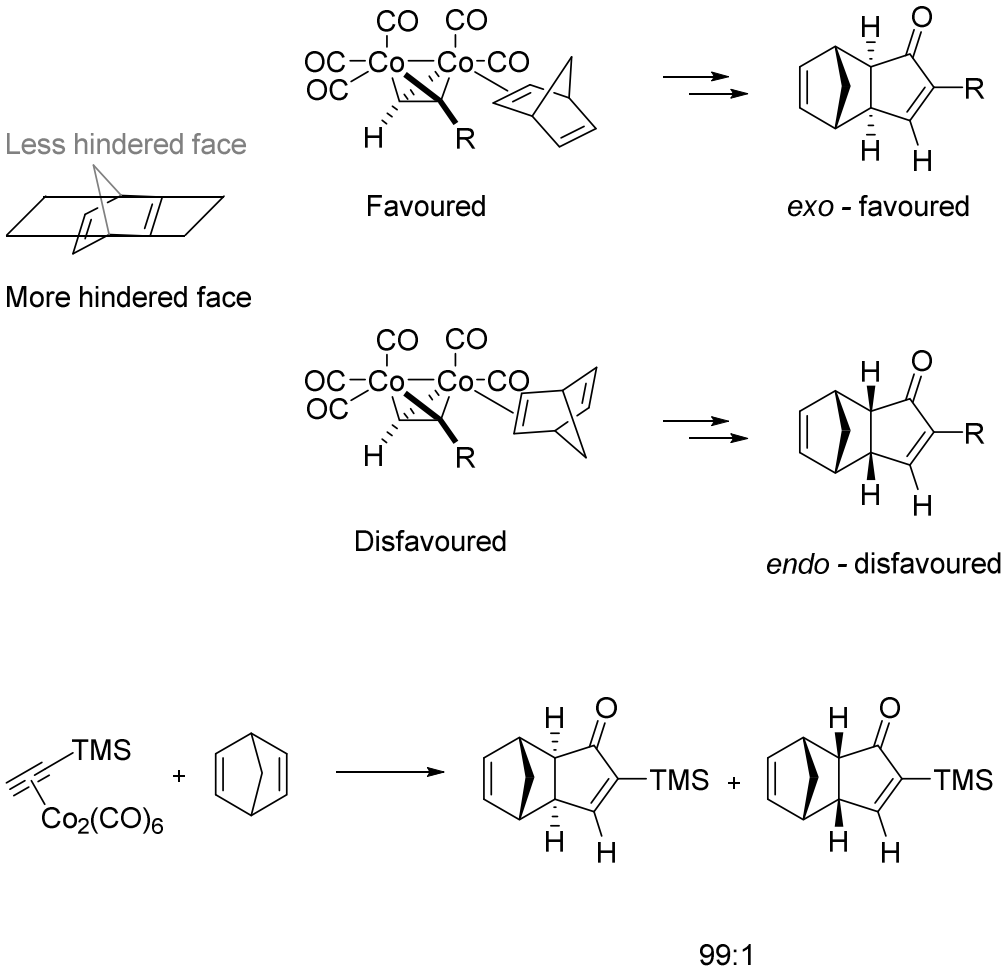


Figure 2: Norbornadiene coordination to yield the *exo* and *endo* isomers.

2.1.5 Use of additives in the PKR

Traditionally, the PKR has required high reaction temperatures or pressures and long reaction times. Considerable efforts were made since the mid-80s in order to facilitate the reaction. These efforts have generally focused on one strategy: to facilitate the ligand exchange that leads to the coordination of the alkene to the cobalt center.

Smit and co-workers were the first to offer a suitable process to promote the PKR[10]. It consisted in adsorbing the cobalt-alkyne complex in a solid support, such as

silica or alumina, and heating it mildly. The reaction times decreased dramatically, and the yields were much better than under traditional, thermal conditions. Later on, they expanded their methodology to the intermolecular PKR[11]. The authors proposed that the donor sites at the surface of the solid support could facilitate the ligand exchange process, therefore increasing the PKR rate. Preorientation of the substrates (in the case of intramolecular PKRs) would also promote the cyclization.

One of the most used activation techniques for the PKR is the use of amine *N*-oxides, first introduced by Schreiber and co-workers[12]. These additives remove one of the CO ligands by oxidizing it to CO_2, thus generating the so desired coordination vacant for the alkene. The most popular amine *N*-oxides are *N*-mehtylmorpholine *N*-oxide (NMO)[12] and trimehtylamine *N*-oxide (TMANO)[13].

The use of molecular sieves has also gained ground over the past few years[14]. These zeolites are supposed to work as micro-reactors, bringing together the alkene and the alkyne-cobalt complex, therefore facilitating the PKR. Pauson himself proposed the use of ultrasounds to promote the PKR in 1988[15]. The use of microwaves in the PKR was first introduced by Evans in 2002[16]. Other additives such as sulfides[17] or thioureas[18] have also been explored, as well as the use of coordinating solvents (acetonitrile or THF).

2.1.6 Catalytic PKR

Transforming the PKR into a catalytic process was a matter of interest since the reaction's early discovery. In 1973, Pauson[19] was successful in the performance of a catalytic PKR. However, this process implied the use of a quite high catalyst loading (10 mol%) and it was only applicable to the most reactive strained alkenes.

A quantitative improvement to the process was reported in 1990 by Rautenstrauch and co-workers[20]. They could lower the catalyst loading significantly, but very harsh conditions were required. Later on, Jeong and co-workers[21] introduced the use of a phosphite ligand in order to make the reaction conditions milder, although their method appeared to be limited to intramolecular PKRs. Following this approach, Krafft expanded the catalytic PKR to intermolecular systems by the use of cyclohexylamine as an additive[22]. Other approaches to the catalytic PKR consist in the use of cobalt supported on charcoal[23] or silica[24] or cobalt nanoparticles[25].

Our group made a very significant contribution to the cobalt-catalyzed intermolecular PKR when the first kinetic study on the reaction was carried out[26]. The catalytic PKR between norbornadiene and trimethylsilylacetylene was followed by FT-IR,

and it could be determined that the rate determining step in this reaction is the alkene insertion, and two of the reaction intermediates could be identified.

In addition to cobalt, other metals have been assayed in the catalytic PKR such as titanium[27], iridium[28], rhodium[29] or ruthenium[30], increasing the versatility and synthetic possibilities of the PKR.

2.1.7 Asymmetric PKR

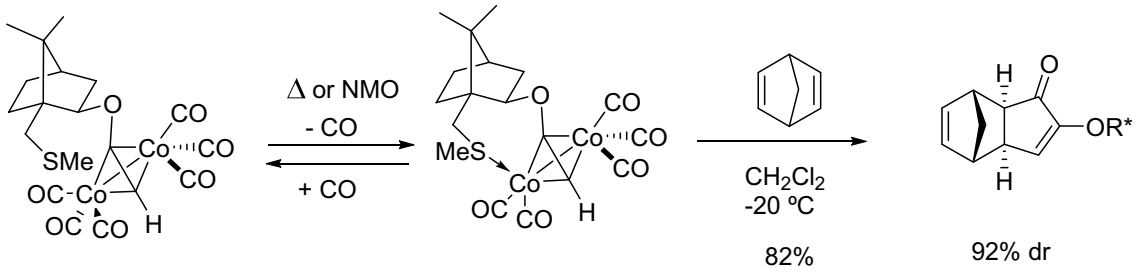
In the PKR two new stereogenic centers are generated, depending on the substitution pattern of the alkene. Soon after the PKR discovery, research began towards the development of asymmetric variants of it. Some of these approaches are based on the use of enantiomerically enriched starting materials that transfer their chiral information to the newly formed cyclopentenone. There are many examples of this approach in the literature, although most of them correspond to intramolecular PKRs and will not be further discussed here.

Chiral promoters have also been used as source of chirality in the PKR, chiral *N*-oxides being the most successful ones[31]. The chiral *N*-oxide appears to perform a selective decarbonylation of one CO ligand in the metal cluster, thus generating an optically enriched cyclopentenone after the cyclization. This approach was the first to enable the synthesis of enantiomerically enriched products from the intermolecular PKR[32], even though it is not practical and far from general. The introduction of chiral auxiliaries granted the access to more synthetically efficient and with better atom-economy processes.

2.1.7.1 Use of chiral auxiliaries in the PKR

Pericàs and co-workers pioneered the use of chiral auxiliaries in the PKR, and they made some of the most valuable contributions to the field. Some of the auxiliaries they explored were chiral sulfoxides[33], sultames[34], oxazolidinones[35] and alkoxyacetylene camphor derivatives[32, 36], all of them bound to the alkyne.

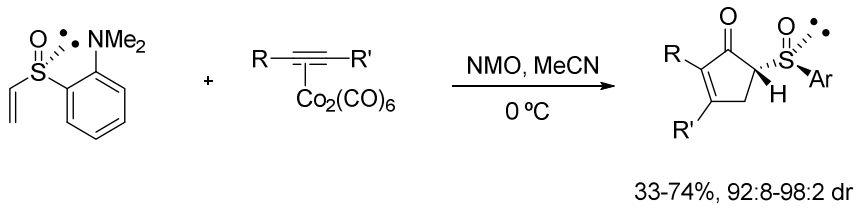
One of the approaches that have turned out more effective is the use of chiral auxiliaries equipped with chelating atoms. They act by transferring their chirality to the metal cluster by coordinating to one of the cobalt atoms and promoting the diasteroselctive coordination of the alkene, thus nourishing an optically active cyclopentenone after the cyclization[37] (Scheme 8).



Scheme 8: Example of the use of chelating agents for the asymmetric intermolecular PKR.

The introduction of the camphor derived sulfur auxiliary shown in Scheme 8 inspired the realization of a series of theoretical and experimental studies to understand how the ligand exactly worked[38]. These studies unveiled that norbornadiene coordinated to the cobalt atom bound to the sulfur. Further theoretical studies confirmed these observations and established that the coordination occurred *via* a coordination vacant created by the loss of the sulfur coordination. That's to say, the ligand could coordinate or de-coordinate directing the alkene to one precise cobalt atom. This ligand was called a *hemilabile* ligand according to this feature, and it was the inspiration for the development of chiral ligands for the PKR that will be discussed in the next section.

Chiral auxiliaries bond to the alkene have also had their role in the asymmetric intermolecular PKR development. Carretero and co-workers[39], for instance, introduced very successfully the use of chiral sulfoxides for the PKR of non-strained alkenes (Scheme 9). The good diastereomeric ratios obtained can be explained by the proximity of the chiral sulfur atom to olefin.

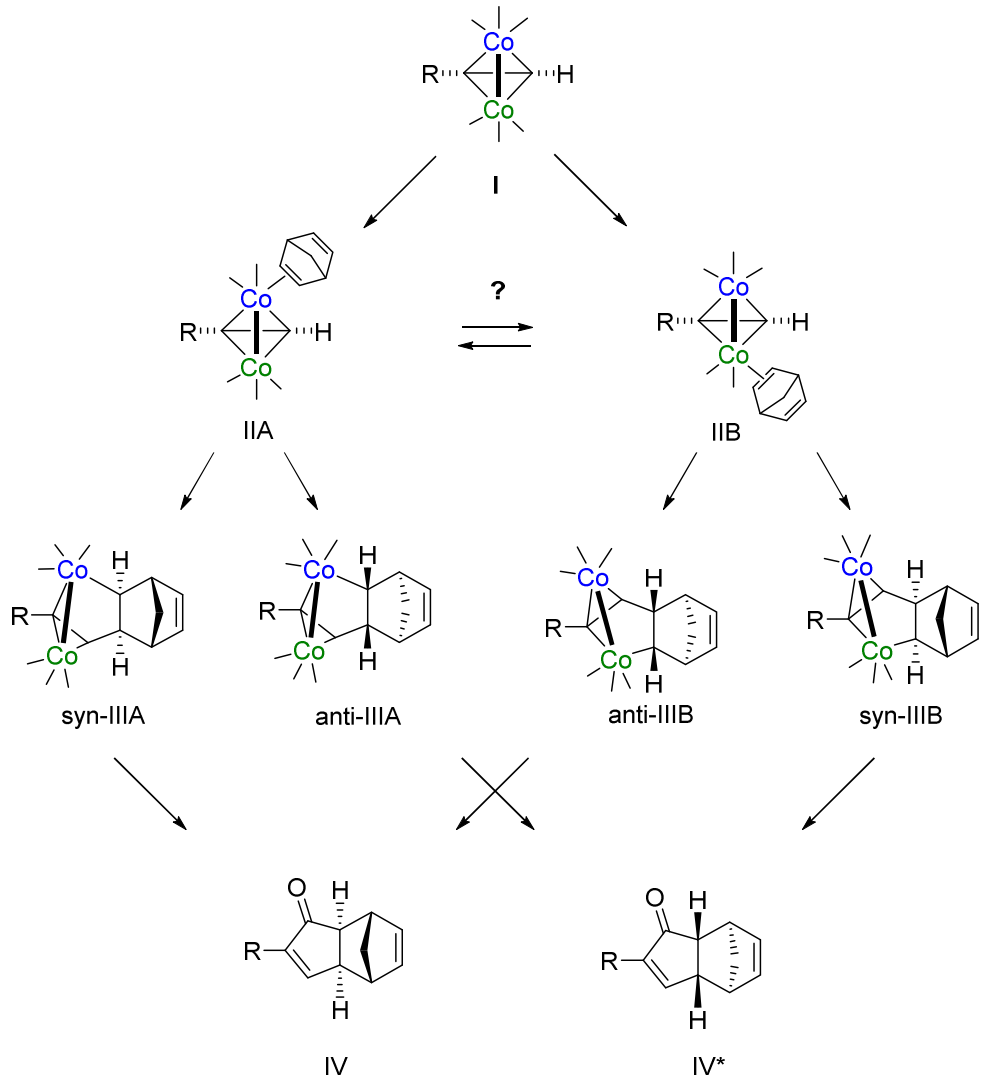


Scheme 9: Carretero's chiral sulfoxides.

2.1.7.2 Use of chiral ligands in the PKR

Mechanistic considerations

Based on the mechanism proposed by Magnus[40], we can depict the different pathways that a cobalt complex of a terminal alkyne and norbornadiene can follow in order to yield the final cyclopentenone. Solely taking into account the formation of the *exo* diastereomers, these pathways can be found in Scheme 10.

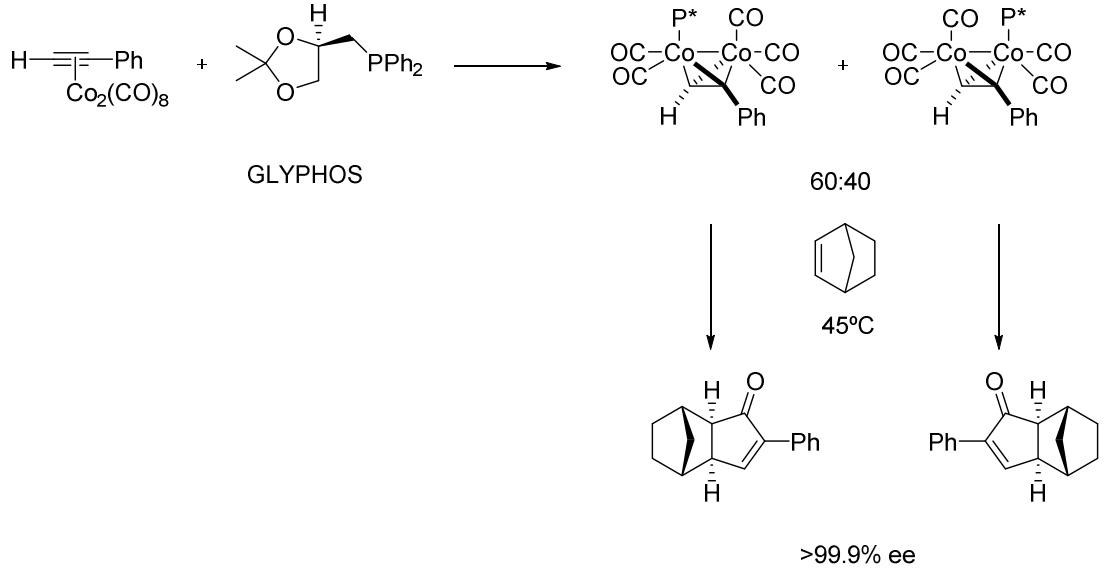


Scheme 10: Mechanistical pathways leading to each enantiomer of cyclopentenone IV. CO ligands have not been depicted for simplicity.

Once the cobalt complex **I** loses a CO ligand, a coordination vacant is generated and norbornadiene can coordinate to the cobalt atom. At this point, the alkene can coordinate indistinctly to any of the two cobalt centers, yielding **IIA** or **IIB**. The following step will be the insertion of the alkene. This will take place, preferentially, in the less hindered Co-C bond. However, norbornadiene can now have two different orientations when inserting the Co-C bond, and can therefore form two different complexes: the **syn** or the **anti** (**syn-IIIA**, **anti-IIIA**, **syn-IIIB** and **anti-IIIB**). Interestingly, both **anti-IIIA** and **syn-IIIB** lead to the same enantiomer of IV, **IV***. The same happens for **syn-IIIA**, **anti-IIIB** and **IV**. However, recent mechanistic studies[41] have shown that *anti* cobaltacycles are more stable than the *syn* ones, and therefore the formation of *anti* cobaltacycles will be preferred. As long as there is not differentiation between the two cobalt centers, the PKR will yield equal amounts of **IV** and **IV***. If the alkene coordinates preferentially to one

cobalt atom, one of the two enantiomers will be exclusively formed. The presence of chiral ligands in the metal cluster plays this differentiation role.

The first attempts to use chiral ligands in the PKR were undertaken by Brunner and Pauson[42] in 1988. As a ligand, they chose the glycerol derived monophosphine GLYPHOS as desymmetrizing element for the cobalt complex. The complexation reaction yielded two diasteromeric complexes in a 60:40 ratio, which could be separated by chromatography. The reaction of each of them with norbornene yielded the opposite enantiomer of the desired cyclopentenone with an excellent enantiomeric excess (Scheme 11).



Scheme 11: Asymmetric PKR with GLYPHOS

The main drawback of GLYPHOS was the fact that there was almost no selectivity in the differentiation of the cobalt atoms by the ligand. In order to prevent his, Gimbert and Greene[43] tested bidentate ligands with C_2 symmetry. The coordination of these complexes to the cobalt cluster yielded one single cobalt complex, but the PKR of these complexes gave, in general, very poor enantiomeric excesses.

In 2000, Pericàs and Riera[44], inspired in the camphor derived sulfur auxiliary discussed earlier (see Scheme 8), introduced a new family of P, S bidentate ligands for the PKR derived from pulegone and camphor: PuPHOS, CamPHOS and MeCamPHOS (Figure 3).

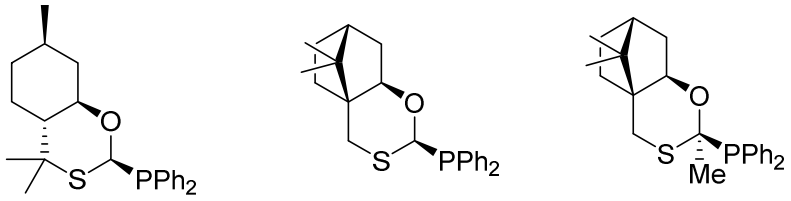


Figure 3: P,S bidentate ligands.

These complexes coordinate to the metal cluster as a bridge between the two cobalt atoms. From this coordination, two diastereomers are obtained, in ratios that vary between 1:1 and 20:1. The major isomer can generally be isolated by crystallization, and their reaction with norbornadiene provided the desired PK adducts in very high yields (typically more than 90%) and remarkable enantioselectivity (70-99%).

Our research group has continued with its research on new ligands for the asymmetric PKR over the past years, nourishing the existing family of ligands with a new, versatile and improved generation of P, S ligands: the PNSO family[45].

PNSO stands for *N*-phosphino sulfonamides, since phosphorous, nitrogen, sulfur and oxygen artoms are placed in a row. In these highly tunable, and postulated as hemilabile ligands, the phosphorous atom provides strong binding to the cobalt centers while the sulfur contains the chiral information. The nitrogen atom acts as a liaison element, transmitting the chiral information through the ligand (Figure 4).

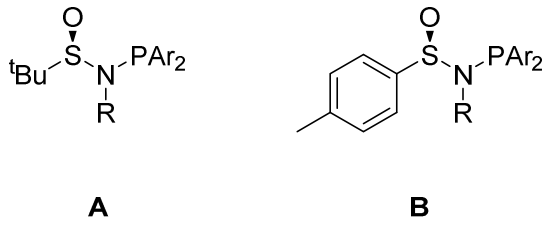
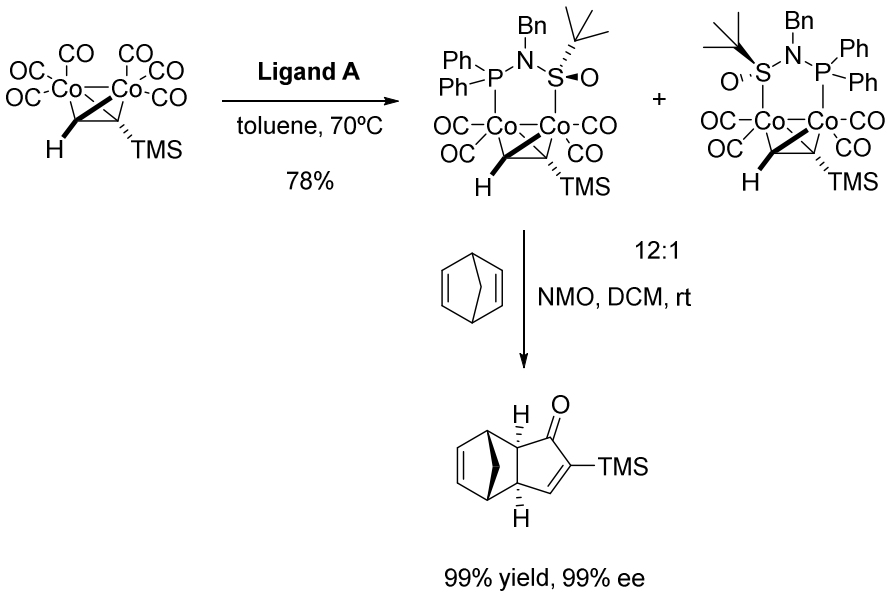
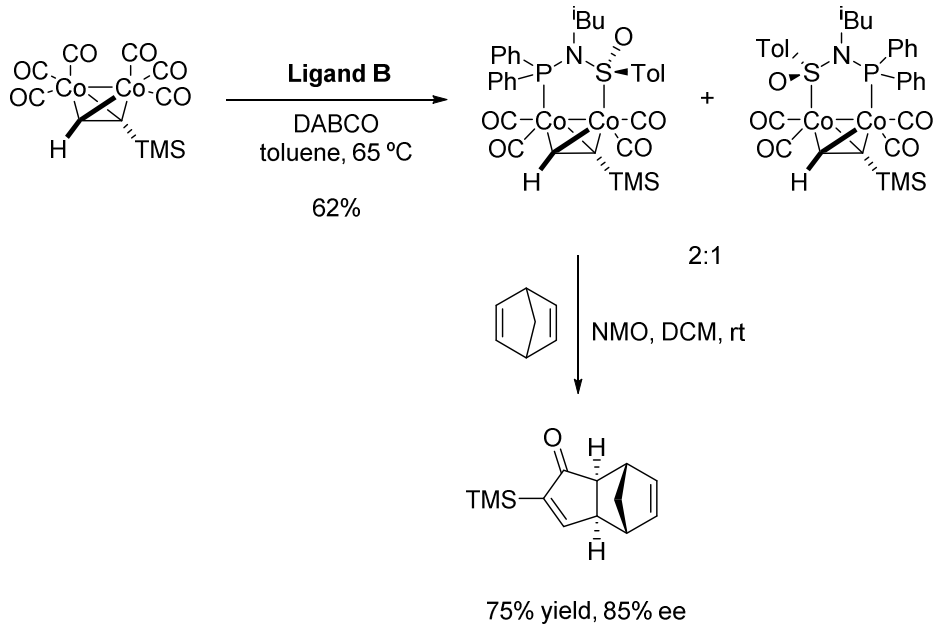


Figure 4: Two different families of PNSO ligands.

N-phosphino-*tert*-butylsulfinamides (**A**) have proved to be highly efficient in the asymmetric PKR, providing brilliant complexation diastereoselectivity and high yields and enantiomeric excess in the PKR. On the other hand, *N*-phosphino-*p*-tolylsulfinamides (**B**) tend to give lower diastereoselectivity in the complexation and moderate enantioselectivities (Scheme 12) but present a higher backbonding of arylsulfinamides to cobalt[45b] that would confer them a smaller hemilabile character than their *tert*-butyl partners.





Scheme 12: Asymmetric PKR results with ligands A and B.

In fact, this loss of hemilabile character allowed our group to report very recently and for the first time an asymmetric PKR of symmetrically substituted alkynes[46]. It is known that directing the alkene insertion to a specific Co-C bond is imperative to achieve stereoselective cyclization, and here is where the greatest difficulty of the process arises (Figure 5).

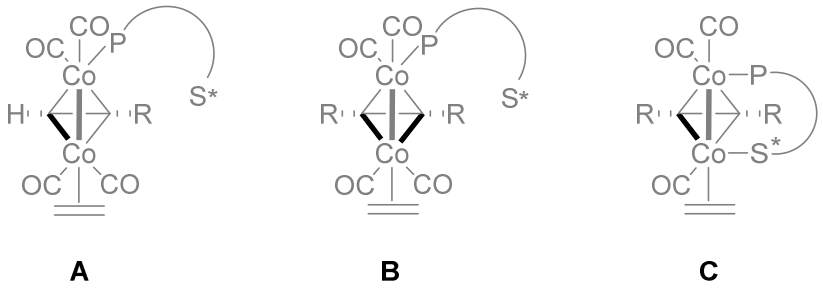
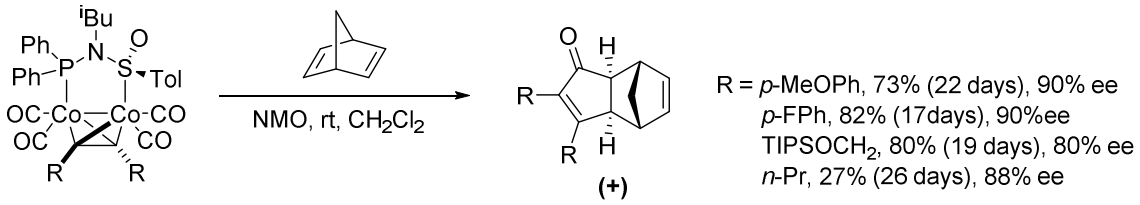


Figure 5: Preferred insertion sites for the alkene.

In the case of a terminal alkyne (**A**), a hemilabile ligand is able to discriminate the two cobalt atoms for the complexation of the alkene and, because of steric hindrance, there is an inherently preferred Co-C bond for insertion: the ligand does not play any role in the distinction of the bond to insert, in this case. However, when dealing with symmetric internal alkynes (**B** and **C**), the selectivity of the alkene insertion on the two available Co-C bond is hard to control. If we use a hemilabile ligand (**B**), both Co-C bonds will be too similar, and the insertion process will take place indistinctively on both of them. However, if the sulfur atom stays bound to the metal center, the chiral information will be close to the alkene insertion site, and both Co-C bonds will be distinguishable.

In spite of the long reaction times, mainly due to the intrinsic low reactivity of internal alkynes, the yields and enantiomeric ratios of these reactions were remarkable (Scheme 13).



Scheme 13: Selected results of the asymmetric PKR of internal symmetric alkynes.

2.1.8 Use of fluorinated substrates in the PKR

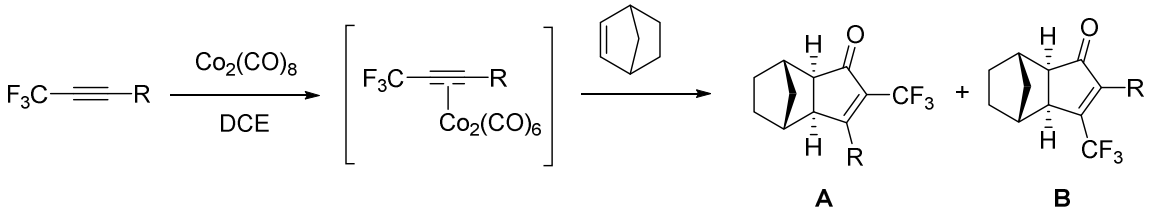
The presence of fluorinated groups strongly affects the properties of the molecules that hold them, mainly because of their strong electronegativity[47]. Fluorine has been widely used in the development of agrochemicals or polymers[48] and, very interestingly, in the modification of the pharmacokinetical properties of drugs such as permeability, metabolism and transport through the organism[49].

In spite of the scientific community's growing interest in fluorine-containing molecules, at the beginning of this work fluorinated substrates had been rarely used in

the PKR, and all the examples we could find in the literature included intramolecular PKRs[50].

Our research group became interested in the study of the behavior of fluorinated alkynes in the intermolecular PKR, and along with Jean-Claude Kizirian (a visiting professor from Tours University in our laboratory) we began our research in the field. Our first results showed that the PKR of fluorinated alkynes with norbornadiene was extremely regioselective and always gave the α-fluorinated cyclopentenones[51]. This topic will be further discussed in Chapter 5 of this Thesis.

Konno and co-workers[52] described, very recently and inspired in our report of the PKR of dissymmetric fluorinated alkynes with norbornadiene[51], the PKR of various internal fluorinated alkynes with norbornene. They observed the formation of the corresponding cyclopentenone derivatives in high yields as a mixture of regioisomers in different proportions depending on the substrate (Scheme 14). However, the minor regioisomers were not thoroughly characterized and no explanation was given for the change in reactivity from norbornadiene to norbornene.



R = *p*-ClPh, 92%, A:B = 68:32
= *p*-EtO_2CPh, 91%, A:B = 73:27
= *p*-MeOPh, 90%, A:B = 71:29
= *p*-MeOPhCH_2, 57%, A:B = 97:3

Scheme 14: Summary of Konno's results for the PKR of fluorinated alkynes with nornornene.

2.2 Prostaglandins and Phytoprostanes

Probably, one of the most well-known cyclopentanic compounds in nature is the family of prostaglandins[53]. They are generated as a product of the action of cyclooxygenase (COX) on the fatty acids that come from the phospholipid bilayer. The most common substrate for this reaction cascade in the human body is arachidonic acid[54] (Figure 6).

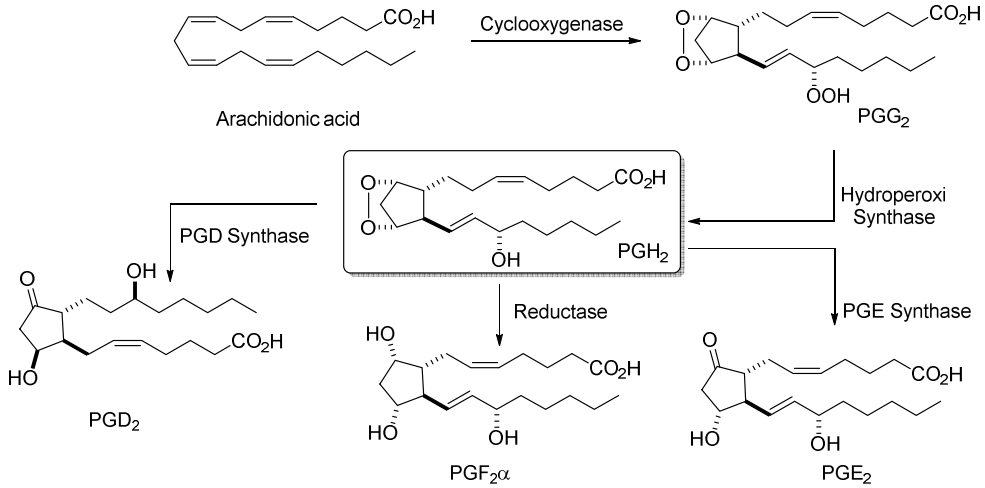


Figure 6: Enzymatic biosynthesis of prostaglandins.

In plants, a similar process occurs with linolenic acid as substrate and phytoprostanes as product. Jasmonic acid is one of the products that are part of this family[55]. It is formed during events of cellular stress, and it is thought to regulate aspects of fruit ripening, production of viable pollen or plant resistance to pathogens and insects, among other features. 12-oxo-phytodienoic acid (12-oxo PDA) is a biosynthetic precursor of jasmonic acid *via* the allene oxide synthase pathway[56] (Figure 7).

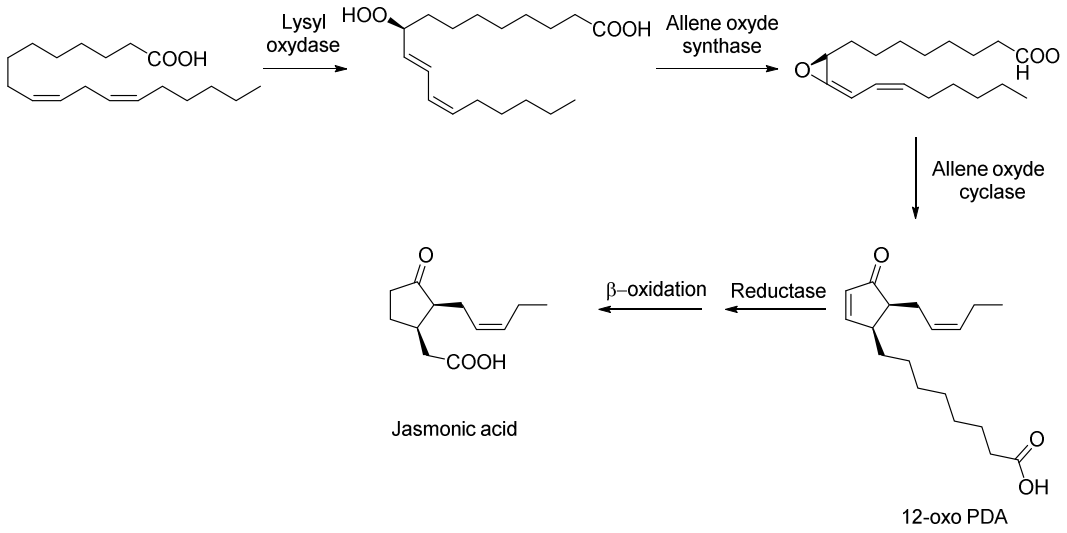


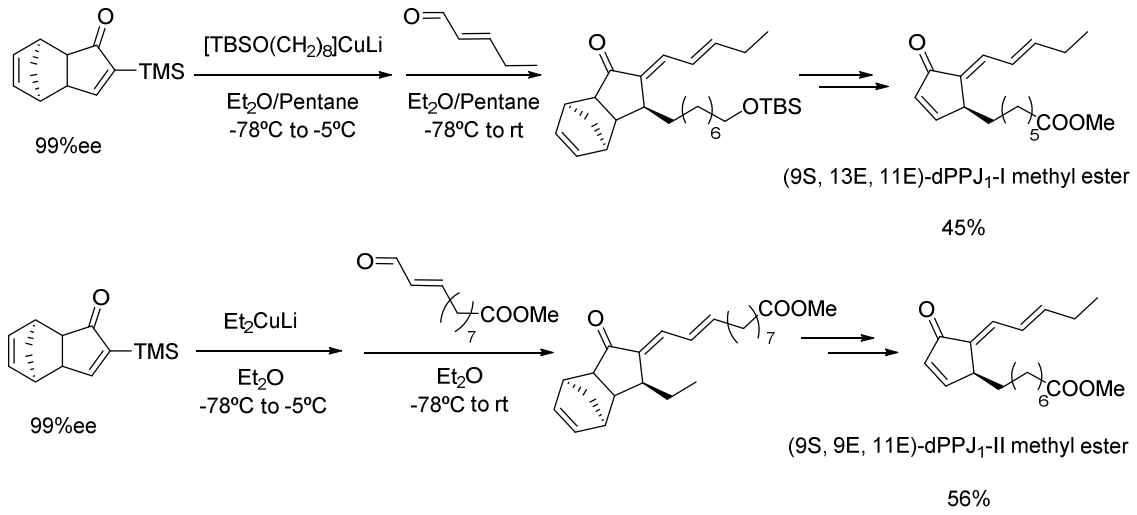
Figure 7: Allene oxide synthase pathway.

Linolenic acid cascade plays a very important role in the regulation of plants' metabolism, although the role of the metabolites is not perfectly established[57]. Furthermore, some unnatural derivatives of prostaglandins have proved to be of interest as antitumor agents[58]. This fact, along with the difficulty to isolate prostaglandins and phytoprostanes from natural sources, has led to an increasing interest on finding simple and efficient methods to access them.

2.2.1 Synthesis of prostaglandins and phytoprostanes *via* the PKR

There is a great variety of bioactive and pharmaceutically interesting products that share a α, β disubstituted cyclopentenone as part of their structure. This fact makes them a perfect set of candidates to be synthesized by the means of a PKR.

In 2005, Professor Evans, in collaboration with our group, reported the synthesis of optically active $dPPJ_1$ using an approach first described by them: the conjugate addition-Peterson olefination one-pot reaction[59]. The starting material was the optically active and readily available PK adduct of norbornadiene and trimethylsilylacetylene. It was synthesized using a pulegone derived ligand and obtained with high yield and enantiomeric excess. On this material, 1,4 conjugate addition and *in situ* Peterson olefination were performed. After a series of steps, two derivatives of $dPPJ_1$-I and $dPPJ_1$-II were obtained and biologically tested (Scheme 15).

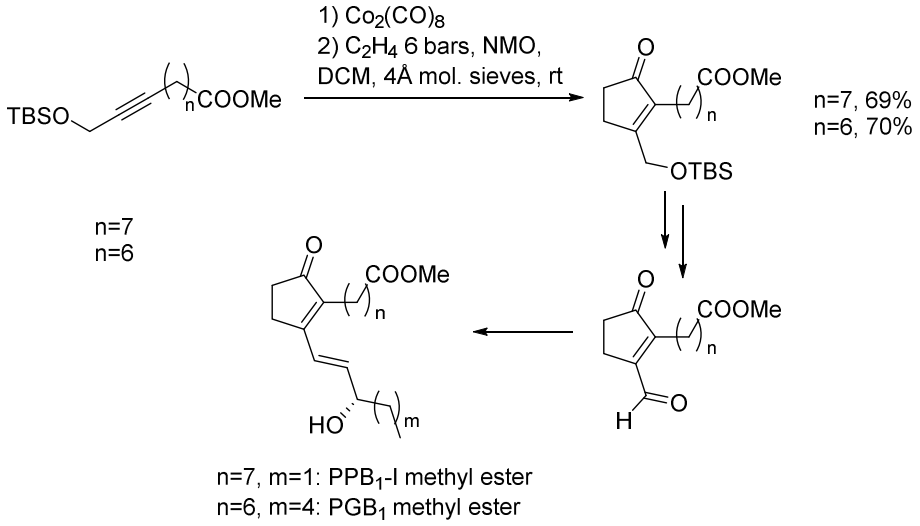


Scheme 15: Evans's synthesis of prostanes.

In 2008, the same authors reported the synthesis a series of PPAR-γ cyclopentanic ligands[60]. PPAR is a group of nuclear receptor proteins that play essential roles in the regulation of cellular differentiation, development, metabolism and tumor genesis of higher organisms. As in 2005, the starting material was the PK adduct of norbornadiene and trimethylsilylacetylene. The same methodology described in 2005 was used this time

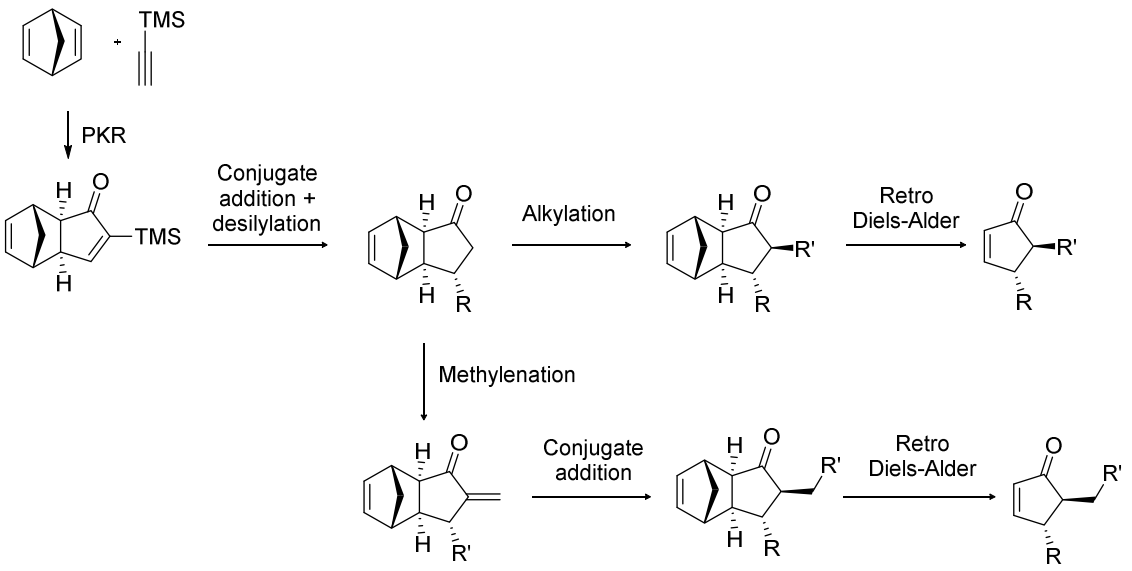
to obtain (±)-TEI-9826, an analogue of PGA_2 with potent antitumor activity, and a series of phytoprostane derivatives in their optically active form.

A year later, our group reported an approach to prostaglandin B_1 and phytoprostanes of the B_1 type[61]. The synthesis of these products was envisaged by an intermolecular PKR between an internal acetylene with a terminal protected alcohol group and ethylene. The desired PK adducts were synthesized *via* a PKR that was extremely regioselective, and after deprotection of the alcohol, oxidation to the aldehyde and olefination, the methyl ester derivatives of PGB_1 and PPB_1 were obtained (Scheme 16).



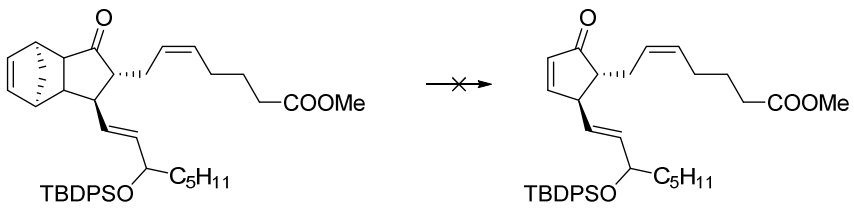
Scheme 16: Synthesis of PPB1 and PGB1 derivatives.

During his PhD thesis, Agustí Lledó[62] also approached the synthesis of prostaglandins *via* the PKR. The chosen prostaglandin was PGA_2, and the starting material was, as for Evans's synthesis, the PK adduct of norbornadiene and trimethylsilylacetylene. The strategy was based upon a conjugate addition reaction followed by desilylation of the PK adduct. The product of these reactions could then be treated in two different fashions. The carbon atom α to the ketone could be alkylated to give an α, β disubstituted adduct that, after a retro Diels-Alder reaction, would yield the desired disubstituted cyclopentenones. Another possibility would be to methylenate the same position to obtain an exocyclic enone on which another conjugate addition could be carried out. Again, after a retro Diels-Alder reaction, the desired products would be obtained (Scheme 17).



Scheme 17: Agustí Lledó's synthetic approach.

The synthesis of the PK adduct, in both the racemic and enantiomerically pure fashion, was carried out satisfactorily. The β chain was installed by means of a conjugate addition very efficiently, and the product could be easily desilylated. With regards to the assembling of the chain in the α position to the carbonyl group, the process turned out to be problematic. The alkylation of the carbon atom α to the carbonyl was found out to be slow and poorly efficient. Under the several conditions assayed, a mixture of starting material, mono and dialkylated products was always detected in different proportions. The strategy was then changed to the methylenation of the same position. The desired metylenketone was obtained in moderate yields, and the following conjugate addition could be performed. It must be said, though, that the exocyclic enone obtained was not very stable and dimerized *via* a hetero Diels-Alder reaction under the reaction conditions. As a matter of fact, this byproduct could be detected in variable proportions in all the methylenation crudes. Once the α, β substituents of choice were attached to the PK adduct, only the retro Diels-Alder reaction was left to get to the desired PGA_2. Unfortunately, the reaction conditions were not compatible with the allylic alcohol located in the β chain, even though different protecting groups and conditions were explored (Scheme 18).



Scheme 18: Final steps of the synthesis of PGA_2.

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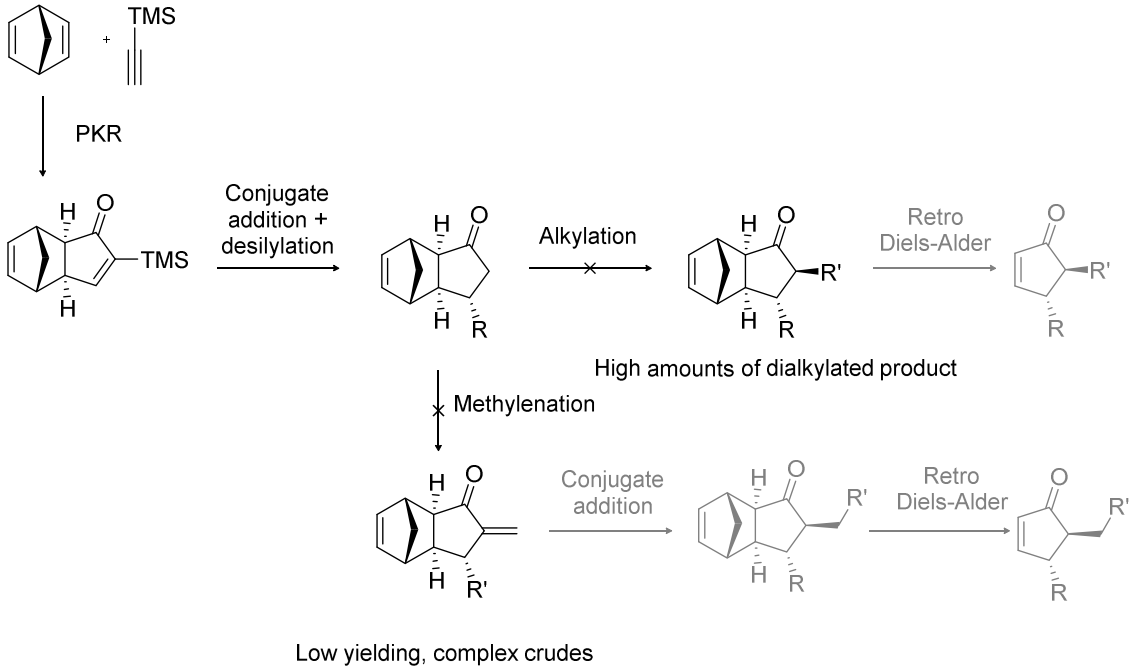
3. Development of a new methodology for the synthesis of 4,5-disubstituted cyclopentenones

3.1 Introduction

As we discussed earlier, our research group had already explored the synthesis of α, β-disubstituted cyclopentenones. Agustí Lledó's approach[1], in spite of being conceptually very elegant, had to be dismissed due to the insurmountable difficulties encountered during its practical application (Scheme 1).



Scheme 1: Main problems of A. Lledó's approach.

Uncovering the enone at the last synthetic step through a retro Diels-Alder reaction is a well-known method pioneered by Grieco, who applied it to the synthesis of natural products starting from dicyclopentadiene derivatives with *endo* stereochemistry[2]. It is worth saying that, contrary to the dicyclopentadiene derivatives, the PK adducts are *exo*. The norbornene moiety in our PK adducts acts as a protecting group for the final cyclopentenone (to be uncovered by a retro Diels-Alder, following Grieco's approach, at the end of the synthesis). Furthermore, the norbornene residue also has a stereodirecting role: it blocks one of the faces of the PK adducts, forcing nucleophiles to attack the enone through the opposite face (Figure 1).

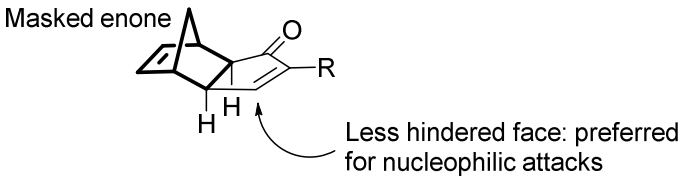
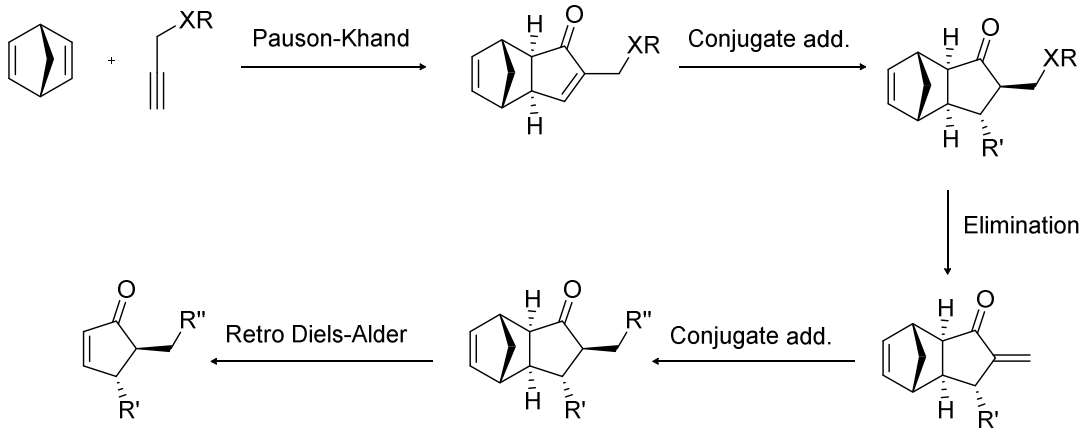


Figure 1: Structural features of the bicyclic PK adducts of norbornadiene and a terminal alkyne.

We envisaged a new synthetic strategy to settle the main problem of our previous approach: the introduction of the substituents in the α position to the carbonyl group (Scheme 2).



Scheme 2: New synthetic approach.

The key feature of our methodology would be the use in the PKR of an alkyne with a potential leaving group (XR) in the propargylic position. This would allow us to perform the desired transformations at the β position and then discard the leaving group (upon the necessary alterations) at will. This would lead to a newly formed exocyclic enone on which we could install the desired substituent by conjugate addition reactions. This strategy would avoid the problematic alkylation or methylenation processes. The final 4,5-disubstituted cyclopentenones would be obtained after a retro Diels-Alder reaction.

3.2 Synthesis and evaluation of different propargylic alkynes bearing a potential leaving group

The choice of the alkynes of study was crucial for the success of our approach. This work was started by Albert Pesquer during his experimental MSc[3]. The alkynes should be readily available, undergo the PKR with good yields and have an easily removable group in the propargylic position so that the exocyclic enone could be obtained after simple transformations. The alkynes selected are depicted in Figure 2.

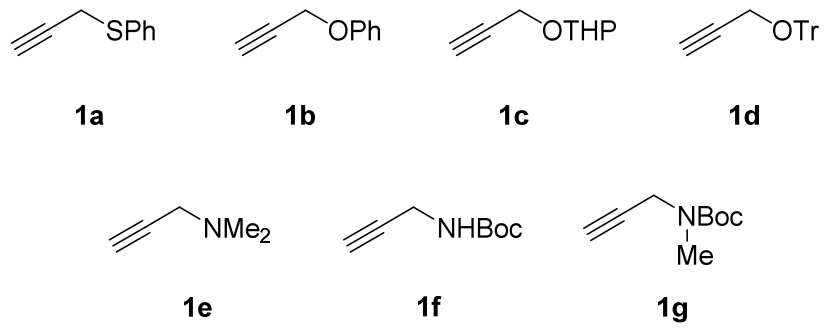
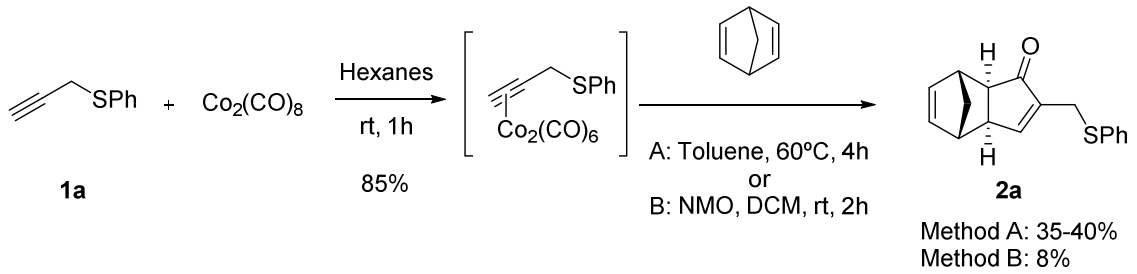


Figure 2: Alkynes selected to study the PKR.

3.2.1 Phenyl propargyl thioether

Our first efforts focused on the commercially available phenyl propargyl thioether. Our intention was to eliminate the sulfur moiety by oxidizing it to the corresponding sulfoxide, therefore obtaining the desired exocyclic enone.

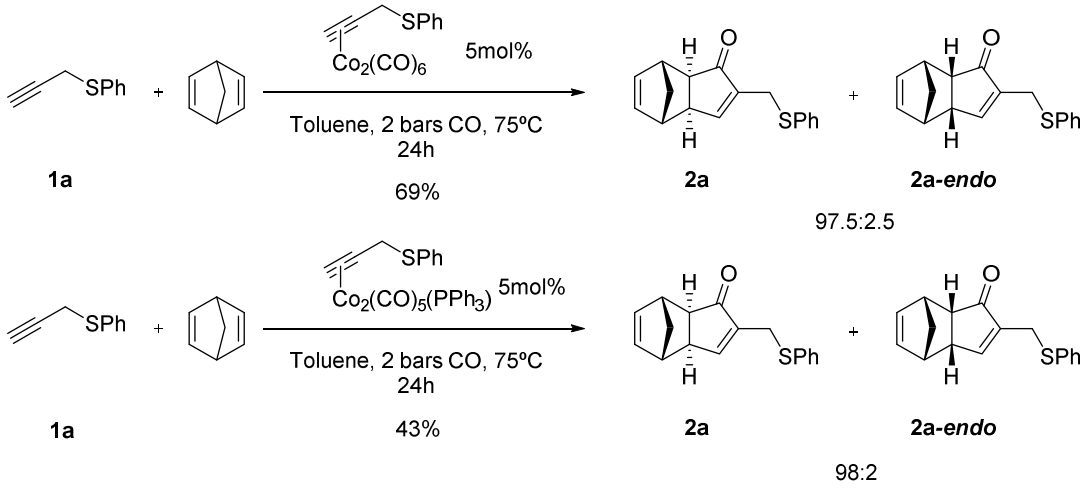
The dicobalt hexacarbonyl complex was obtained without any inconvenience. Then, the PKR was carried out in both thermal and *N*-methylmorpholine-*N*-oxide (NMO) activation conditions (Scheme 3).



Scheme 3: Reactivity of phenyl propargyl thioether in the PKR with norbornadiene.

Even though the PKR proceeded under both conditions, the yields were moderate in the thermal version and very low when run with NMO. We blame this low yield on partial oxidation of sulfur by NMO. The *endo* adduct was not detected under any of these conditions.

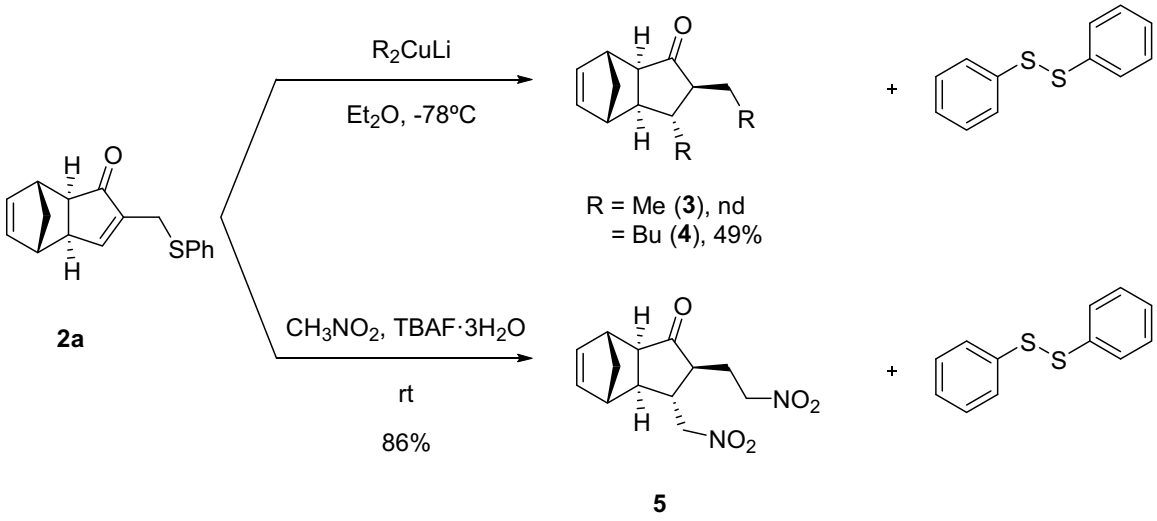
Once established that thermal conditions were the most suitable for this substrate, the next step was the obtention of the adduct by means of a catalytic PKR. This reaction was conducted with a 5 mol% of catalyst under 2 bars of CO at 75°C during 24h. The yield rose up to almost 70%, and for the first time we could observe traces of the *endo* isomer (2.5%). To diminish the presence of this undesired isomer, the complex was modified by changing one of the CO ligands for a PPh_3 moiety. Under the same conditions, the yield dropped to a modest 43% and the *endo* isomer amount was lowered to a 2% (Scheme 4).



Scheme 4: Catalytic PKR of phenyl propargyl thioether and norbornadiene.

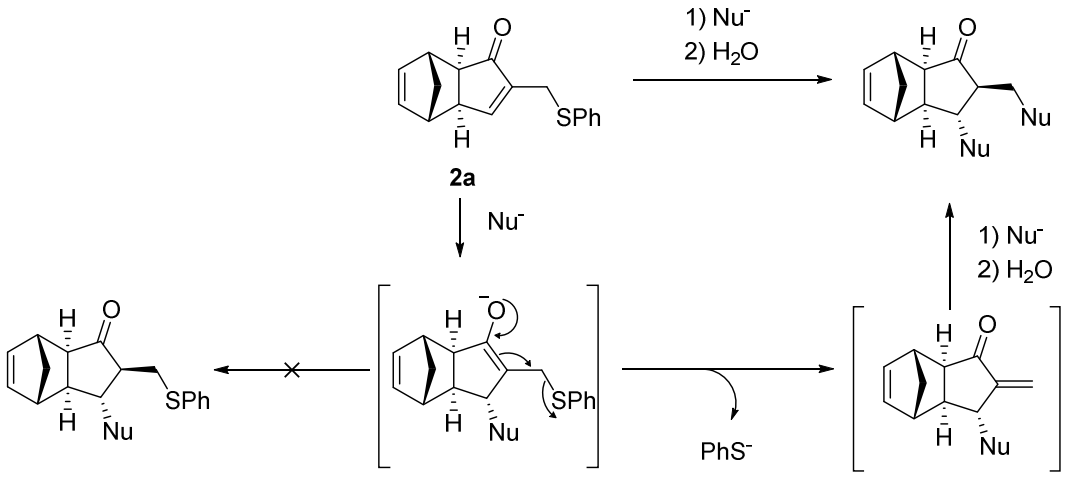
Once we had the PK adduct in hand, its reactivity was tested. Three model reactions were chosen: the conjugate addition of dibutyl lithium cuprate and dimethyl lithium cuprate, as representative of organocopper reagents; and the conjugate addition of nitromethane as a non-organometallic reagent.

The results were surprising in all cases. Instead of obtaining the desired 1,4-addition adducts, we recovered a set of products that corresponded to the double addition of the nucleophile, along with diphenyl disulfur as a by-product, in moderate yield in the case of the addition of dibutyl lithium cuprate and excellent yield in the conjugate addition of nitromethane (Scheme 5). The yield in the case of the addition of dimetyl lithium cuprate could not be determined, as the product could not be isolated due to its high volatility and unstability to flash chromatography.



Scheme 5: Conjugate addition reactions on adduct **2a**.

These unexpected experimental results required some mechanistic enlightenment. We proposed that, after the first conjugate addition, the enolate reacts rapidly in the reaction mixture, affording an exocyclic enone. This enone could again react *in situ* in a 1,4-addition manner with the reagent surplus, thus providing the double-addition products obtained (Scheme 6).



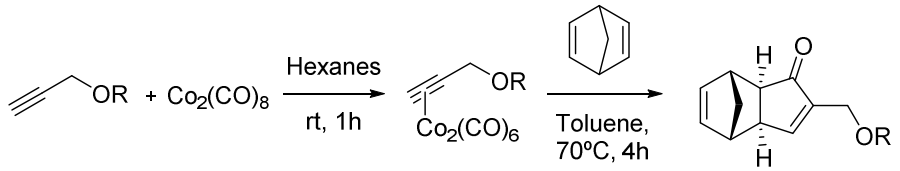
Scheme 6: Proposed mechanism for the double-addition products formation.

Even though we tried to isolate the desired single addition products by reducing the excess of nucleophile and by quenching the reaction at low temperature, we never succeeded to observe them. All attempts to trap the enolate by addition of another electrophile also failed.

Given that the use of this alkyne turned out not to be suitable for our prospects, we decided to change to an *a priori* more robust and worse leaving groups: propargyl alcohol derivatives.

3.2.2 Propargyl alcohol derivatives

Propargyl alcohol was transformed into three different alkynes that were, as for phenyl propargyl thioether, assayed as PKR substrates. We wanted to obtain the PK adducts in the most straight forward fashion as possible, so that we could test their reactivity and then decide if it was worth or not to optimize the PKR. For this reason, we only performed the thermally activated, stoichiometric PKR. The PKR yields were excellent in all cases and, although we detected the *endo* products for alkynes **1b** and **1c** in different proportions, they could be easily separated from the desired *exo* adducts by flash chromatography (Table1).

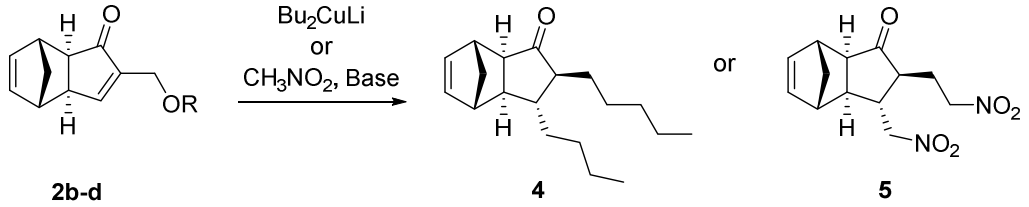


1b-d **2b-d**

Entry	Alkyne	R	*exo:endo*	Product	Yield[a]
1	**1b**	Ph	96:4	**2b**	71%
2	**1c**	THP	94:6	**2c**	86%
3	**1d**	Tr	>99:1	**2d**	85%

Table 1: Reactivity of propargyl alcohol derivatives in the PKR with norbornadiene. a: corresponds to the combined yield of the cobalt complexes formation and the PKR.

Once these products were obtained, we proceeded to test their reactivity. The chosen model reactions were the conjugate additions of dibutyl lithium cuprate and nitromethane. When products **2b-d** were treated under the standard reaction conditions for the conjugate addition of these reagents, we observed that the outcome of the reactions was identical as for adduct **2a**: instead of obtaining the desired single addition products, the potential leaving group was lost *in situ* to yield the exocyclic enone, which reacted again with the nucleophile to give the double addition products **4** and **5** (Table 2).



2b-d **4** **5**

Entry	Starting material (sm)	Nucleophile	Product	Yield
1	**3b**	Bu	**4**	56%
2	**3b**	CH_2NO_2	**5**	99%
3	**3c**	Bu	**4**	55%
4	**3d**	Bu	sm	-

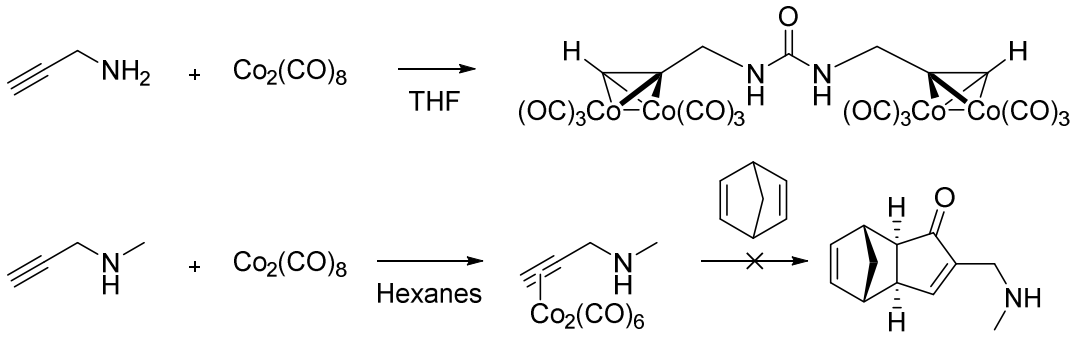
Table 2: Conjugate addition reactions on adducts 3b-d.

At sight of these discouraging results, we decided not to study propargyl alcohol derivatives any further and to devote all our efforts to the exploration of the reactivity of propargylamine derivatives.

3.2.3 Propargylamine derivatives

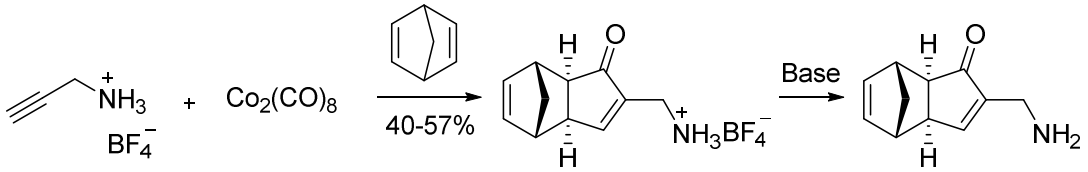
Since sulfur and oxygen derivatives were too labile for our porpouse and eliminated *in situ*, we decided to move towards less acidic groups that would, in theory, make worse leaving groups: propargylamine derivatives, that would be eliminated by permethylatilating the free amines.

PKR with primary and secondary amines has been, until recent times, a big challenge. Hong and co-workers[4] reported that propargylamine formed a symmetric urea-type complex when reacting with $Co_2(CO)_8$ and *N*-methylpropargylamine, in spite of forming well its hexacarbonylic complex with $Co_2(CO)_8$, yielded very complex crudes when reacting with norbornadiene (Scheme 7).



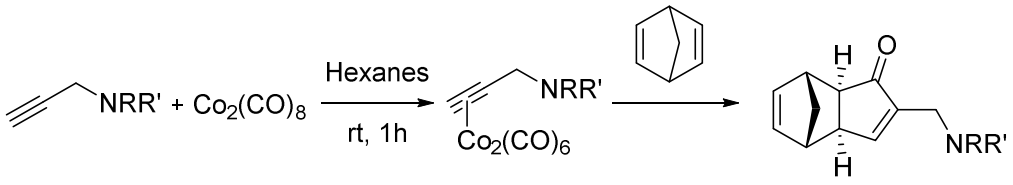
Scheme 7: Reactivity of primary and secondary amines with dicobalt octacarbonyl.

Our group proposed a solution to this problem[5] by performing the PKR of these amines' ammonium salts with norbornadiene, also providing the first description of PKR with salts of acetylenic compounds as a reagent (Scheme 8).



Scheme 8: PKR of ammonium salts with norbornadiene.

These compounds weren't included in our study because the presence of salts would suppose a detrimental environment for conjugate addition reactions. Furthermore, these saline substrates are not yet available in their optically active form. The propargyl amines chosen were *N,N*-dimethyl-propargylamine, *N*-methyl-*N*-Boc-propargylamine and *N*-Boc-propargylamine (Table 3).

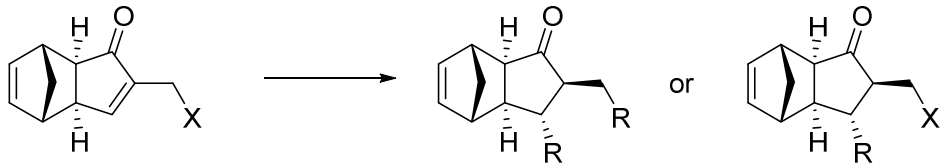


1e-g **2e-g**

Entry	Alkyne	NRR'	PKR Conditions	*exo:endo*	Product	Yield[a]
1	**1e**	NMe_2	Hexanes, 60°C, 3h	>99:1	**2e**	87%
2	**1f**	NHBoc	Hexanes, 60°C, 3h	11:1	**2f**	61%
3	**1g**	NMeBoc	Toluene, 65°C, 24h	40:1	**2g**	85%

Table 3: Reactivity of propargylamine derivatives in the PKR with norbornadiene. a: corresponds to the combined yield of the cobalt complexes formation and the PKR.

Once these products were synthesized, we tested their reactivity towards our two model reactions: the conjugate additions of dibutyl lithium cuprate and nitromethane. However, the results obtained with these substrates were somewhat surprising (Table 4).



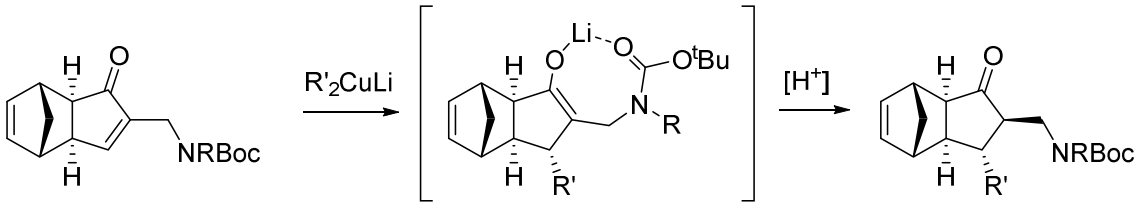
2e-g **4/5** **6-8**

Entry	PK adduct	X	Conditions	R	Product	Yield
1	**2e**	NMe_2	Bu_2CuLi, Et_2O, -78°C	Bu	**4**	40%
2	**2e**	NMe_2	CH_3NO_2, 80°C	CH_2NO_2	**5**	46%
3	**2f**	NHBoc	Bu_2CuLi, Et_2O, -78°C	Bu	**6**	71%
4	**2f**	NHBoc	CH_3NO_2, TBAF·$3H_2O$, rt	CH_2NO_2	**7**	99%
5	**2g**	NMeBoc	Bu_2CuLi, Et_2O, -78°C	Bu	**8**	89%

Table 4: Conjugate addition reactions on adducts **2e-g**.

As can be seen in Table 4, only the dimethylated amine led to the disubstituted product, whereas neither of the adducts containing a Boc protected amine experienced the process of *in situ* elimination and nourished the desired single-addition products in

good yields. Apparently, the presence of the Boc protecting group was decisive in the behavior of compounds **2f** and **2g**. The hypothesis we elaborated at this point was that the intermediate enolate formed after the conjugate addition would be stabilized by the formation of a lithium chelate complex between the oxygen of the enolate and the carbonyl of the Boc group. This complex would be stable in the reaction conditions and only hydrolyzed after the aqueous quenching performed at the end of the reaction, preventing the Boc protected amines to eliminate (Scheme 9).



Scheme 9: Proposed mechanism for the prevention of the exocyclic enone formation.

Mechanistic hypothesis

With the objective of giving to our mechanism proposal some theoretical support, we carried out a computational study on the elimination of the potential leaving group after the conjugate addition of dimethyl lithium cuprate and the subsequent lithium enolate formation to PK adducts **2e, 2f** and the hypothetical **2h** (Figure 3). For simplicity, these products will now be referred as **IB, IC** and **IA** respectively. These studies were carried out using the Density Functional Theory (DFT) model, more concretely the B3LYP hybrid functional with the 6-31G* set of basis. All the calculations were run using Spartan '10[6].

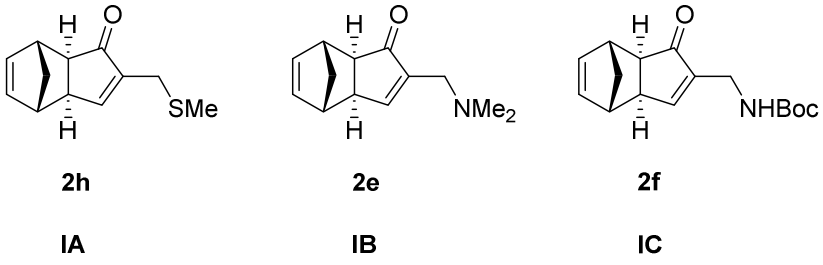
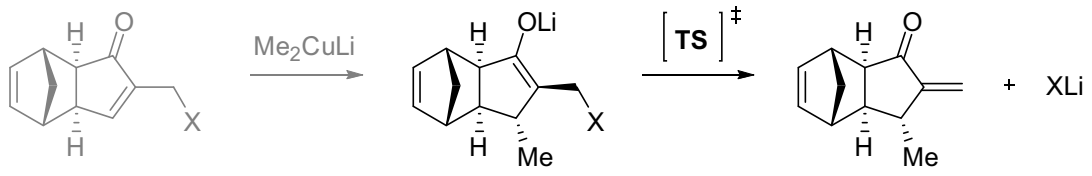


Figure 3: Studied PK adducts.

For all the substrates, we calculated the geometries and energies of the intermediates (**II**) and final products (**III** and **IV**) in the model reaction shown in Scheme 10 and the transition states (**TSA, TSB** and **TSC**) for the transformation of **II** into **III**.



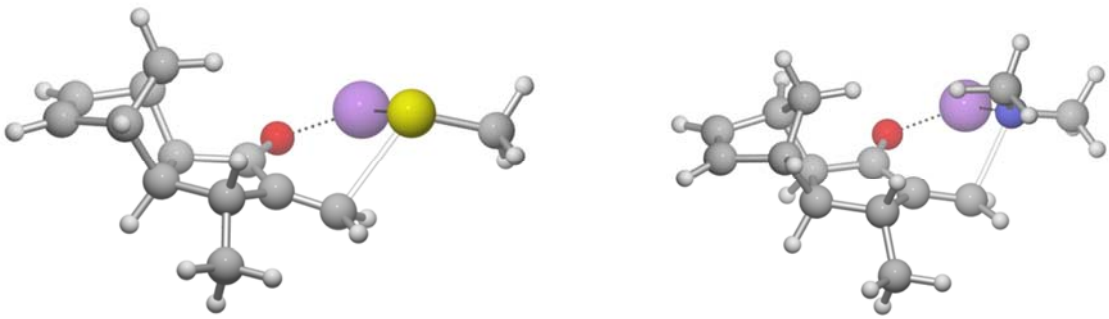
Scheme 9: Model reaction studied.

The calculations of the geometries of compounds **I, III** and **IV** occurred uneventfully. When calculating compounds **II** we found that our hypothetic chelated intermediates could be characterized as energy minima for **IIA, IIB** and **IIC.** The transition states (**TS**) were also found satisfactorily, although for simplicity they were calculated using the Semi-Empirical PM3 method and, once located, recalculated with DFT-B3LYP. The results can be seen in Table 5.

	Energy (Kcal/mol)		
X	**II**	**TS**	**IV**
SMe	-619086,23	-619086.29	-279645.79
NMe_2	-428617.49	-428585.35	-89158.74
NHBoc	-522298.06	-522272.81	-182861.42
	III	-339403.26	

Table 5: DFT-B3LYP energies of reaction minima and transition states.

The calculations on the transition states revealed that, in all three cases studied, a chelate species where the leaving group, the lithium and the enolate interacted was formed (Figure 4).



TSA **TSB**

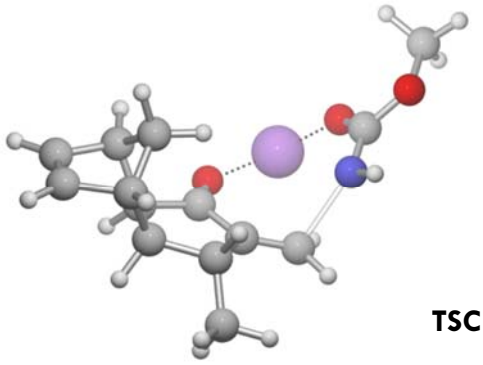
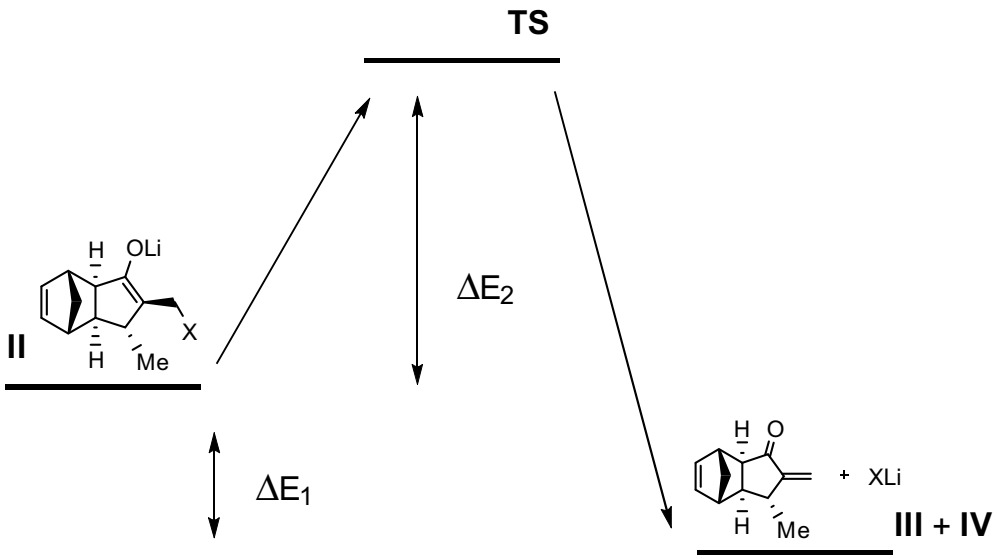


Figure 4: Geometries found for **TSA, TSB** and **TSC**.

The relative energy gaps between starting material and transition state (ΔE_1) and starting material and final products (ΔE_2) are depicted in Table 6.



Entry	R	ΔE_1 (Kcal/mol)	ΔE_2 (Kcal/mol)
1	SMe	-37.18	8.96
2	NMe_2	-55.49	32.14
3	NHBoc	-33.38	25.25

Table 6: Energy gaps ΔE_1 and ΔE_2 for the three model reactions.

The values obtained show a good correlation between the theoretical tendency to eliminate according to the acidic character of the conjugated acid (R-H), but not to the experimental observations. Our calculations correctly suggest that **IA** should have the strongest tendency to eliminate, followed by **IC** and **IB**. These calculations are in agreement with the pK_as of the conjugate acids of the leaving groups **IVA-C**. However, they don't predict the easy elimination of **IB** that is detected experimentally. Further

bibliographic research unveiled a precedent for the elimination of a dimethylamino moiety in a β-substituted enone after the conjugate addition of lithium dimethylcuprate[7] (Figure 5).

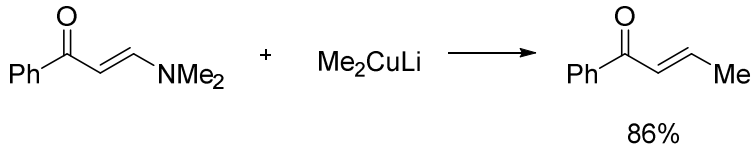


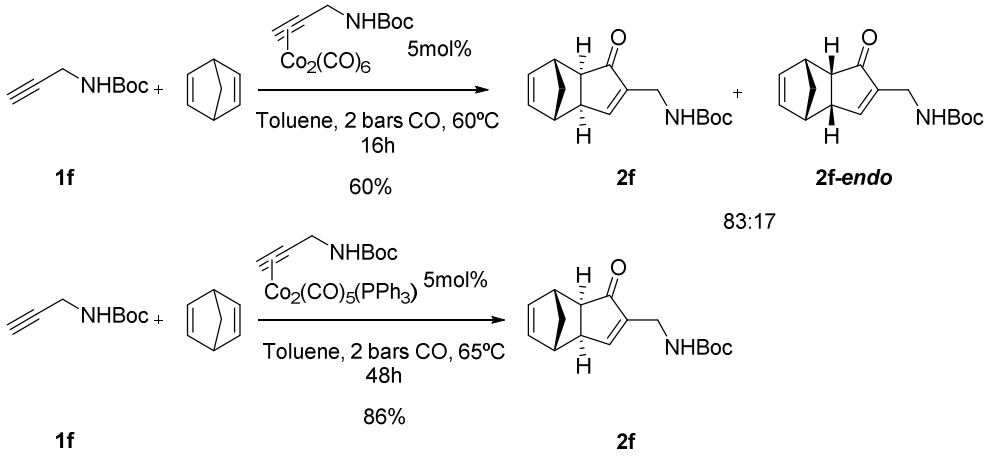
Figure 5: Stereoselective elimination of NMe_2 in the conjugate addition of Me_2CuLi.

In this report, the authors invoked a mechanism for the elimination of NMe_2 that was proposed a year before by Dieter and Silks[8] and that included a reductive elimination step from an intermediate copper species. Given the similarities with our examples, we think that a similar mechanism might be occurring in our case, and plan to study it further in the future.

3.3 Study of the PKR of *N*-Boc-propargylamine derivatives

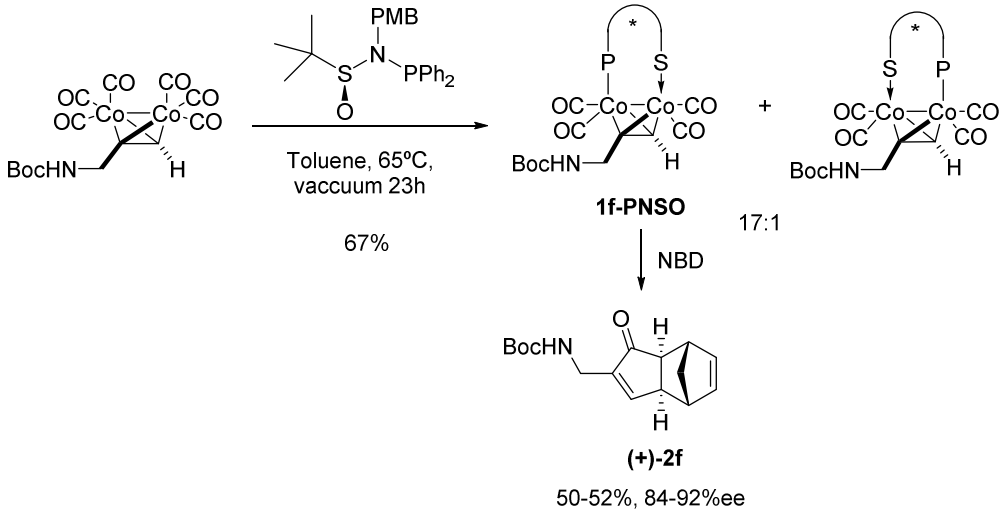
N-Boc-propargyl amine derivatives were, at light of the results obtained, the only adduct of this study that we could use for our purpose. Once at this point, the optimization of the synthesis of the adducts with Boc protected amines was faced. It had been previously described in our group[9] that the optically active version of the PKR gave better results in terms of yield and enantiomeric excess for the *N*-Boc-propargylamine adduct **2f** than for its *N*-methyl derivative **2g**. With these results in mind, we decided to work exclusively on **2f**.

The conditions for the stoichiometric, thermally activated reaction have already been described in section 3.2.3. The catalytic version of the reaction was conducted with a 5 mol% of catalyst under 2 bars of CO at 60°C during 16h. Upon reaction completion, a 60% of the desired product was obtained along with an 11% (83:17 ratio) of the *endo* isomer. To reduce the presence of this undesired isomer, the complex was modified by changing one of the CO ligands for a PPh_3 unit. The reaction was then performed at 65°C and 2 bars of CO for 48h. The yield rose up to an excellent 86%, and the *endo* product could not be detected by thin layer chromatography or ^{1}H-NMR (Scheme 10).



Scheme 10: Catalytic PKR of *N*-Boc-propargylamine.

Once the PKR had been optimized in its racemic form, an enantioselective version was pursued. PNSO ligands had already been used in the PKR of *N*-Boc-propargylamine with tetramethylnorbornadiene[10]. The dicobalt-PNSO tetracarbonyl complex (**1f-PNSO**) was obtained in good yield and a 17:1 diastereomeric ratio. The mixture of diastereomers could be enriched in the major one by digestion in hexanes and methanol. Once the major complex was isolated, it was treated with norbornadiene in toluene at 60ºC. After 5h, the final product was purified by flash chromatography and isolated in a 50% yield and an enantiomeric excess of 84-92% depending on the purity of the starting complex. The reaction could also be carried out under NMO activation conditions. The yield and enantiomeric excess were similar to the ones obtained by thermal activation, but the crude was harder to purify, as many cobalt by-products were formed. For this reason, the reaction was always performed under thermal conditions (Scheme 11).

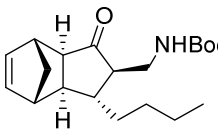
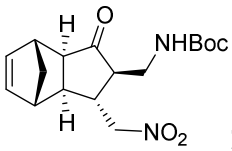
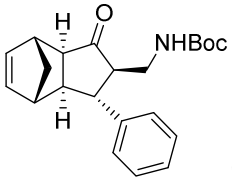
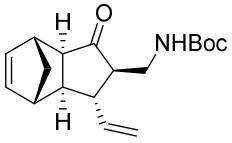


Scheme 11: Asymmetric PKR of N-Boc-propargylamine.

3.3.1 Reactivity of *N*-Boc-propargylamine adduct (2f)

We knew, so far, that the *N*-Boc-propargyamine PK adduct yielded the desired 1,4-addition products when treated with dibutyl liyhium cuprate and nitromethane in presence of base. However, we still had to test our methodology further and extend it to other chains and functional groups. Furthermore, we also needed to perform the elimination of the amine and the retro Diels-Alder reaction to get to our desired α, β-disubstituted products. The optimization of this methodology was always carried out with **2f** as a racemate.

We performed a series of different conjugate addition reactions. We assayed typical organocopper reagent additions with aromatic, allylic and aliphatic chains, with good to excellent yields in all cases except for the addition of vinyl. In this case, we found that the product obtained was highly volatile, and the low yield isolated might be due to this property. Non-organometallic nucleophiles worked as well as organocopper reagents. The photochemical addition of methanol was also carried out successfully. The high tolerance of adduct **2f** to such varied reaction conditions made it perfect for our synthetic strategy (Table 7).

Entry	Conditions	Product	Yield
1	Bu_2CuLi, THF, -78°C	 **6**	71%
2	CH_3NO_2, TBAF·$3H_2O$, rt	 **7**	99%
3	MgPhBr, CuI, THF, -78°C	 **9**	77%
4	CH_2CH-MgBr, CuI, Et_2O, -78°C	 **10**	20%

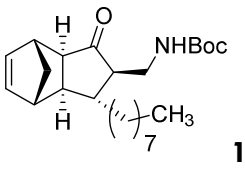
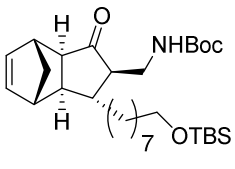
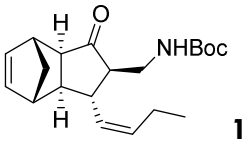
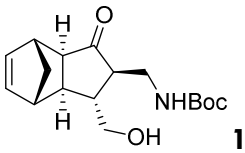
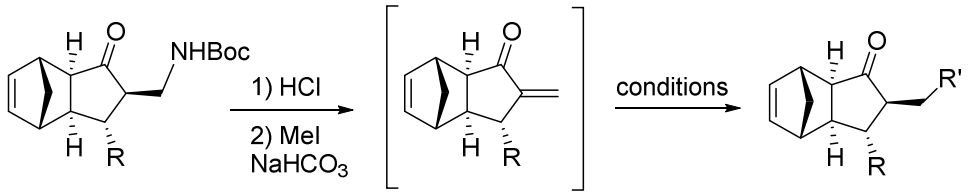
5	$C_8H_{17}MgBr$, CuI, THF, -78°C	 **11**	74%
6	$(C_8H_{16}OTBS)_2CuLi$, THF, -78°C	 **12**	65%
7	EtLi, CuI, THF, -78°C then acetylene	 **13**	86%
8	MeOH, benzophenone hυ=254nm	 **14**	73%

Table 7: Conjugate addition reactions of **2f**.

We selected some of these products to deprotect the amine, eliminate it and perform a second conjugate addition on the resulting exocyclic enone.

The Boc group was deprotected under two different conditions: with HCl/MeOH and with TFA/DCM. Initially, we found no reason to choose one reaction over the other, since the yields were quantitative in all cases and no purification (further than extraction) was needed in any case. We did detect different proportions of the trifluoroamide when brand new TFA was used. For this reason, we decided to perform all the deprotections with the commercially available mixture of HCl/MeOH.

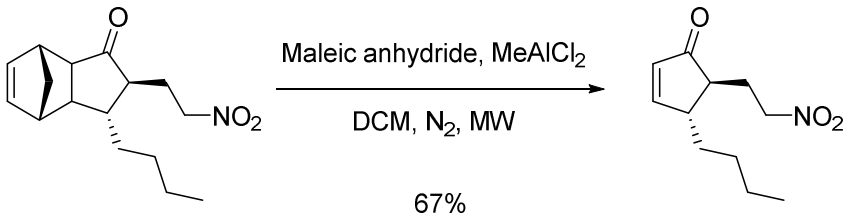
The substrates were treated with HCl/MeOH at room temperature and, after addition of base, the free amines were recovered in quantitative yields. The products were used directly in the elimination reaction. They were exposed to MeI and $NaHCO_3$ in DMF at room temperature and allowed to react overnight. These reactions yielded the corresponding exocyclic enones with quantitative yields in all cases with no further purification than extraction needed. It must be said that the exocyclic enones were highly sensitive and had to be used at once, immediately after its isolation. Their treatment with different nucleophiles afforded the α, β-disubstituted products with moderate to good yields (Table 8).



Entry	sm	R	Conditions	Product	R'	yield
1	**6**	Bu	CH_2CH-MgBr, CuI, THF, -78°C	**15**	Vinyl	30%[a]
2	**6**	Bu	CH_3NO_2, TBAF·$3H_2O$, 75°C	**16**	CH_2NO_2	82%
3	**10**	Vinyl	Bu_2CuLi, THF, -78°C	**17**	Bu	25%[a]

Table 8: Exocyclic enone obtention and second conjugate addition tests. a: low yield due to the volatility of the product.

Due to the possible volatility of the enones, we decided to try only the more polar nitro substituted product **16** in the retro Diels-Alder reaction under microwave conditions. **16** was dissolved in anhydrous dichloromethane in a microwave vial provided with magnetic stirring under nitrogen. Then, 15 equivalents of maleic anhydride were added, followed by one equivalent of methyl aluminum dichloride. The mixture was then irradiated with microwaves (250W, 110°C, 30 psi of inner pressure) for 60 seconds. After this time, the reaction crude was treated with base and further extracted with dichloromethane. Flash chromatography yielded enone **18** in good yield (Scheme 12).



16 **18**

Scheme 12: Retro Diels-Alder reaction under microwave conditions.

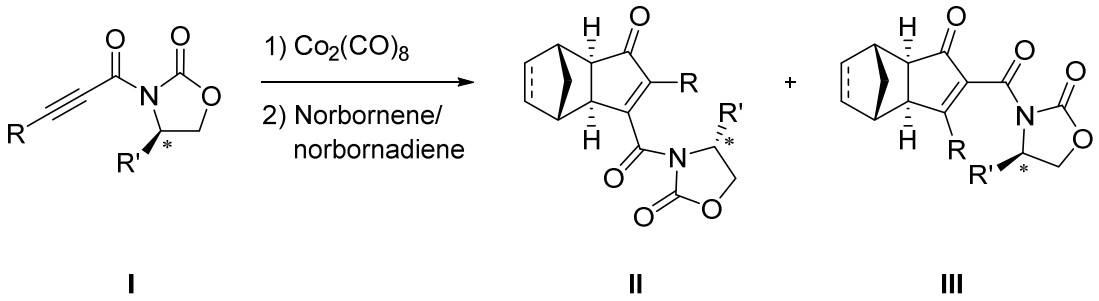
3.4 Enantioselective versions.

In the synthesis of 4,5-disubstituted cyclopentenones from the PK adduct of norbornadiene and *N*-Boc-propargylamine, the Boc protected amine had to be eliminated in order to generate the exocyclic enone. We thought that the use of a chiral auxiliary instead of Boc would be an easy way to generate optically active PK adducts, since the auxiliary would have to be introduced and eliminated just as the protecting

group, and its use would not represent an increase on synthetic steps. With this approach, we would avoid the preparation of a PNSO ligand, its complexation to the dicobalt cobalt complex resulting from **1f** and the separation of the diastereomers.

As we discussed in the introduction of this Thesis, the use of chiral auxiliaries bound to the alkene or the alkyne has been one of the most widespread approach to access optically active PK adducts throughout the years. Camphor derived acetylenic esters[11], sultame[12] and oxazolidinone[13] derivatives have previously been used by our group as source of chirality.

N-(2-alkynoyl) derivatives of 2-oxazolidinones were first presented by our group at the end of the 90s[14], and they were used in the intramolecular PKR and the intermolecular PKR of internal dissymmetric alkynes with strained alkenes (Scheme 14).



Scheme 14: PKR of *N*-(2-alkynoyl) 2-oxazolidinone derivatives.

The reactions took place in mild conditions and yielded the products in high yield. The regioselectivity depended on the substitution pattern of the alkyne. The diastereoselectivity was controlled by the substitution pattern of the chiral auxiliary, and diastereomeric ratios up to 18:1 could be achieved. Furthermore, the diastereomers could generally be separated by column chromatography.

With this background in mind, we envisioned that a similar approach could be applied for our synthesis of 4,5-disubstituted cyclopentenones using alkynes that structurally resembled **I** (Figure 6).

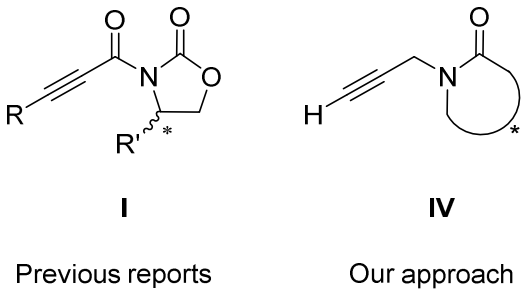
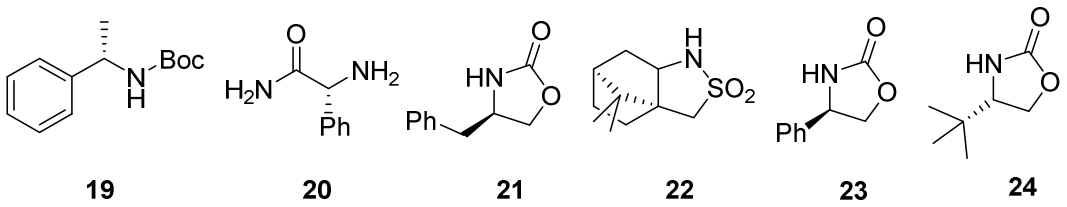


Figure 6: General structure of the chiral propargylamides proposed.

Based on our experience, we knew that a carbamate was very likely not to eliminate upon a conjugate addition reaction, and the fact that we were to use terminal alkynes would prevent the regioselectivity problems our group experienced in the past[14]. The high diasteroselectivities reported, along with the fact that the diastereoisomers could be separated by chromatography supported our strategy.

3.4.1 Synthesis and reactivity of PK adducts

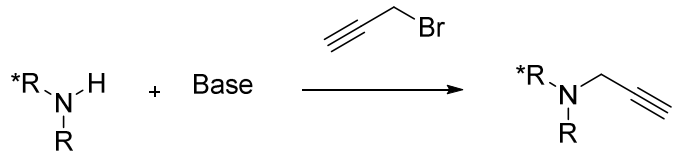
We chose six chiral auxiliaries bearing carbamates, an amide and a sulfone to explore the feasibility of our strategy (Figure 7).

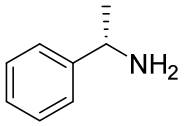
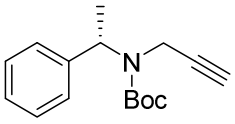
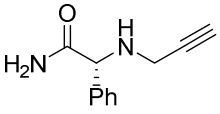
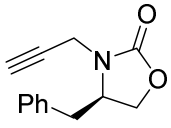
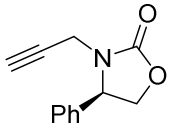


19 **20** **21** **22** **23** **24**

Figure 7: Chosen chiral amine derivatives.

The six substrates were allowed to react with propargylbromide and base to obtain the corresponding alkynes. The best conditions found for each substrate are shown in Table 9.



Entry	SM	Conditions	Product	Yield
1		1) K_2CO_3, ACN 2) Boc_2O, DMAP, DCM	 **25**	37%
2	**20**	K_2CO_3, ACN	 **26**	42%
3	**21**	NaH, THF	 **27**	57%
4	**23**	BuLi, THF	 **28**	80%

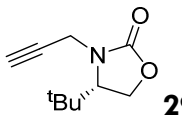
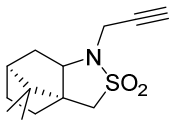
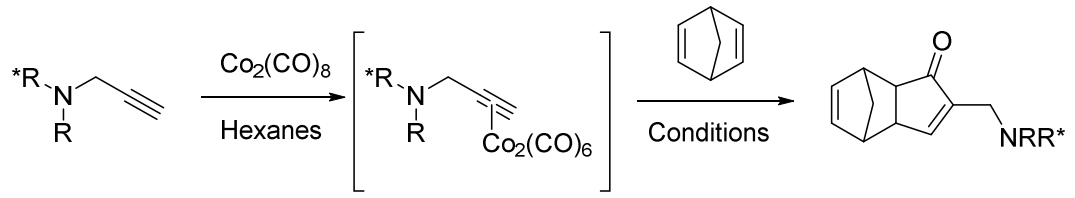
5	**24**	BuLi, THF	 **29**	94%
6	**22**	BuLi, THF	 **30**	82%

Table 9: Alkylation of the selected substrates.

Once with the alkynes in hand, we proceeded to explore their reactivity in the PKR with norbornadiene. The best reaction conditions found for each substrate are shown in Table 10.



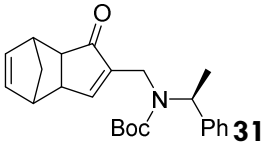
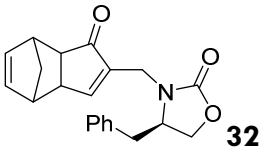
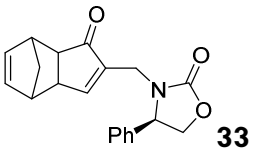
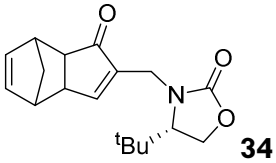
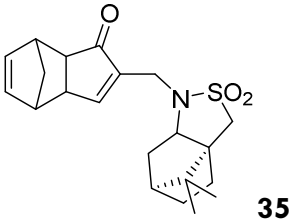
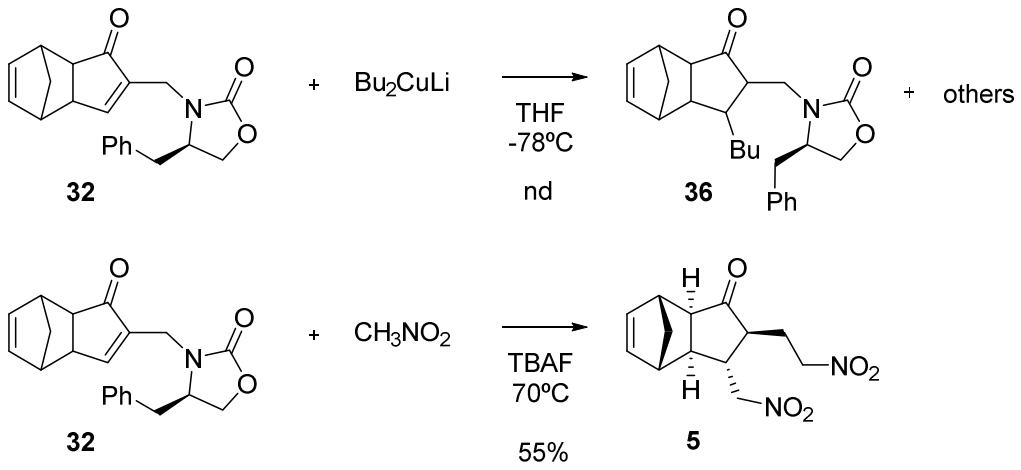
Entry	Alkyne	Conditions	Product	dr	Yield
1	**25**	Toluene, 70°C	 **31**	1:1	90%
2	**26**	Toluene, 70°C or NMO, DCM, rt	sm	-	-
3	**27**	NMO, DCM, rt	 **32**	1:1.5	90%
4	**28**	NMO, DCM, rt	 **33**	1:1.5	83%
5	**29**	Toluene, 70°C	 **34**	1:1.6	85%
6	**30**	Toluene, 70°C	 **35**	1:1	46%

Table 10: PKRs of the chiral propargylamine derivatives chosen with norbornadiene.

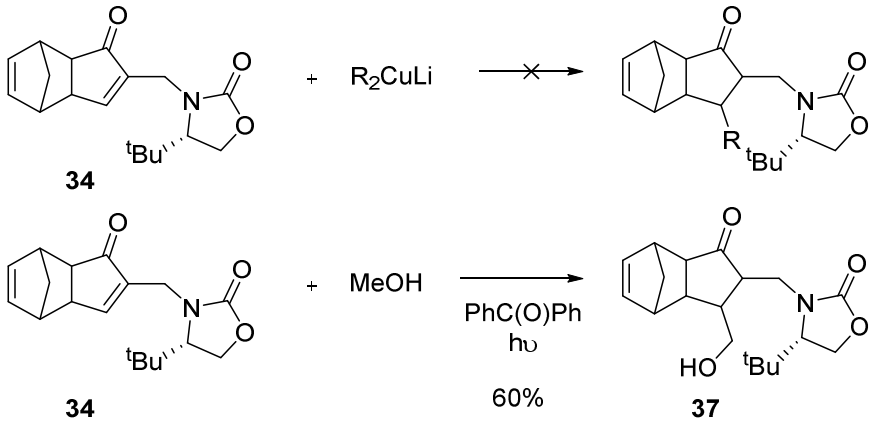
As it can be seen in Table 10, the diastereoselectivities were almost nonexistent in all of the substrates assayed. What is worse, the diastereomers were difficult to separate by chromatography or crystallization. The only PK adduct that could be separated into the two different diastereomers was **34**. However, and in spite of the bad results, we decided to explore the reactivity of these PK adducts to see how their reactivity towards conjugate addition was and whether we could eliminate the chiral auxiliary in order to obtain a free amine or an exocyclic enone.

The selected PK adducts were treated with dibutyl lithium cuprate and nitromethane in basic conditions. **31** did not yield any of the desired products, probably due to the high steric congestion around the enone, which would prevent nucleophilic attack. On the other hand, **32** experienced the conjugate addition of dibutyl lithium cuprate (although a yield could not be determined, since the product couldn't be separated from some unknown reaction by-products) and showed a particular reactivity when being treated with nitromethane in basic conditions. Instead of obtaining the single addition product we expected, we obtained the double addition product **5**. Even though it was not the behavior we expected, we were encouraged by the fact that it proved that the auxiliary could somehow be eliminated to nourish the exocyclic enone we pursued (Scheme 15).



Scheme 15: Conjugate addition reactions of **32**.

Adduct **34** didn't show any reactivity when it was treated with dibutyl or dimethyl lithium cuprate. However, we could perform the photochemically induced conjugate addition of methanol and continue working with the product obtained (Scheme 16).



Scheme 16: Conjugate addition reactions on 17.

Our first efforts focused on trying to force the reactivity we had observed in the reaction of **32** with nitromethane in basic conditions (see Scheme 15). Unfortunately, when we treated compound **34** with nitromethane under a series of conditions (TBAF, DABCO and ^{t}BuOK as bases, at room temperature or reflux) we could only recover starting material and decomposition by-products. The reaction of **34** with base (DBU, ^{t}BuOK, KHMDS, $NaHCO_3$...) in order to force a E_1Cb elimination were also fruitless.

Last of all, we tried to obtain the corresponding exocyclic enone from adduct **37**. The free alcohol was protected with a *tert*-butyldimethylsilyl group, and the resulting product was treated under a series of reaction conditions (^{t}BuOK, NaOH, DBU…). Unluckily, our efforts were unsuccessful.

At sight of these discouraging results, we decided not to continue working on this approach any longer.

3.5 Conclusions

We have designed and tested a new synthetic methodology to access α, β disubstituted cyclopentenones starting from the PK adduct of norbornadiene and *N*-Boc-propargylamine.

1) We have explored a series of PK adducts of norbornadiene and alkynes with potential leaving groups in the propargylic position and have uncovered that the PK adduct of norbornadiene and *N*-Boc-propargylamine (**2f**) is the only suitable one to carry out our proposed method, since it is the only adduct that yields the monoaddition products upon treatment with organometallic and non-organometallic nucleophiles

2) We have optimized the racemic and asymmetric synthesis of **2f,** and its reactivity has been tested. We have performed several conjugate addition reactions on **2f,** and we have deprotected the amine and eliminated it to obtain an exocyclic enone. A second conjugate addition reaction has been performed to obtain α, β disubstituted PK adducts. We have descrived one example of how the desired α, β disubstituted cyclopentenone can be unveiled after a retro Diels-Alder reaction.

3) We have explored the use of chiral auxiliaries as source of chirality for the preparation of 4,5-disubstituted cyclopentenones. Even though we could obtain a series of PK adducts holding a set of chiral auxiliaries with good yields, the diastereoselectivities were almost nonexistent in most of the cases, and all our aims to eliminate the auxiliaries in order to nourish free amines or exocyclic enones failed.

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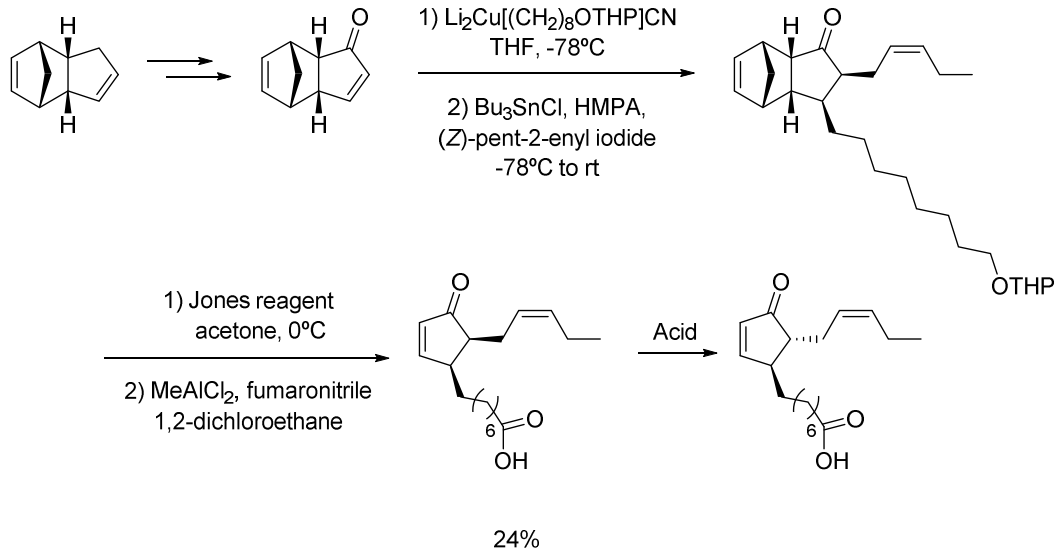
4. Methodology application: synthesis of 13-*epi*-12-oxo phytodienoic acid (PDA) methyl ester

4.1 Synthetic background to 12-oxo PDA and 13-*epi*-12-oxo PDA

As we discussed in Chapter 2, the linolenic acid cascade is responsible for the formation of jasmonic acid from linolenic acid, and it plays a very important role in the regulation of plants' metabolism. In spite of the importance of this metabolic route, the role of most of the metabolites implied in this cascade is not perfectly established[1]. 12-oxo phytodienoic acid (12-oxo PDA) is a biosynthetic precursor of jasmonic acid *via* the allene oxide synthase pathway[2] and as we said, its function in plants is not well known. The difficulty to obtain 12-oxo PDA from natural sources, as well as the increasing interest of the scientific community in the study of its properties, moved many chemists to face its synthesis during the past decades.

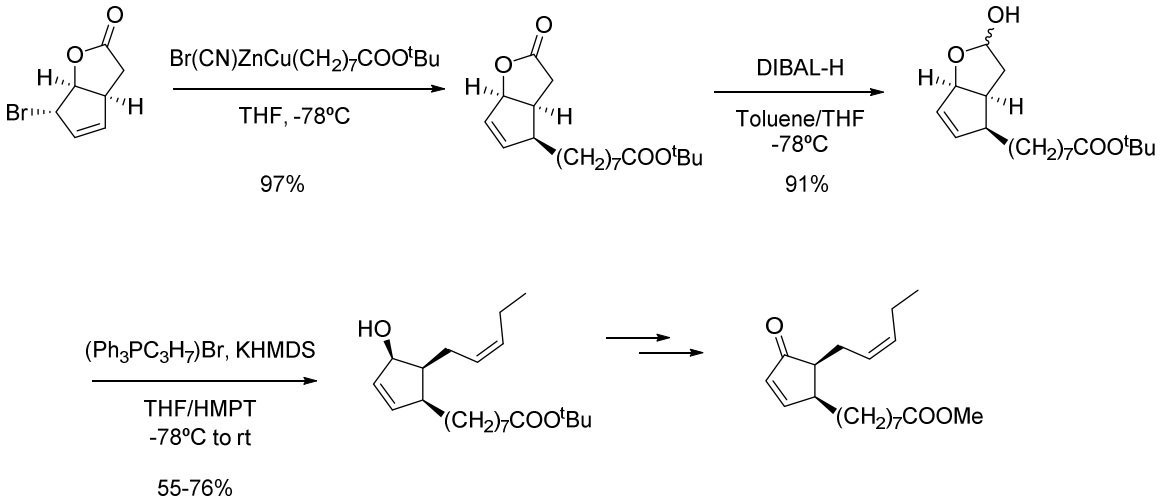
In the late 80s and mid-90s, the first syntheses of 12-oxo PDA, its methyl esters and its epimer (13-*epi*-12-oxo PDA) in its racemic form were reported[3]. The first asymmetric synthesis of 12-oxo PDA was described by Grieco and Abood in 1989[4]. Starting from enantiomerically pure *endo* norbornene derivatives (process implying enzyme-catalyzed kinetic resolution), they synthesized 12-oxo PDA by a three component coupling process followed by a retro Diels-Alder reaction. Once obtained, it was epimerized to yield 13-*epi*-12-oxo PDA by exposing it to acidic conditions. No details of this epimerization process were given (Scheme 1).



Scheme 1: Grieco and Abood's synthesis.

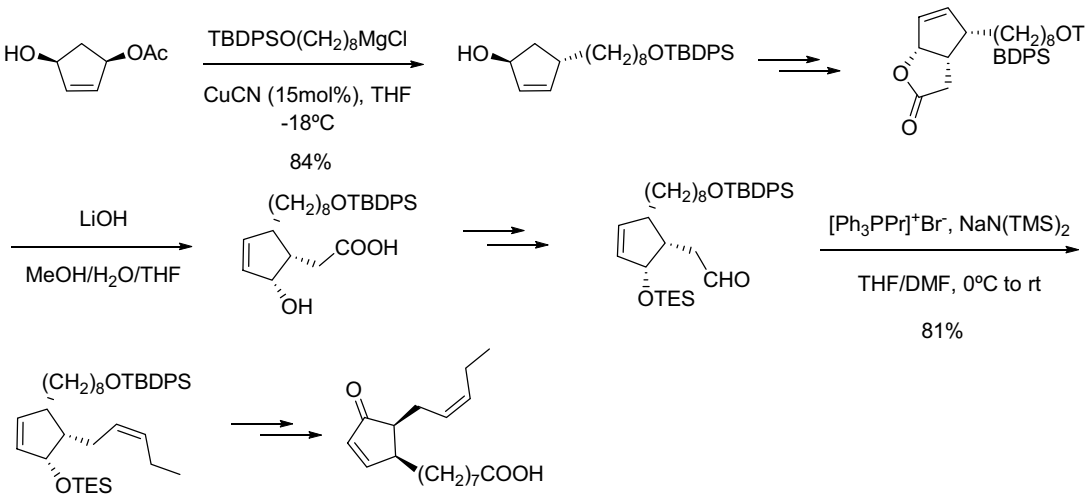
In 2002, two more syntheses were published. Ernst and Helmchen[5] synthesized the non-natural enantiomer of 12-oxo PDA and its methyl ester by the transformation of an enantiomerically pure lactone. The β chain was introduced by a S_N2'-*anti* reaction of a

zinc organocuprate ("Knochel cuprate") on an allylic bromide. On the other hand, the α chain was installed by performing a Wittig reaction on a lactol (Scheme 2).



Scheme 2: Ernst and Helmchen's approach.

Kobayashi and co-workers[6] obtained both 12-oxo PDA and 13-*epi*-12-oxo PDA starting from an optically pure acetate. The synthesis diverges at an early intermediate nourishing both products. The installation of the alkyl chains was performed by using a methodology previously described by the authors[7] and a modified Wittig reaction. The starting acetate was treated with a Grignard reagent with copper catalysis to yield the desired addition product. After a series of transformations, which include a Mitsunobu reaction to invert the stereochemistry of the alcohol, the authors reached a similar lactone as Ernst and Helmchen's. It was then transformed in a similar fashion to get to 12-oxo PDA (Scheme 3). Regarding 13-*epi*-12-oxo PDA, the process was basically the same, but the Mitsunobu reaction was not performed, consequently maintaining the *trans* relation among substituents.

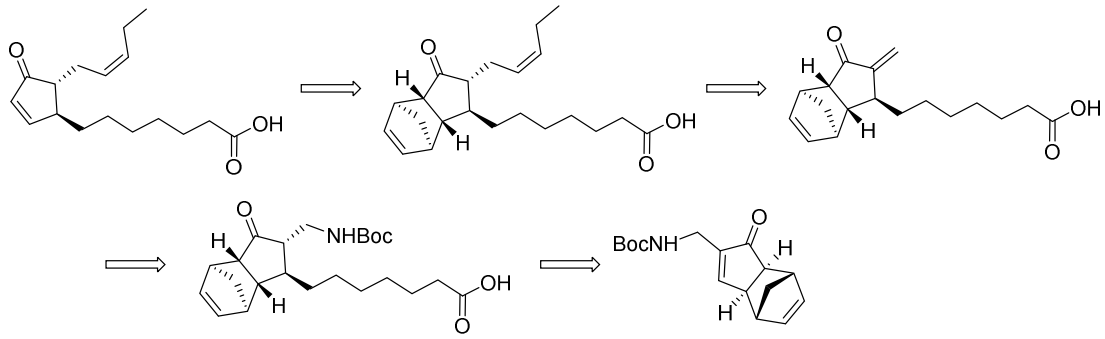


Scheme 3: Kobayashi's synthesis for 12-oxo PDA.

In 2003, the same authors[8] expanded their work by making their synthesis extensive to OPC-8:0, another metabolite of the allene oxide synthase pathway structurally very similar to 12-oxo PDA. Some years later, in 2010, they reported the synthesis of a few more metabolites in the allene oxide synthase path way and the improvement on the efficiency of the 12-oxo PDA synthesis by applying some changes to the process[9]. This basically implied variations on the lactonization process, hence reducing the number of steps necessary to reach this intermediate.

4.2 13-*epi*-12-oxo PDA: retrosynthetic analysis

Our retrosynthetic analysis is shown in Scheme 4:



Scheme 4: Retrosynthetic analysis of 13-epi-12-oxo PDA.

13-epi-12-oxo PDA would come from a retro Diels-Alder reaction of an α, β-disubstituted PK adduct. The α chain would be assembled to the exocyclic enone by a conjugate addition, being this enone the product of the elimination of Boc protected amine. The β chain would be the first one to be attached to the PK adduct of norbornadiene and *N*-boc-propargylamine (**2f**), that would be synthesized as described in Chapter 3. The more challenging structural elements of 13-*epi*-12-oxo PDA would be:

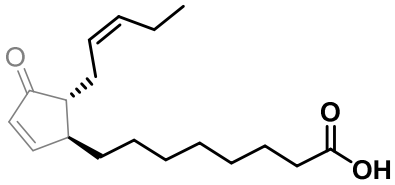
1) The *trans* disposition of the chains α, β to the ketone group: this feature would be achieved by the protonation of the enolate generated after the conjugate addition of the desired substituent on the exocyclic enone, that would lead to the more stable *trans* disubstituted cyclopentenone.

2) The α, β unsaturated carbonyl: this functionality is latent in the starting material, and would be uncovered after a retro Diels-Alder reaction.

3) The *Z* bond located in the α chain: installed by the conjugate addition of the *Z* isomer of the organocopper reagent on the exocyclic enone.

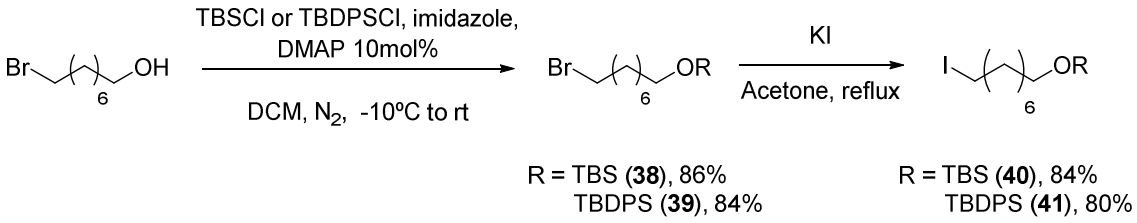
4.3 Synthesis of 13-*epi*-12-oxo PDA

4.3.1 Synthesis of the precursors



13-*epi*-12-oxo PDA presents an aliphatic chain with a terminal carboxylic acid at its β position. Our strategy was to mask the carboxylic acid functionality as a silyl ether that could be later deprotected and transformed.

Commercially available 8-bromo-1-octanol was protected with a *tert*-butyl-dimethylsilyl group under standard conditions. The product was obtained with a 86% yield after distillation. Once protected, it was derivatized to the corresponding iodide in order to facilitate the metalation. We treated the protected product with KI in acetone at reflux and after 12h of reaction, we obtained the desired product in an 84% yield. No further purification than filtration was needed. Since our synthetic route included the selective deprotection of the Boc protected amine, we also protected 8-bromo-1-octanol as *tert*-butyl-diphenylsilyl ether (**39**), a less labile silyl ether, in order to avoid the deprotection of the alcohol in acidic media. The same route as for the *tert*-butyl-dimethylsilyl ether was followed, and the desired iodide was obtained uneventfully (Scheme 5).



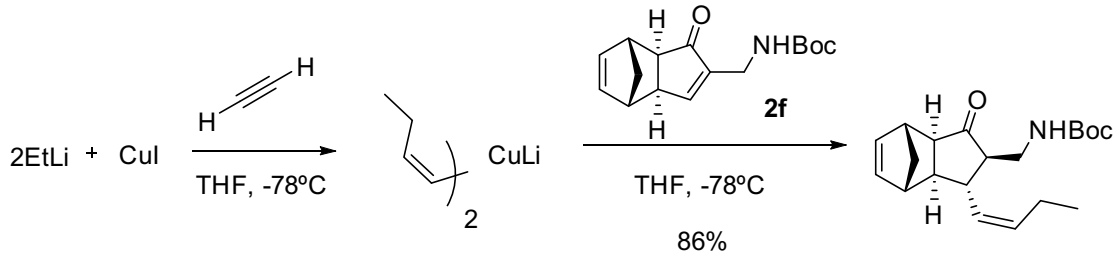
Scheme 5: Preparation of **40** and **41**.

13-epi-12-oxo PDA has a Z-pentenyl chain bound to the carbon α to the carbonyl. Since our starting material, the exocyclic enone, already provided us with one carbon atom, the chain we would have to add in a 1,4-fashion would be a Z-butenyl residue.

Alexakis and co-workers described, in 1979, a process to obtain the cuprate we needed starting from ethyl lithium, copper iodide and acetylene[10]. Since the exocyclic enone was relatively difficult to obtain and coudn't be stored for long periods of time,

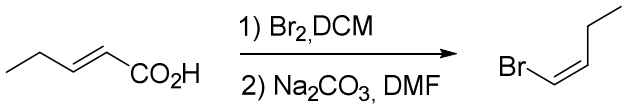
we decided to run some tests on **2f** as a model enone before studying the addition on the exocyclic enone. The reaction setting consisted on an acetylene bottle coupled to a T-shaped plastic piece trough which we could regulate the entrance of acetylene, nitrogen or vacuum. Next, a trap at -78°C was put to separate the gas from the acetone used as stabilizer. This trap was followed by another one containing sulfuric acid to dry the acetylene and, finally, a security trap and our reaction flask. In this flask, previously flame-dried, we formed Et_2CuLi by treating CuI with EtLi in THF at -78°C. Afterwards, acetylene was bubbled though the reaction mixture until the crude, initially blue, changed its color to deep green. Finally, **2f** was added to the cuprate. Upon reaction completion and purification, the conjugate addition product **13** was isolated in an excellent 86% yield (Scheme 6).

Reaction setting



Scheme 6: Conjugate addition of *cis*-butenil lithium cuprate on **2f**.

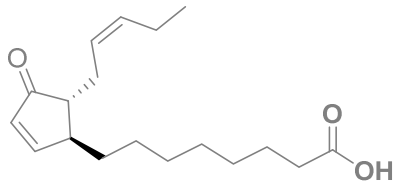
Unfortunately, this procedure was not reproducible in our hands due to the difficulty of measuring an exact amount of acetylene and the poor stability of the commercially available ethyl lithium, which decomposed rapidly. Therefore, we opted for exploring alternative, more robust, methodologies. We envisaged (*Z*)-1-bromobut-1-ene as the ideal precursor of *Z*-butenyl lithium cuprate since the corresponding bromide is readily accessible using Brevet's methodology[11] (Scheme 7).



Scheme 7: preparation of (Z)-1-bromobut-1-ene

Metallation of the bromide at low temperature with ^{t}BuLi, followed by addition to a copper (I) source would give us the desired organocopper derivative.

4.3.2 Conjugate additions: installation of the β chain

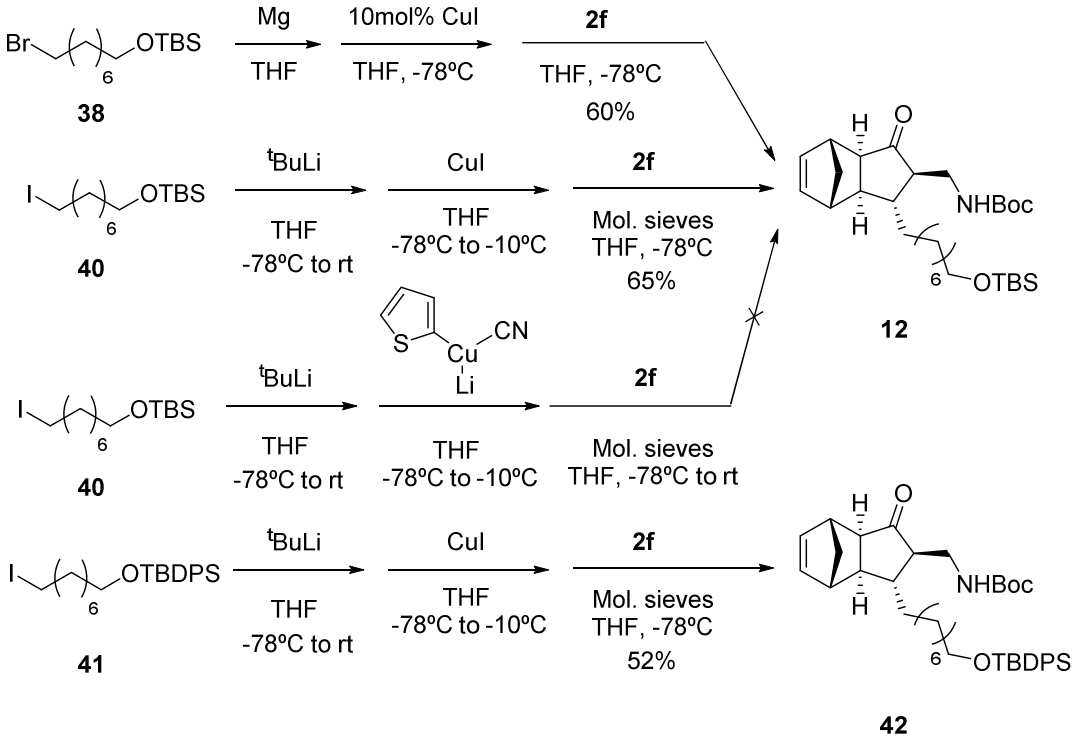


Once with the suitable precursors in hand, we proceeded to study their conjugate addition reactions to adduct **2f**.

We began by the installation of the β chain. Our first approach was to perform the conjugate addition of the Grignard reagent derived of **38** with copper (I) catalysis. The main advantage of this method is that we could use just one equivalent of **38** for each equivalent of **2f**. However, the initiation of the Grignard reaction turned out to be highly difficult and poorly reproducible in small scale.

Our attempts to use a more robust method led us to try the conjugate addition of the dialkyl lithum cuprate derived from **40**. **40** was metalated with ^{t}BuLi at low temperature, and the subsequent lithium derivative was allowed to react with copper (I) in stoichiometric amount. The metallation/organocopper formation protocol was also followed for the conjugate addition of **41**. Although the reaction was highly reproducible and robust it had the drawback of the use of two equivalents of the alkyl iodide for each equivalent of starting material.

To try to reduce the amount of **40** we had to use for every addition, we decided to assay the addition of a higher order cuprate. The copper source chosen was lithium 2-thienyl cyanocuprate, which has the 2-thienyl residue as non-transferable radical[12]. The metalation process with ^{t}BuLi was carried out as we did previously. Once we had our desired lithium derivative, we treated it with the commercially available 0.25M solution of lithium 2-thienyl cyanocuprate in THF. When adduct **2f** was added to the reaction mixture, no evolution to the desired product was detected. Our hypothesis was that the Boc group is too bulky to let a big copper species such as the higher order cuprate to insert the double bond and transfer the desired substituent (Scheme 8).



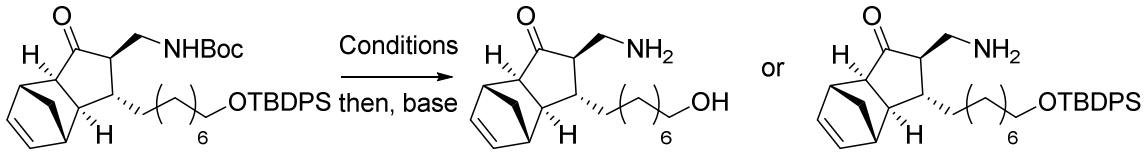
Scheme 8: Obtention of **12** and **42**.

Taking into account the advantages and disadvantages of the methods assayed, we decided to carry out the synthesis of **40** and **42** *via* the metallation/organocopper reagent formation protocol, since it was the most robust and reproducible method.

4.3.3 Hydrolisis and elimination of the *N*-Boc protected amine

The next step to our final product was the deprotection of the amine and its elimination. The best conditions we found during the development of our methodology (Chapter 3) were the use of the commercial mixture of HCl in MeOH at room temperature. Unfortunately, treatment of **12** under these conditions led to the deprotection of both the amine and the alcohol in quantitative yield. The same result was obtained at shorter reaction times, with lower excess of HCl/MeOH or if the reaction was carried out at low temperature.

At sight of these results, we decided to move on to the *tert*-butyldiphenylsilyl ether derivative **42**, hoping that the higher resistance to acidic conditions of this silyl ether would allow us to selectively deprotect the amine. In spite of our efforts, neither of the different conditions assayed allowed us to selectively deprotect the amine over the alcohol (Table 1).



42 **43** **44**

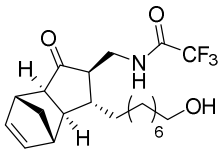
Entry	Conditions[a]	Product
1	HCl/MeOH (1.25M), 10 eq., rt	**43**
2	HCl/MeOH (1.25M), 10eq, 0°C	**43**
3	HCl/MeOH (1.25M), 2.5 eq., 0°C to rt	sm
4	HCl/Et_2O (2M), 10eq, rt	**43**
5	HCl/dioxane (4N), 20 eq, rt	**43**
6	TFA:DCM (2%), 0.5 eq, rt	sm
7	TFA:DCM (20%), 0.5 eq, rt	sm
8	TFA:DCM (80%), 0.5 eq, rt	sm
9	TFA:DCM (10%), 10eq, 0°C	
10	TsOH/ACN, 10 eq, rt	Decomposition

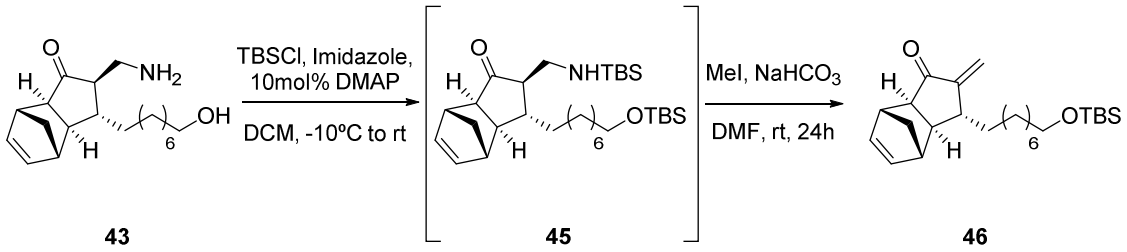
Table 1: Alcohol and amine selective deprotection tests. a: all reactions were allowed to progress until no starting material could be detected by TLC or, if there was no reaction, 24h.

In view of the impossibility of selectively deprotecting the Boc group, and since the synthesis of **12** was slightly higher yielding than the one of **42**, we decided to continue working on **12** and put aside **42**.

It is known that amines can be protected with silyl groups, but they have not been extensively used due to their high instability to moist, although they can be prepared and used under anhydrous conditions[13]. We envisaged that we could re-protect the free alcohol as a *tert*-butyl-dimethylsilyl ether, and since the reaction is carried out under nitrogen and with anhydrous solvents, the free amine would most likely be also protected

as a silylamine. We would then take advantage of the high reactivity of these functional groups to eliminate ours and reach our desired exocyclic enone.

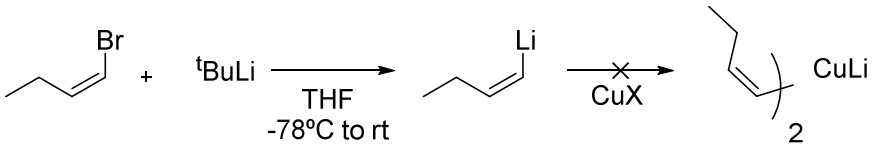
43 was treated under standard protection conditions to yield the disilylated product **45**. Without isolation, it was then treated with MeI and $NaHCO_3$ in DMF at room temperature for 24h. The crude was treated with water and DCM, and the product was extracted. A sample of the crude was analyzed by ^{1}H-NMR, and we were happy to see the exocyclic enone **46** had been formed satisfactorily. The crude enone was dried under high vacuum and used in the next step without further purification (Scheme 9).



Scheme 9: Preparation of **46**.

4.3.4 Conjugate additions: installation of the α chain

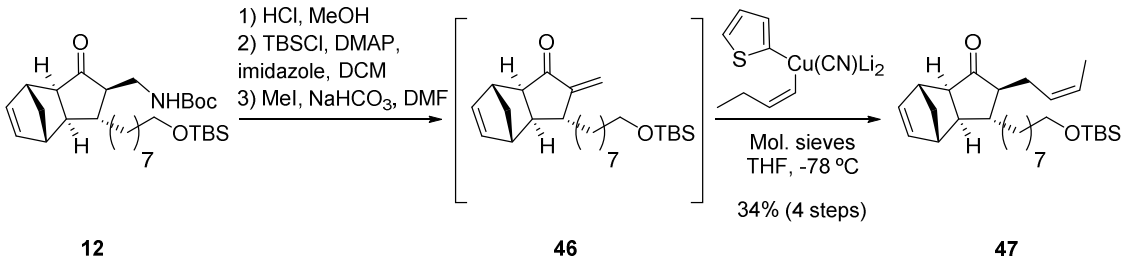
Initially, the metallation of (Z)-1-bromobut-1-ene at low temperature with ^{t}BuLi, followed by addition to a suspension of usual copper salts was investigated. However, we obtained insoluble and unreactive reagents in all cases (Table 2).



Entry	Solvent	CuX	Conditions	Result
1	THF	CuI	-78°C	-
2	THF	CuI	-78°C to -30°C	-
3	THF	CuBr	-78°C to -35°C	-
4	THF	CuBr	-78°C to -10°C	-
5	THF	CuBr·SMe_2	-78°C to -35°C	-

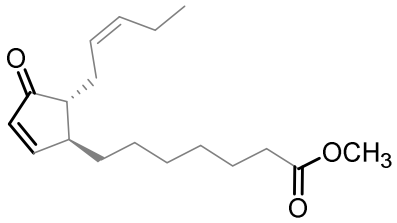
Table 2: cis-butenyl lithium cuprate formation assays.

Since our attempts to form the lithium di(Z-butenyl) cuprate failed, a higher order cuprate[12] was envisioned. The bromide was metalated with ^{t}BuLi, and lithium 2-thienyl cyanocuprate was then added to the mixture. We knew that higher order cuprates could not perform conjugate addition reactions on **2f**, so the reagent was tested directly on the exocyclic enone. Once the cuprate was formed, we added **46** *via* canula. Upon reaction completion and purification, we were delighted to isolate product **47** in a remarkable 34% yield over four steps. More importantly, this procedure was highly reproducible and robust (Scheme 10).



Scheme 10: Synthesis of **47**.

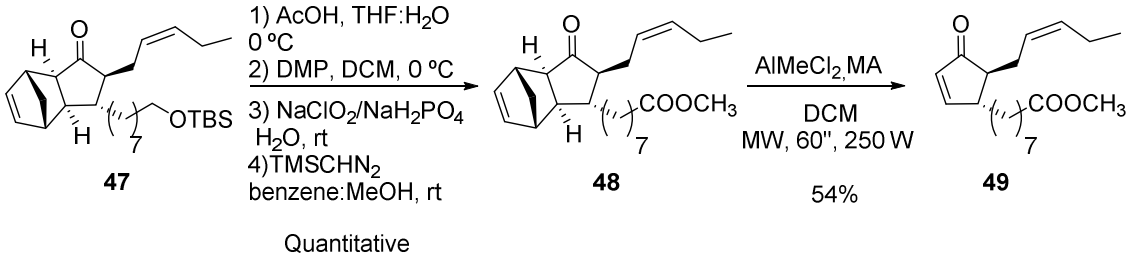
4.3.5 Final steps and retro Diels-Alder reaction



We had been successful on installing the α, β substituents of interest to the PK adduct **2f**, but there were still some steps ahead to accomplish the synthesis. First of all, we had to transform our protected alcohol into a carboxylic acid. Secondly, we had to withdraw the norbornadiene residue to reveal the enone. And, lastly, we had to repeat the optimized synthesis starting from optically active **(+)-2f**.

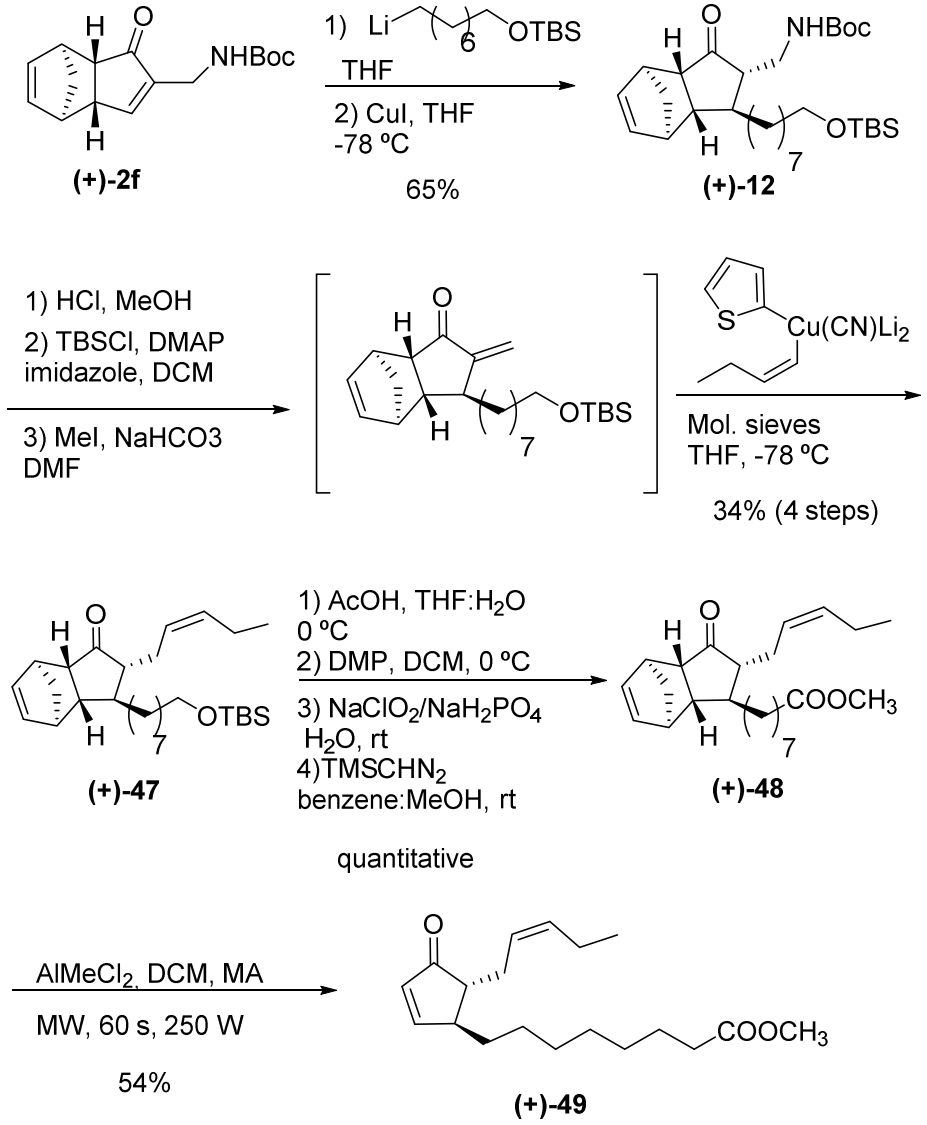
Deprotection of alcohol **47** was carried out uneventfully. The free alcohol was oxidized to the corresponding aldehyde with Dess-Martin periodinane, and this aldehyde was further oxidized to the corresponding carboxylic acid with a Pinnick oxidation[14]. The purification of the carboxylic acid was rather difficult, but we could isolate it after careful flash chromatography. Once we had it pure, we performed the retro Diels-Alder reaction. The final product could be detected by ^{1}H-NMR spectroscopy however, we could not isolate it pure. In order to avoid purification problems, we decided to derivatize the carboxylic acid to its corresponding methyl ester **48**. This transformation occurred without any incident in quantitative yield, and **48** was then

irradiated with microwaves in the presence of maleic anhydride and $MeAlCl_2$. Upon reaction completion, flash chromatography yielded (±)-13-*epi*-12-oxo PDA methyl ester **49** in a total of 11 synthetic steps and a global yield of 11% (Scheme 11).



Scheme 11: Synthesis of **49**.

Finally, all the process was repeated starting from optically active adduct **(+)-2f**. The summary of the enantioselective synthesis is depicted in Scheme 12.



Scheme 12: Asymmetric synthesis of **(+)-49**

4.4 Conclusions

We have synthesized 13-*epi*-12-oxo PDA methyl ester both in its racemic and optically active forms, proving that the methodology we designed for obtaining α, β disubstituted cyclopentenones starting from PK adducts with potential leaving groups is valid.

1) The substituent in the β position was obtained from 8-bromo-1-octanol and could be installed by performing a conjugate addition of the metalated iodine derivative of the *tert*-butyl-dimethylsilyl protected alcohol.

2) The exocyclic enone could be obtained after the cleavage of the Boc group of the amine and the *tert*-butyl-dimethylsilyl ether. Both groups were re-protected with *tert*-butyl-dimethylsilyl chloride, and the silyl amine could be readily eliminated to nourish the desired exocyclic enone.

3) This enone was treated with the higher order cuprate reagent of the previously lithiated (Z)-1-bromobut-1-ene. This conjugate addition led to the desired 1, 4-disubstituted PK adduct.

4) The alcohol group was successfully transformed into a carboxylic acid and a methyl ester. The carboxylic acid derivative, direct precursor of 13-*epi*-12-oxo PDA was hard to isolate, whereas the methyl ester was very easy to handle.

5) The retro Diels-Alder reaction of both derivatives was carried out satisfactorily. Although 13-*epi*-12-oxo PDA could not be isolated pure, we could easily obtain its methyl ester in its racemic and optically active form.

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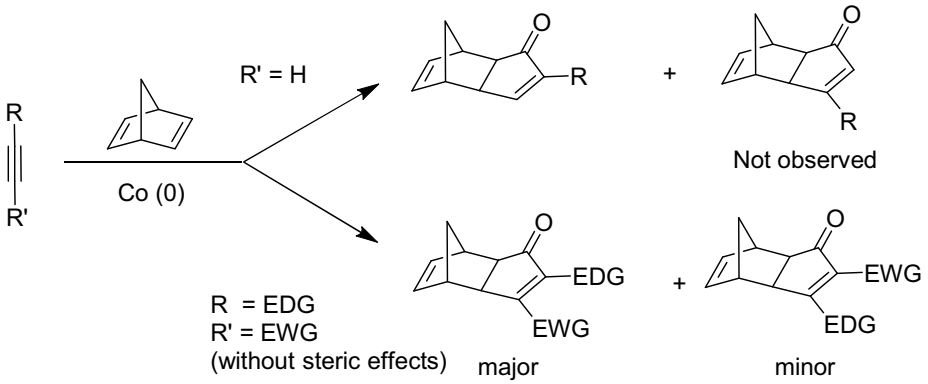
5. Intermolecular PKR of dissymmetric fluorinated alkynes

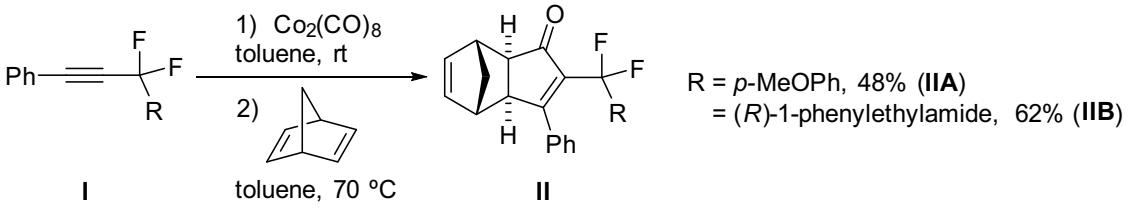
5.1 Introduction

The PKR has been extensively used in organic chemistry since its discovery in 1971[1]. The intramolecular PKR has been widely applied in the preparation of complex polycyclic structures. In this version of the reaction both regio and stereochemistry are controlled by the substrate and are, in general, highly predictable. On the other hand, intermolecular PKRs have been less exploited mainly because of the smaller range of reactive alkenes[2] and the difficulty to predict the regiochemical outcome of the reaction[3]. The intermolecular PKR of terminal alkynes always yields α-substituted cyclopentenones, whereas internal alkynes can lead to two regioisomers. The regiochemistry appears to be influenced by the steric and electronic properties of the substituents of the alkyne and may be difficult to predict. In general, the bulkiest group ends up in the α position. In the absence of steric effects, electron-donating groups (EDGs) show preference for the alpha position whereas electron-withdrawing groups (EWGs) tend to be displaced to the β position[3a]. However, recent studies have shown that the electronic effects are much less significant than previously described and can, therefore, be overcome by the steric effects[3d] (Scheme 1).



Scheme 1: Regioslectivity of the PKR.

At sight of the very little reports on the PKR of fluorinated alkynes, our group became interested in the PKR of internal dissymmetric fluorinated alkynes in 2009. Albert Pesquer, during his experimental MSc[4], carried out the first preliminary studies on these particular substrates. He tested two internal fluorinated alkynes and observed that, for both substrates, only one product was obtained from the PKR with norbornadiene (Scheme 2). This work was done in collaboration with the group of Professor Santos Fustero, from the University of Valencia.



Scheme 2: First intermolecular PKR of dissymmetric fluorinated alkynes.

The regiochemistry of products **II** was very thoroughly studied by NMR on the basis of the coupling between carbon and fluorine atoms. NMR data strongly suggested that the fluorinated moieties were α to the carbonyl. Contrary to our expectations, the bulky phenyl group was β to the carbonyl and the strongly electron-withdrawing group, in the α position. These surprising and interesting results made our group become eager to learn more about the behavior of fluorinated substrates in the PKR and to unambiguously determine the regiochemistry of the corresponding adducts. The work of the present Thesis began at this point.

5.2 Study of the regiochemistry of IIA

Before further exploring the reactivity of fluorinated PK adducts, we wanted to prove indubitably that adduct **IIA** held the fluorinated group in the α and not the β position. We were able to obtain a crystal of **IIA** that was suitable for X-Ray diffraction, and this experiment confirmed the regiochemistry of **IIA** (Figure 1).

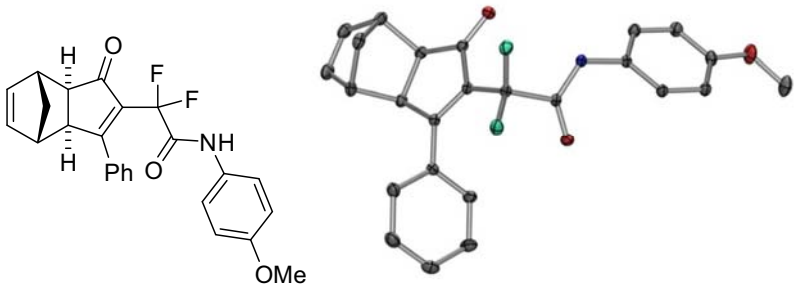
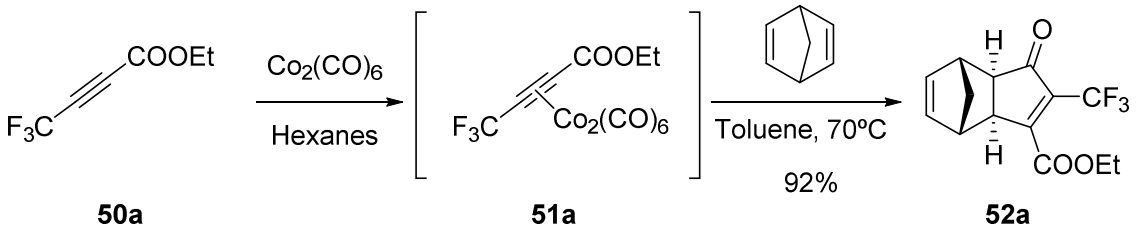


Figure 1: Crystal structure of **IIA**.

Once with the confirmation that these fluorinated groups preferred the α position rather than the β, we proceeded to explore other fluorinated alkynes.

5.3 Alkyne scope

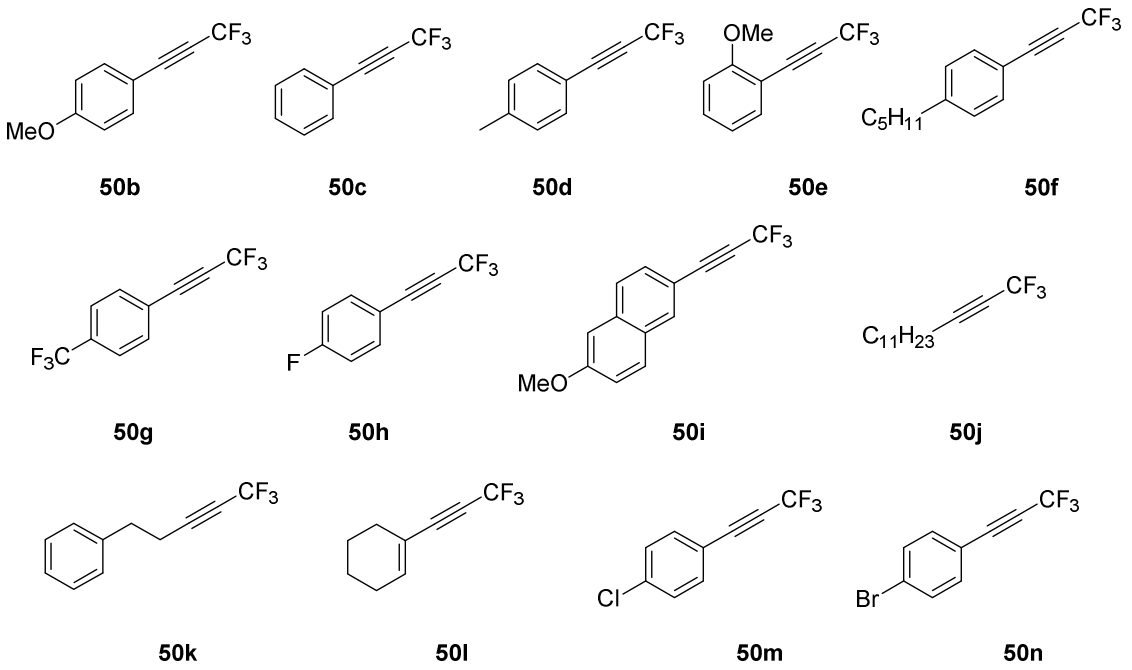
The first fluorinated alkyne we chose to explore the range of applicability of the reaction was the commercially available ethyl 4,4,4-trifluorobut-2-ynoate (**50a**). Its dicobalt hexacarbonyl complex was formed and submitted to the thermally activated PKR. Once the reaction was finished, a ^{1}H and ^{19}F-NMR of the reaction crude was acquired. Both experiments showed that there was one single product present, and column chromatography yielded the α-trifluoromethylated PK adduct **52a** in an excellent 92% yield (Scheme 3).



50a **51a** **52a**

Scheme 3: PKR of 4,4,4-trifluorobut-2-ynoate (**50a**).

To explore the preference of fluorinated groups for the α position in PK adducts, we chose a broad set of model trifluoromethyl alkynes bearing aromatic groups with electron-donating and electron-withdrawing groups, a double bond and aliphatic chains[5] (Figure 2).



50b **50c** **50d** **50e** **50f**

50g **50h** **50i** **50j**

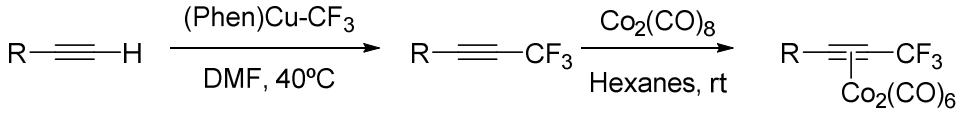
50k **50l** **50m** **50n**

Figure 2: Selected alkynes.

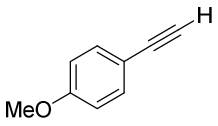
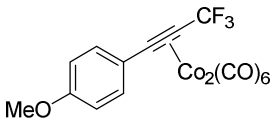
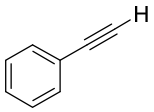
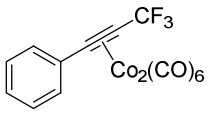
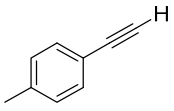
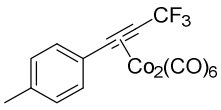
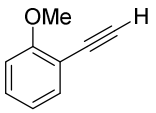
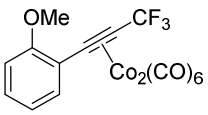
None of the selected substrates were commercially available. Nevertheless, a method reported by Qing and co-workers[6] describes the preparation of trifluoromethyl

alkynes starting from their terminal partners which, in our case, were commercially available. Although we had to apply minor modifications to their process in order to be able to reproduce it and to adapt it some non-described substrates, the trifluoromethylations proceeded successfully in all cases.

The trifluoromethyl alkynes generated were hard to manipulate. Most of them were volatile and all of them showed a very lipophilic character, feature that made chromatographic separation of the desired products from other reaction byproducts very complicated. For these reasons, we decided to proceed with the complexation of the trifluoromethyl alkynes with $Co_2(CO)_8$ without isolating them. Upon quenching of the trifluoromehtylation reaction, the organic components were extracted with hexanes. This extracts were immediately treated with $Co_2(CO)_8$. The reaction was carried out at room temperature until no more starting dicobalt octacarbonyl complex could be detected by TLC. The crude was then purified by silica gel chromatography, and the desired cobalt complexes of the trifluoromehtyl alkynes were obtained with good to excellent yields (Table 1).



50 **51**

Entry	Alkyne	Complex	Yield (2 steps)
1		 **51b**	43%
2		 **51c**	55%
3		 **51d**	91%
4		 **51e**	70%

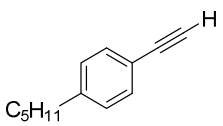
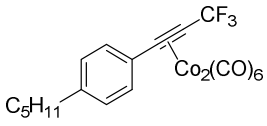
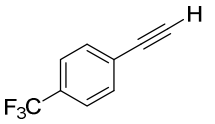
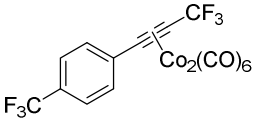
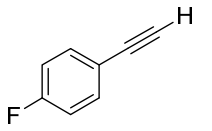
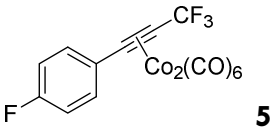
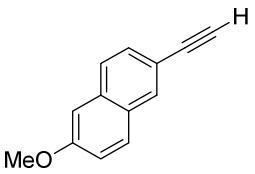
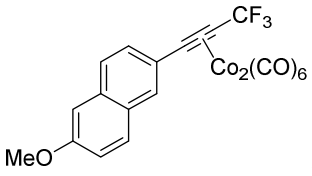
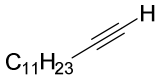
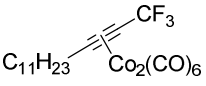
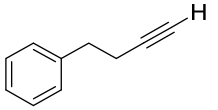
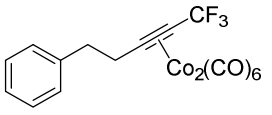
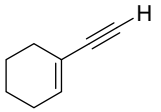
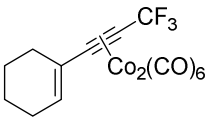
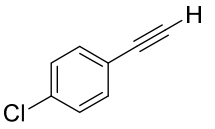
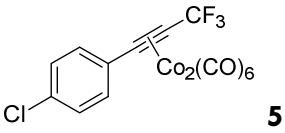
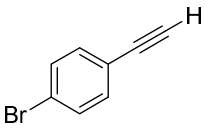
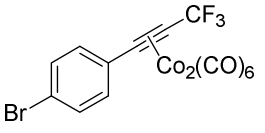
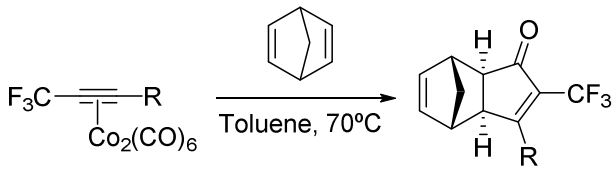
5		 **51f**	69%
6		 **51g**	44%
7		 **51h**	62%
8		 **51i**	70%
9		 **51j**	87%
10		 **51k**	60%
11		 **51l**	70%
12		 **51m**	45%
13		 **51n**	84%

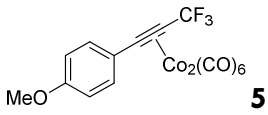
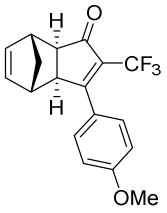
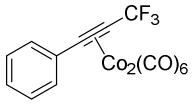
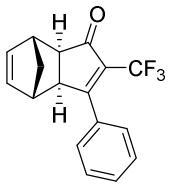
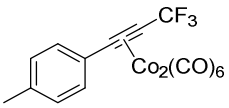
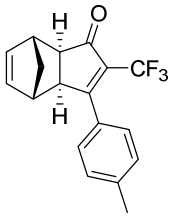
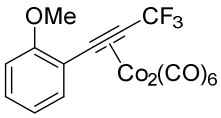
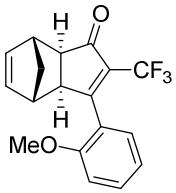
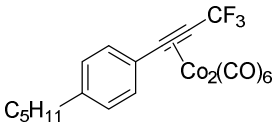
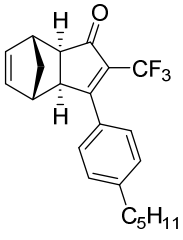
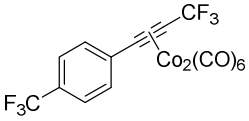
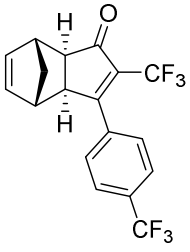
Table 1: Preparation of dicobalt hexacarboynl complexes **51b-n**.

These cobalt complexes were submitted to the PKR. They were dissolved in anhydrous toluene, norbornadiene was added and the system has heated up to 70°C until no starting complex could be detected by TLC. Both ^{1}H and ^{19}F NMR analysis of the

reaction crudes showed only one product. The corresponding PK adducts were isolated with good to excellent yields after chromatographic purification (table 2).



51 **52**

Entry	Complex	Product	Yield
1	 **51b**	 **52b**	81%
2	 **51c**	 **52c**	77%
3	 **51d**	 **52d**	95%
4	 **51e**	 **52e**	74%
5	 **51f**	 **52f**	99%
6	 **51g**	 **52g**	70%

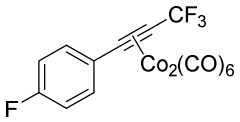
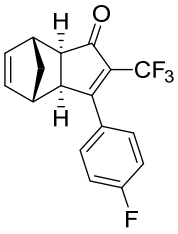
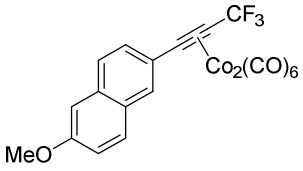
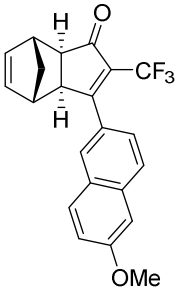
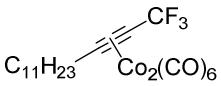
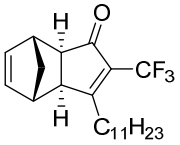
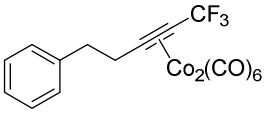
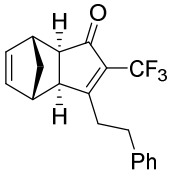
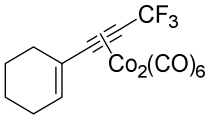
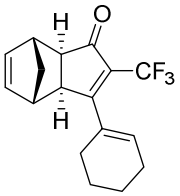
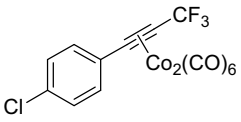
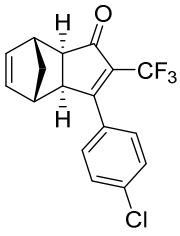
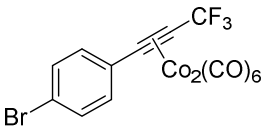
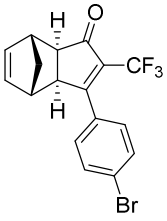
7	 **51h**	 **52h**	81%
8	 **51i**	 **52i**	80%
9	 **51j**	 **52j**	79%
10	 **51k**	 **52k**	77%
11	 **51l**	 **52l**	70%
12	 **51m**	 **52m**	51%
13	 **51n**	 **52n**	67%

Table 2: PKR of complexes **51b-n**.

The regiochemistry of the adducts was assigned by studying long-distance couplings to fluorine in the ^{13}C-NMR spectra of the products.

If we had the β-trifluoromethylated isomer, the CF_3 group would be much closer to the β CH (depicted in green in Figure 3), and this group should then be detected as a

quadruplet; whereas the α CH (red in Figure 3) would be at a 4-bond distance from the CF_3, and it would be seen as a quadruplet (with a small *J*) or maybe even a singulet (Figure 3). These coupling patterns weren't detected in any case. We were able to see, however, a quadruplet multiplicity in the CH α to the carbonyl group. These quadruplets showed a *J* value of 1-2 Hz, which is in the range of the expected for a long-distance coupling[7]. The CH β to the ketone was always seen as a singulet. This is consistent with the regiochemical assignation we did. It must be noted that, in the α regioisomer, the CF_3 group is at the same distance from both CH groups. The presence of the ketone between the CF_3 and the CH group in the α position is very likely the responsible for the detection of only one of the CH as a quadruplet, whereas the other is seen as a singulet.

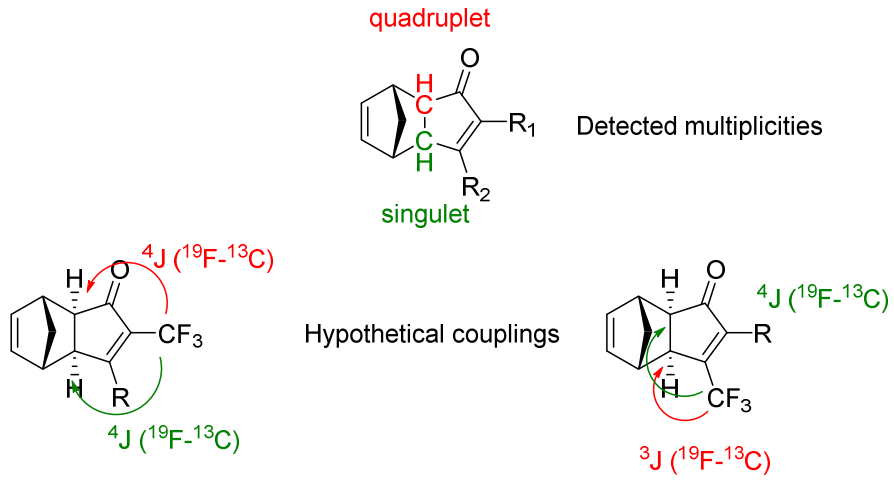


Figure 3: Detected and hypothetical couplings of both possible regioisomers.

The fact that different alkynes with such different electronic and steric properties led invariably to the α-trifluoromethylated PK adducts suggested that the fluorine substituent's electronic effect is either much weaker than expected or it is overridden by steric hindrance.

5.4 Alkene scope

5.4.1 Norbornene

Konno and co-workers[8] explored the reactivity and regioselectivity of trifluoromethyl alkynes in the PKR with norbornene instead of norbornadiene, and they reported that the regioselectivity of the PKR was not complete (Figure 4).

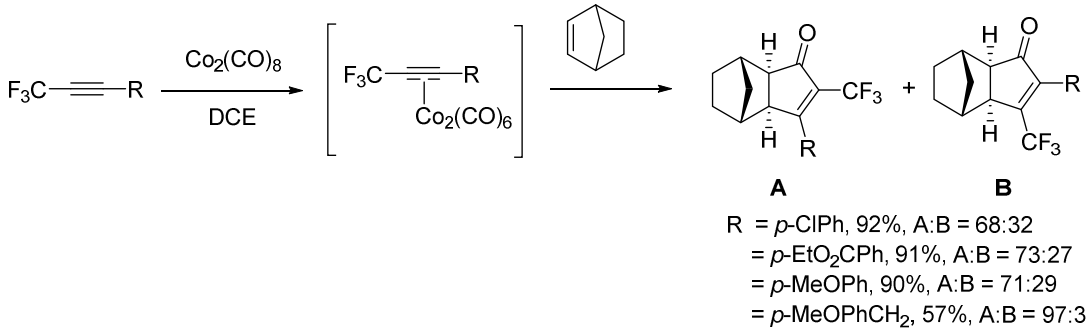
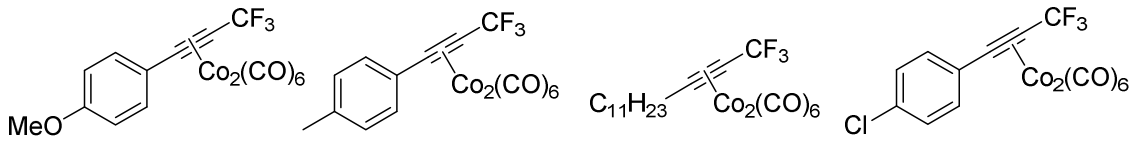


Figure 4: Summary of Konno's results for the PKR of fluorinated alkynes with nornornene.

However, their product characterizations were not complete and the regiochemical assignment of the adducts was poorly studied. They based their assignment on the fact that, in our first report of the intermolecular PKR of norbornadiene and dissymmetric fluorinated alkynes[9], we had never detected the *endo* isomers. They assumed that the additional products detected were the regioisomeric α-trifluoromethyl PK adducts and not the *endo* products. In order to explore the regioselectivity of the PKR with norbornene and to check Konno's results, we decided to broaden our study with this alkene.

We chose four model alkynes for the PKR: two aromatic substrates with electron-donating groups, one with an electron-withdrawing group and an aliphatic chain (Figure 5).



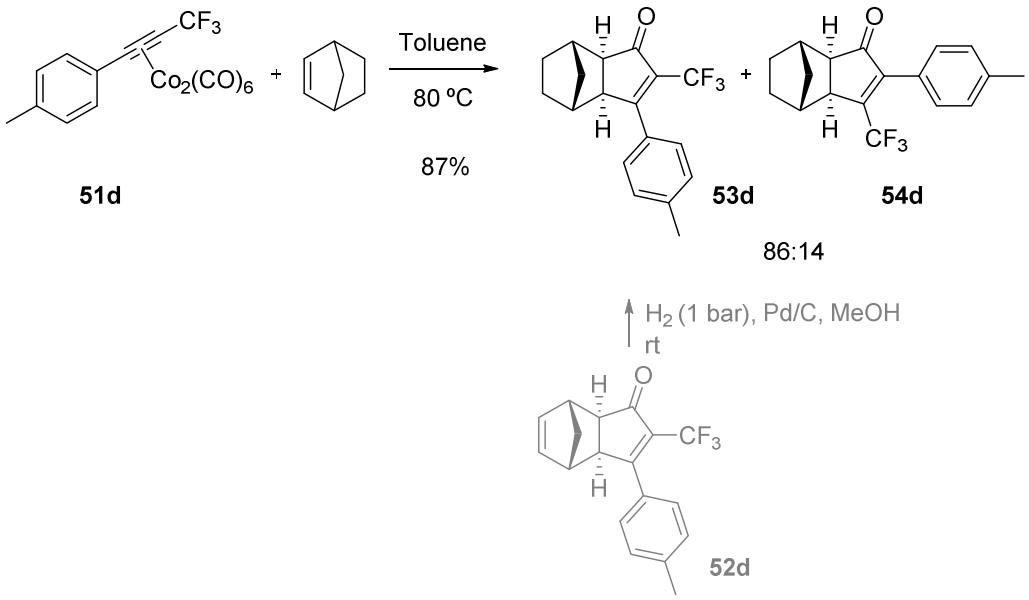
51b **51d** **51j** **51m**

Figure 5: Selected substrates.

We carried out the thermally activated PKR with **51d** in the first place. The regiochemistry of adduct **52d** had been well established, and that its partial hydrogenation would lead to the α-trifluoromethyl PK adduct of **51d** and norbornene

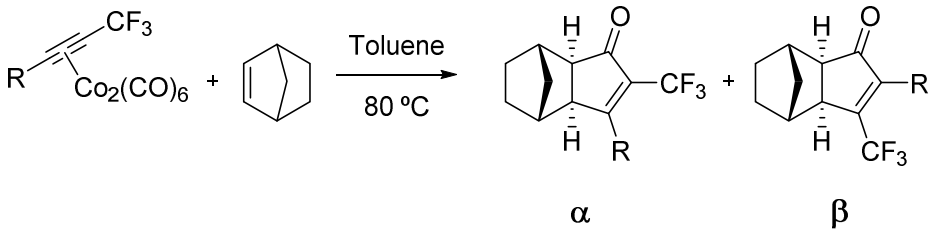
(**53d**). We envisioned this transformation as the ideal confirmation of the fact that the major isomer of the reaction was the *exo* α-trifluoromethyl adduct.

The PKR proceeded smoothly and gave a mixture of two products in a 86:14 ratio and an excellent 87% yield. The major product was confirmed to be the *exo* α-trifluoromethylated adduct by chemical correlation with the partially hydrogenated adduct **52d**. The minor isomer was further studied by NMR (NOESY experiments) and determined to be the *exo* β-trifluoromethylated product (Scheme 4).



Scheme 4: Reactivity of **51d** with norbornene and regiochemistry confirmation.

The same reaction conditions were applied to the rest of substrates and, in all cases, the two regioisomeric PK adducts could be detected by ^{1}H and ^{19}F-NMR. In the case of the alkyl chain substituted substrate (**50j**), only the α regioisomer was isolated (**53j**). The minor β regioisomer was marginal and could only be detected by ^{19}F-NMR (Table 3).



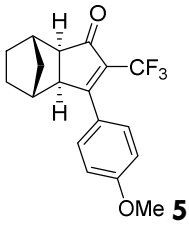
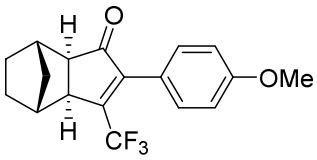
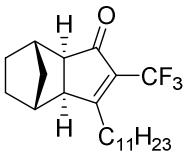
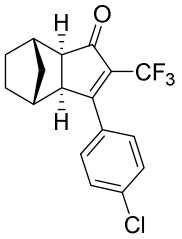
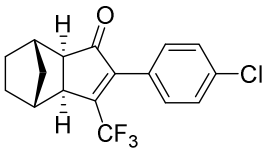
Entry	SM	Major product	Minor product	α:β	Yield[a]
1	**50b**	 **53b**	 **54b**	86:14	51%
2	**50j**	 **53j**	-	>95:5	41%
3	**50m**	 **53m**	 **54m**	71:29	40%

Table 3: Reactivity of the selected alkynes with norbornene. a: yield corresponds to the major and minor regioisomers combined.

These experiments ratified the general trend of fluorinated substituents to occupy the α position in the final PK adducts. We could also confirm that the selectivity in the case of norbornene is lower than for norbornadiene, although the selectivities we obtained were not fully concordant with Konno's report[8]. The fact that the regioselectivity was poorer with an electron-withdrawing substituent in the alkyne (entry 3) than with an electron-donating substituent (entry 1) adds more difficulty to the understanding of the regiochemistry of the PKR. If we assume that the trifluoromethyl group will preferentially occupy the α position in the final product mainly for steric reasons, we could argue that this tendency should be reinforced when having an electron-withdrawing substituent partner (since it would prefer the β position), and diminished with an electron-donating group (that would compete for the α position). However, the experimental results disagree with this reasoning.

5.4.2 Ethylene

Given the generally narrow alkene applicability of the PKR[10], we decided to test one of the classical reactive alkenes in the PKR: ethylene. We chose five different substrates to test their reactivity and regioselectivity. We wanted to explore a significant set of substrates comprising different electronic and steric properties. With these criteria in mind, we selected two aromatic substrates with electron-donating groups, one with an electron-withdrawing group, an aliphatic chain and a naphthalene derivative (Figure 5).

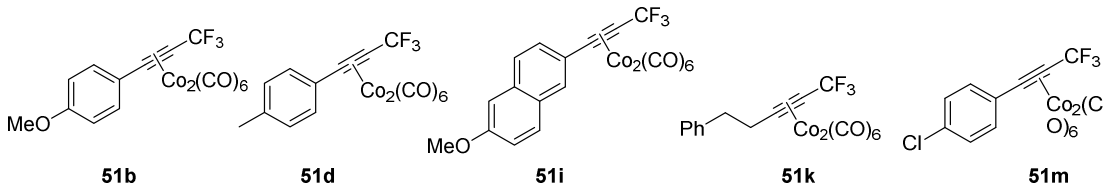
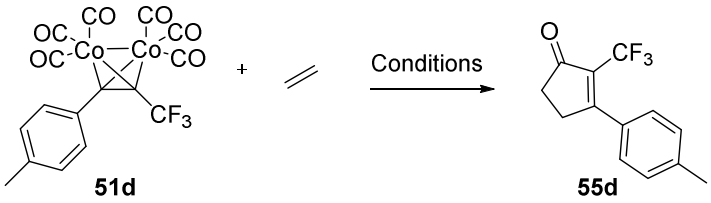


Figure 6: Selected substrates.

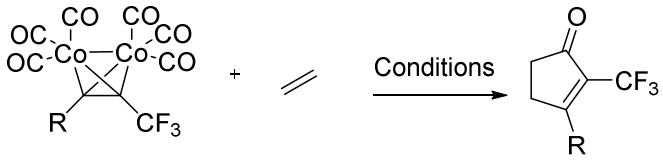
We first carried out an optimization of the reaction with the cobalt complex **51d** as a model. The use of molecular sieves as an additive for the PKR has been known for some years[11]. Our group had experience in the use of this additive in PKRs with ethylene, in which the yields increased dramatically in the presence of the zeolite[12]. At sight of these antecedents, we decided to include molecular sieves in our optimization reactions (Table 4).



Entry	Conditions	Yield
1	6 bars ethylene, NMO (10 eq; 1eq/20min), 4Å mol. sieves (fully activated[a]; 15x alkyne mass), rt, DCM	18%
2	6 bars ethylene, NMO (10 eq; 1eq/20min), 4Å mol. sieves (dry[b]; 8x alkyne mass), rt, DCM	20%
3	6 bars ethylene, NMO (10 eq; 1eq/20min), rt, DCM	25%
4	6 bars ethylene, NMO (10 eq; 1eq/20min), 0 °C, DCM	9%
5	6 bars ethylene, 70°C to 80°C, toluene	53%

Table 4: Reaction optimization conditions. a: dried at 200°C under high vacuum for 8 hours, then stored in a vacuum oven. b: dried in an oven during 4h at 125°C.

We began by testing the PKR activated by NMO. Unfortunately, the yields we obtained were very low in all cases (entries 1-4). The use of molecular sieves did not improve the reaction yield (entries 1-3), and our attempt to carry out the reaction at lower temperature to slow down the oxidation of our cobalt complex by NMO and to increase the solubility of ethylene in the solvent was fruitless (entry 4). Our best result was obtained when activating the reaction thermally and carrying it out without the presence of molecular sieves. Once explored the reaction conditions, we proceeded to test the selected substrates (Table 5).



51 **55**

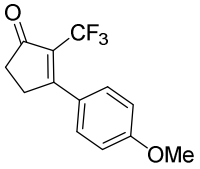
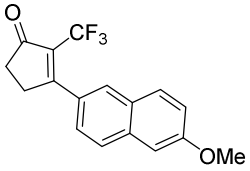
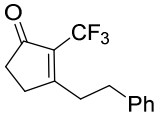
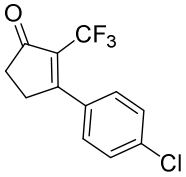
Entry	SM	Conditions	Product	Yield
1	**51b**	6 bars ethylene, 80°C to 85°C, toluene	 **55b**	58%
2	**51i**	6 bars ethylene, 85°C, toluene	 **55i**	41%
4	**51k**	6 bars ethylene, 85°C, toluene	 **55k**	23%
5	**51m**	6 bars ethylene, toluene	 **55m**	56%

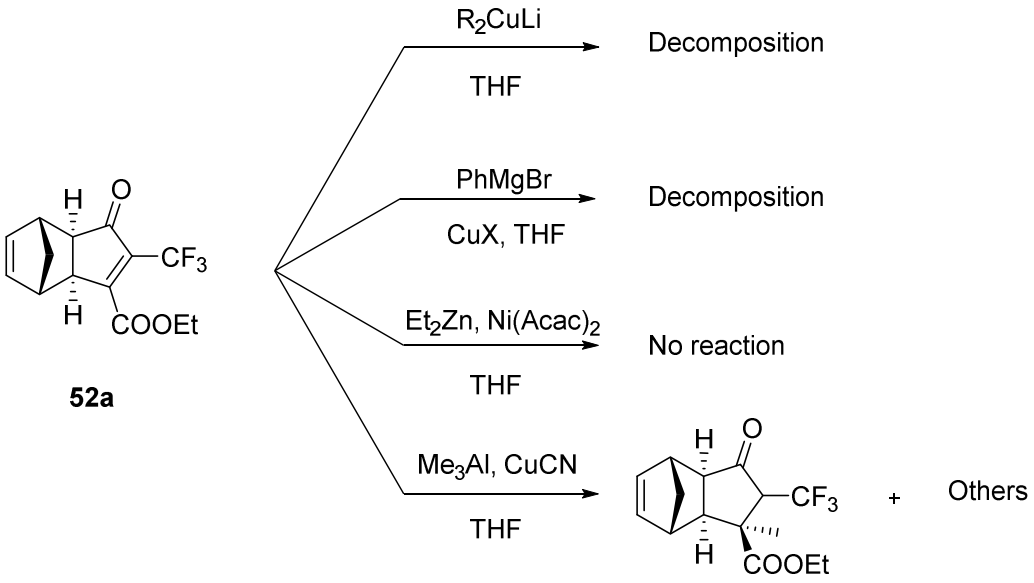
Table 5: Reactivity of the selected alkynes with ethylene.

In all the cases studied, only one product could be isolated from the reaction crude which was assigned, after careful analysis of the NMR data, as the regioisomer bearing the trifluoromethyl group α to the ketone.

5.5 Reactivity of PK adducts

At this point, we had explored the range of applicability of trifluoromethyl alkynes in the intermolecular PKR and studied the general regiochemical outcome of the reaction, the investigation of the reactivity of fluorinated PK adducts drew all our attention. For this purpose, we chose adducts **52a** and **52b** as model substrates and the conjugate addition of dialkyl lithium cuprates and nitromethane as main reactions.

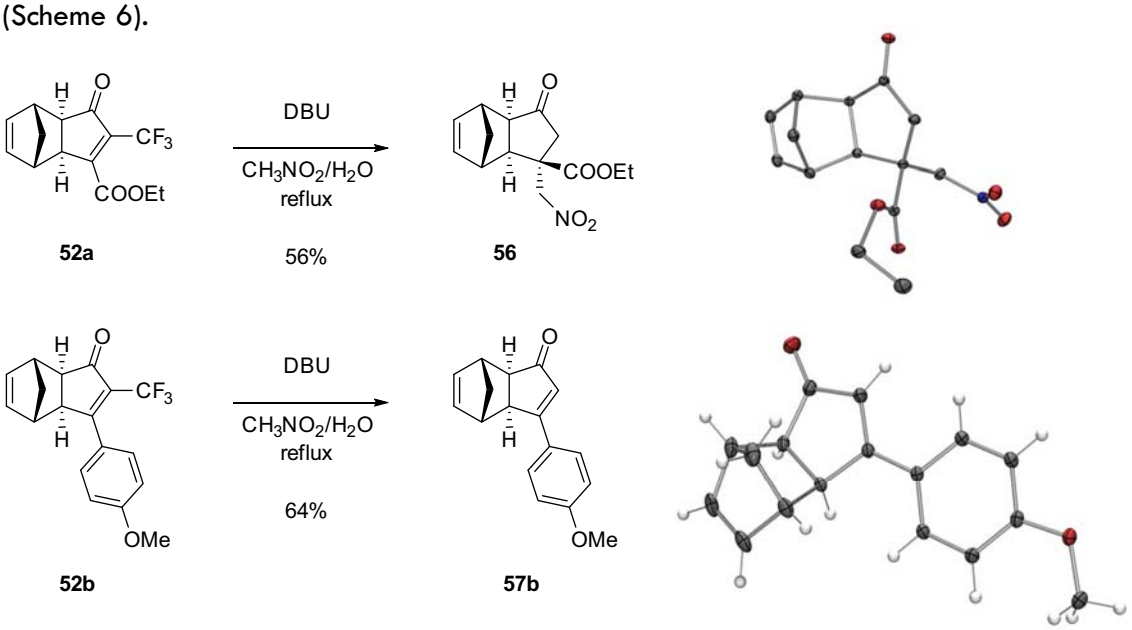
When **52a** was treated with dialkyl lithium cuprates under the classical conjugate addition reaction conditions, we could only observe the rapid decomposition of the product into very complex reaction crudes. The decomposition of α-trifluoromethyl lithium enolates is known[13], and the fact that our PK adduct decomposed so quickly did only confirm the assigned regiochemistry and the known reactivity. We carried out a series of conjugate additions avoiding the presence of lithium in the reaction media, such as the conjugate addition of Grignard reagents catalyzed by different sources of copper (CuI, CuCN and CuBr) and the nickel (II) catalyzed conjugate addition of diethylzinc. Unfortunately, we weren't successful in any of the cases. Conjugate addition of trimethyl aluminum catalyzed by CuCN gave the expected conjugate addition product but, unluckily, the reaction mixture was very complex and the product unstable, which made its isolation and characterization impossible (Scheme *5*).



Scheme 5: Reactivity of **52a** to organometallic reagents.

On the other hand, the reactions of **52a** and **52b** with nitromethane in basic conditions gave a very clean reaction with only one product in both cases. NMR analysis of these products revealed that they had lost the trifluoromethyl moiety during the reaction. Gratifyingly, we could obtain a single crystal from both products that was

suitable for X-Ray analysis and could confirm the surprising outcome of the reactions (Scheme 6).



Scheme 6: Crystal structures of **56** and **57b**.

This unexpected reactivity required some mechanistic explanation. It would be reasonable to think that adduct **56** could be a formal precursor of **57b**. **57b** could be the result of the loss of nitromethane from an intermediate like **56**. Regarding the loss of the trifluoromethyl group, we knew that α-trifluoromethyl enolates appeared to be highly unstable and tended to lose fluorine[13]. With this data in hand, we proposed the following mechanism (Figure 7):

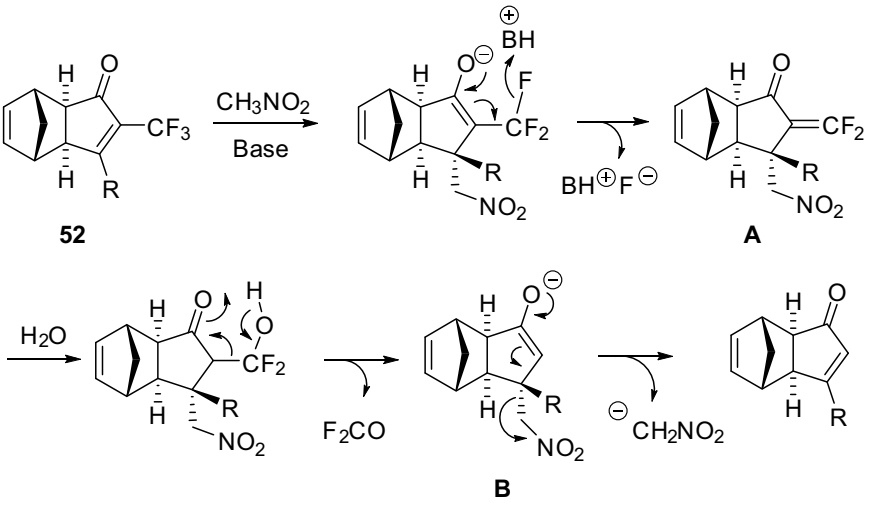
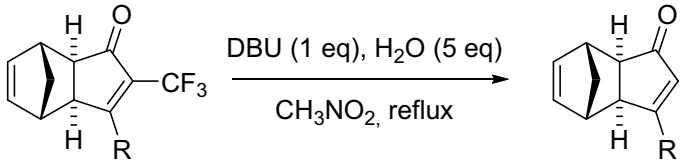


Figure 7: Proposed mechanism.

After conjugate addition of nitromethane on adduct **52.** Elimination of fluorine would give a difluoroenone **A** which, after conjugate addition of water followed by a retro-aldol reaction would afford an intermediate enolate **B.** In the case of **52a,** the

ketone corresponding to enolate **B** would be the final product. However, adduct **52b** goes one step further. Retro-Michael reaction of nitromethane on this substrate would yield the observed product **57b**.

The fact that **52a** and **52b** led to two different results under the same reaction conditions made us wonder how all the other substrates we had prepared would behave. We exposed adducts **52c-m** to the same reaction conditions as for **52a** and **52b**. We were delighted to see that all the substrates behaved like **52b** and yielded the unprecedented regioisomeric PK adducts of terminal alkynes (Table 6).

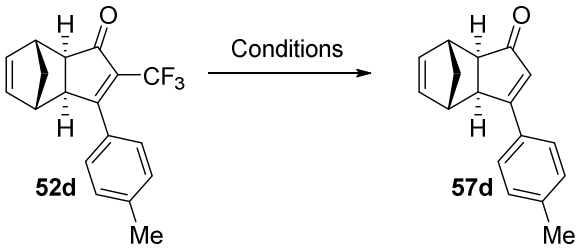


52 **57**

Entry	PK adduct	R	Product	Yield
1	**52c**	phenyl	**57c**	55%
2	**52d**	tolyl	**57d**	64%
3	**52e**	2-methoxyphenyl	**57e**	51%
4	**52f**	4-pentylphenyl	**57f**	68%
5	**52g**	4-(trifluoromethyl)phenyl	**57g**	57%
6	**52h**	4-fluorophenyl	**57h**	59%
7	**52i**	6-methoxynaphtalene-2-yl	**57i**	58%
8	**52j**	undecyl	**57j**	61%
9	**52k**	phenylethyl	**57k**	nd[a]
10	**52l**	cyclohex-1-en-1-yl	**57l**	40%
11	**52m**	4-chlorophenyl	**57m**	57%

Table 6: Des-trifluoromethylation of adducts **52**. a: the product could be detected by NMR, but not separated from reaction by-products.

In order to look for experimental support for our proposed mechanism, we carried out a series of experiments to confirm the importance of water, nitromethane and base in the reaction of **52b** to yield **57b** (Table 7).



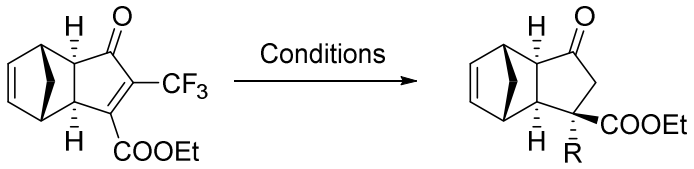
Entry	Conditions	Product	Conversion	Yield
1	DBU (1 eq), H_2O (5 eq), CH_3NO_2[a], reflux, 1h	**57d**	100%	64%
2	DBU (1 eq), H_2O (5 eq), toluene or dioxane, reflux, 24h	**52d**	-	-
3	DBU (1 eq), H_2O (5 eq), CH_3NO_2[a]:toluene (1:3), reflux, 19h	**57d**	100%	46%
4	DBU (1 eq), CH_3NO_2[b], reflux, 18h	**57d**	20%[c]	nd
5	DBU (1 eq), H_2O (5 eq), CH_3NO_2[b], reflux, 1h	**57d**	100%	65%
6	KCN (10 eq), acetonitrile, reflux, 24h	**57d**	76%	16%
7	TBAF (1 eq), CH_3NO_2[a], reflux, 18h	**57d**	100%	20%
8	TBAF (1 eq), CH_3NO_2[b], reflux, 18h	**57d**	34%[c]	nd

Table 7: Study of the influence of water, nitromethane and base in the des-trifluoromethylation reaction. a: used without drying. b: dried overnight by stirring with anhydrous $CaCl_2$ and distilled over molecular sieves. c: determined by ^{1}H-NMR of the reaction crude.

The essential role of nitromethane was readily confirmed since the reaction did not take place in toluene or in dioxane (entry 2). In a mixture of toluene/nitromethane, the reaction occurred at a lower rate and yield (entry 3). Small amounts of water also play an essential role in the reaction. Its complete removal using dry nitromethane led to a dramatic decrease of the conversion, and the reaction did not reach completion even after 18 hours (entry 4). Addition of 5 eq. of water to dry nitromethane gave the same reaction yield than using nitromethane directly without purification (entry 5). Other nucleophiles such as DABCO or cyanide in acetonitrile (without nitromethane) were

successful only in the latter case, but with a lower conversion or yield (entry 6). The base was substituted by TBAF and the same dependence of nitrometane/water was observed (entries 7, 8). These experiments are consistent with the observation that the loss of fluoride occurred after the Michael addition of nitromethane to the enone.

Regarding the conversion of **52a** into **56**, we carried out a similar set of experiments to check whether the experimental results supported the proposed mechanism (Table 5).



52a **56/58/59**

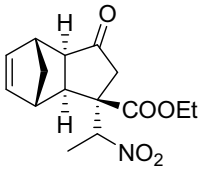
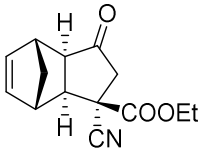
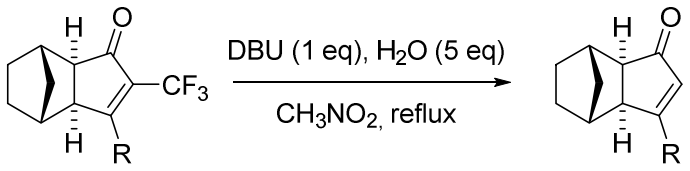
Entry	Conditions	Product	Yield
1	DBU (1 eq), H_2O (16 eq), CH_3NO_2, reflux, 1.5h	**56**	56%
2	DBU (0.2 eq), CH_3NO_2, 80°C, 18h	**56**	36%
3	TBAF·$3H_2O$ (1 eq), CH_3NO_2, reflux, 3h	**56**	99%
4	TBAF·$3H_2O$ (0.4 eq), CH_3NO_2, 80°C, 15h	**56**	65%
5	TBAF (0.4 eq), $CH_3CH_2NO_2$, 65°C, 1.5h	 **58**	57%
6	KCN (10 eq), acetonitrile, 90°C, 1.5h	 **59**	50%

Table 8: Study of the influence of water, nitromethane and base in the des-trifluoromethylation of **52a**.

In this case, we could observe that the same reaction (conjugate addition and loss of the trifluoromethyl group) also occurred when nitroethane or cyanide were used as nucleophile (entries 5 and 6). The yields improved using 1 equivalent of base instead of

a catalytic amount of it (entries 1 to 4) and, in the case of DBU, by addition of a small amount of water (entry 1). The reaction was monitored by ^{19}F NMR and a signal at -155 ppm corresponding to HF-DBU was detected. These observations indicated that the proposed mechanism was very likely to be occurring in both the reactions of **52a** and **52b**. However, we have not been able to find a reason to why **52a** doesn't evolve like adducts **52b-m**. Furthermore, all our attempts to trap enol **B** or detect intermediate **A** were unsuccessful.

The des-trifluoromethylation reaction was also tested with the PK adducts of norbornene **53**. We submitted adducts **53** to the same conditions we had used for **52** and we were delighted to see that, indeed, the reaction was general and yielded the destrifluoromethylated adducts in moderate yields (Table 9).



53 **60**

Entry	PK adduct	R	Product	Yield
1	**53b**	4-methoxyphenyl	**60b**	49%
2	**53d**	tolyl	**60d**	28%
3	**53j**	undecyl	**60j**	nd[a]
4	**53m**	4-chlorophenyl	**60m**	30%

Table 9: Des-trifluoromethylation reaction of adducts **53**. a: the product could be detected by NMR, but not separated from reaction by-products.

The reaction was also assayed with the PK adducts with ethylene (**55**). However, even though we could follow the disappearance of the starting material by TLC, we weren't able to isolate any of the des-trifluoromethylated PK adducts, since they were probably evaporated during the elimination of the nitromethane used as reaction solvent.

5.6 Synthetic Applications: Formal Synthesis of α- Cuparenone

It has been thoroughly discussed during this Thesis that cyclopentanic compounds are extremely abundant in nature and varied both in structure and function. Although we have proved that many of these compounds can be synthesized by a PKR, some of them remain evasive to their synthesis by these means. Some of the products that have not been accessible through a PKR until now are those derive from a β-substituted cyclopentenone. This is due to the fact that in the reaction of a terminal alkyne in a PKR the bulkiest group will end up, inevitably, in the α position of the ketone (Figure 8).

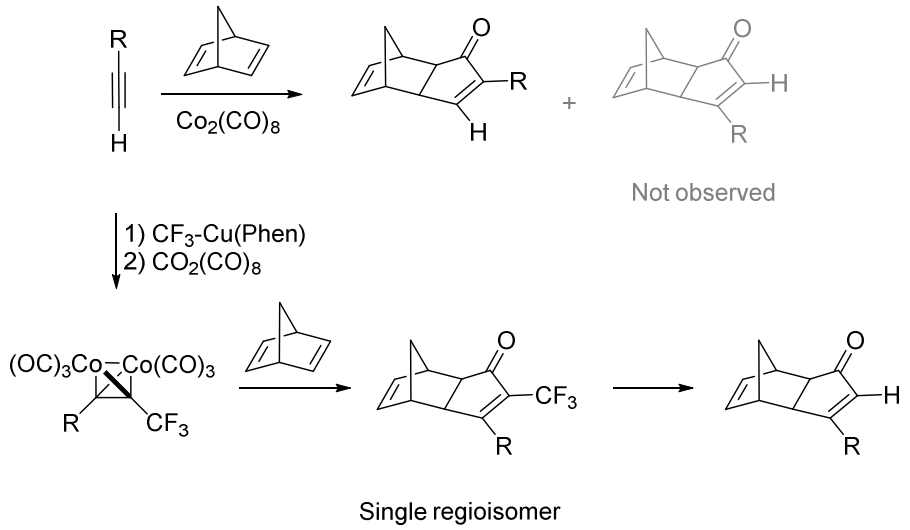


Figure 8: Regiochemical outcome of the PKR of a terminal alkyne and norbornadiene and new route to the regioisomeric PK adducts of terminal alkynes *via* trifluoromethyl alkynes.

One of these elusive substrates for the intermolecular PKR is α-cuparenone. It is a bicyclic sesquiterpene that belongs to the cuparene family (Figure 9). It was isolated from *Thuja Orientalis*, an evergreen coniferous tree endemic of Asia, by Sukhdev and coworkers in 1964[14].

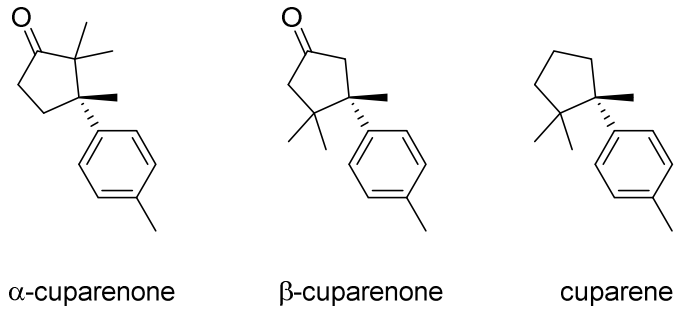
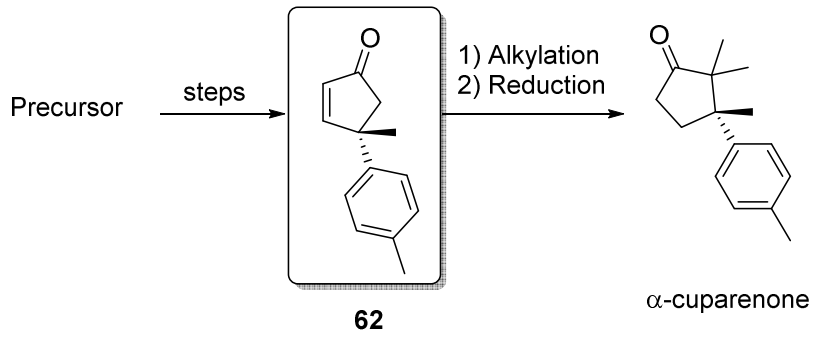


Figure 9: Cuparene-family sesquiterpenes.

α-cuparenone presents basically two structural features that make its synthesis a challenging objective: a cyclopentanone ring and two contiguous quaternary centers.

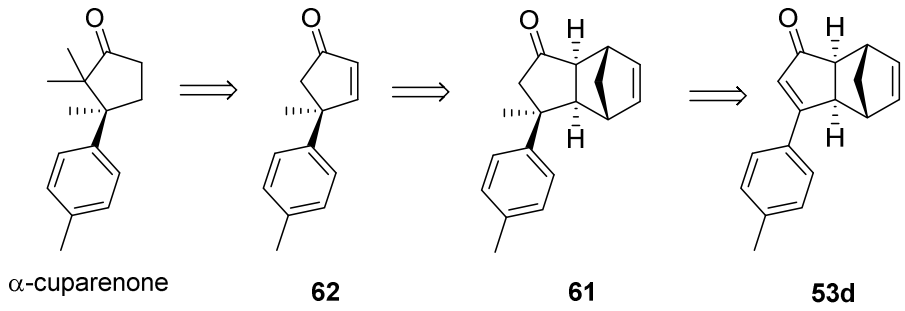
These characteristics made that many synthetic chemists focused their attention on the preparation of these products, and several syntheses have been reported since they were isolated.

The synthesis of α-cuparenone has been faced using different approaches. Many of them construct the cyclopentanic ring by ring-closing of an open chain intermediate[15] and others transform cyclopentane ring derivatives[16]. Many of these reports include a common intermediate (**62**) in their approach to α-cuparenone[17] (Scheme 7).



Scheme 7: General synthesis of α-cuparenone.

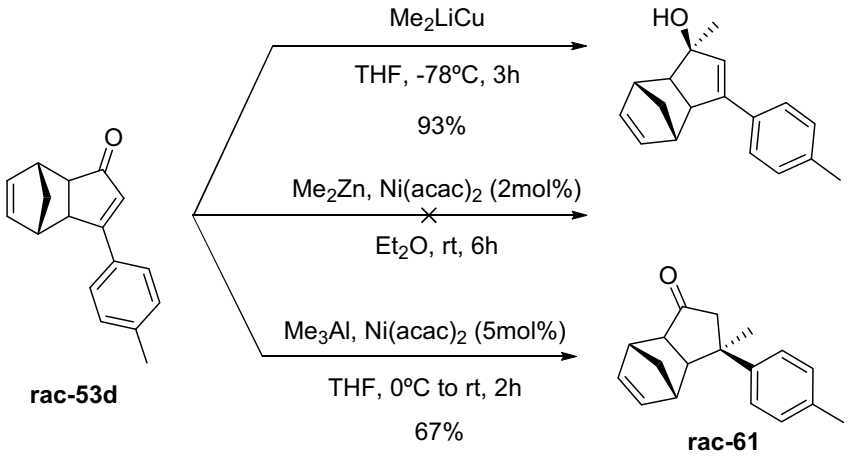
We set about to obtain this key intermediate by a retro Diels-Alder reaction of **61**, which in turn would be prepared by methyl conjugate addition on the corresponding regioisomeric PK adduct **53d** (Scheme 8).



Scheme 8: Retrosynthetic analysis.

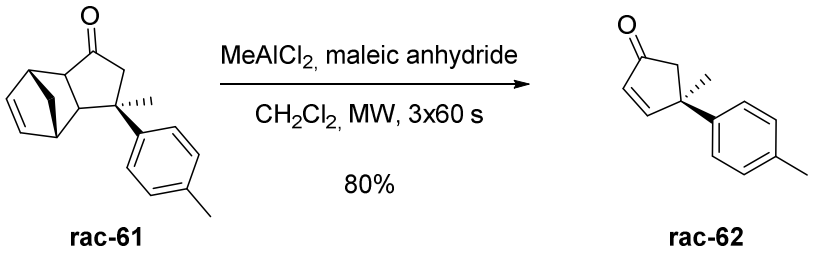
The methyl conjugate addition to enone **53d** required some experimentation. This reaction has been widely studied in the case of other hindered enones[18]. Although conjugate addition of the standard dimethyl lithium cuprate has been reported to not be successful in similar substrates to ours, we decided to assay its addition to our enone. Not surprisingly, the final product was not isolated from the reaction crude. Instead, we recovered the product corresponding to the 1,2-addition of methyl to the carbonyl with a very high yield. We could find precedents in the literature that reported similar results[19].

Organozinc reagents have been reported to have a huge potential in the conjugate addition reactions to hindered enones[20]. Nickel is known to ease these conjugate additions when combined with dialkyl zinc species[21]. Hindered enones have been reported to successfully undergo the conjugate addition of methyl when treated with dimethyl zinc in the presence of a catalytic amount of $Ni(acac)_2$[22]. Our attempts to obtain the desired product by this method resulted fruitless. No reaction was detected at all, and we could only recover starting material after more than 24 hours of reaction. Another method that has been studied for the conjugate addition of methyl to hindered enones is the nickel-catalyzed addition of trimethylaluminium[18b,22]. We were very happy to see that our substrate reacted very rapidly with these reagents and yielded the desired 1,4-addition product in a satisfactory 67% yield and as a single diastereomer (Scheme 9).



Scheme 9: Conjugate addition of methyl on **53d**.

The final step, the retro Diels-Alder reaction, was carried out under microwave conditions and yielded the desired product in high yield. Our spectroscopical data coincided with that reported in the literature[23] (Scheme 10).



Scheme 10: Microwave promoted retro Diels-Alder reaction.

5.7 Conclusions

We have explored the PKR of internal dissymmetric fluorinated alkynes with different norbornadiene and ethylene.

1) The thermal PKR of differently substituted dissymmetric trifluoromethyl alkynes with norbornadiene and ethylene proceeded smoothly in all cases and yielded the α-trifluoromethylated PK adducts in moderate to excellent yields and as a single regioisomer. In the case of norbornene, the PKR also proceeded smoothly, and yielded majorly the α-trifluoromethylated PK adducts in moderate yields, although the regioselectivities were lower.

2) The reactivity of these adducts towards conjugate addition reactions of organometallic nucleophiles wasn't successful, but their reaction with non-organometallic nucleophiles such as nitromethane enabled us to access the previously unknown β-substituted PK adducts of terminal alkynes except of in one case, where a quaternary center was formed. The unprecedented des-trifluoromethylation reaction proved to be general. A reasonable mechanism for this reactivity has been proposed.

3) We have applied the newly discovered methodology to the formal synthesis of α-cuparenone.

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[5] NOTE: products **50e**, **50g**, **50h**, **50i** and **50l** and their norbornadiene derivatives were prepared by the group of Professor Santos Fustero in Valencia. Norbornene derivatives were synthesized by Mrs Elsa Martínez-Arce during her Bachelors' Degree in our lab under Professor Riera's and my own supervision. They have included in the discussion because of their importance in our general discussions.

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6. Asymmetric intermolecular PKR of dissymmetric fluorinated alkynes with norbornadiene

6.1 Introduction

In Chapter 2, we discussed the different approaches to the asymmetric version of the PKR. Probably the most extended methodologies for the cobalt-mediated asymmetric PKR of terminal alkynes developed during the past decade relies on the use of chiral phosphine ligands[1]. The complexation of these ligands with a dicobalt complex of a terminal alkyne provides two new diatereomeric complexes. Once separated, their reaction with a strained olefin usually leads to the corresponding PK adduct in high optical purity. The success of these ligands depends on the selectivity of the olefin coordination to the phosphine-free cobalt atom and its selective insertion into one Co-C bond (Figure 1).

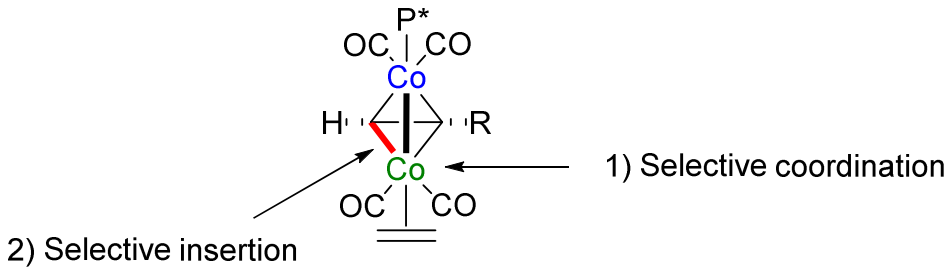
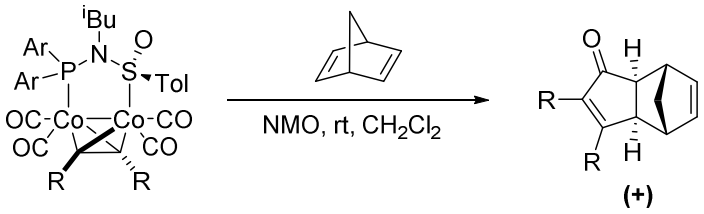


Figure 1: Alkene insertion sites.

N-phosphino sulfonamide (PNSO) ligands were developed by our group and have been extensively used during the past years. As we discussed in Chapter 2, *N*-phosphino-*tert*-butylsulfinamides have proved to be highly efficient in the asymmetric PKR, providing excellent complexation diastereoselectivity and high yields and enantiomeric excess in the PKR. From the stereochemical point of view, the PK adduct results from the cobalt complex with the olefin coordinated to the cobalt atom bond to sulfur. As other sulfur ligands, PNSO ligands have been postulated to be hemi-labile. That's to say, the olefin coordinates to cobalt through a vacant left by the decoordination of the sulfur atom. *N*-phosphino-*p*-tolylsulfinamides tend to give lower diastereoselectivities in the complexation and moderate enantioselectivities, but present the interesting characteristic of being less hemi-labile than their *tert*-butyl partners, due to the higher backbonding of arylsulfinamides to cobalt[2]. This feature allowed our group to describe for the first time the asymmetric PKR of symmetric internal alkynes[3] (Table 1).



R	Ar	Time (days)	Yield (%)	er
phenyl	phenyl	20	71	96:4
phenyl	4-methoxyphenyl	17	77	97:3
4-methoxyphenyl	phenyl	22	73	95:5
4-fluorophenyl	4-methoxyphenyl	26	85	97:3
4-chlorophenyl	4-methoxyphenyl	26	85	97:3
$TIPSOCH_2$	4-methoxyphenyl	24	57	93:7
n-propyl	4-methoxyphenyl	26	27	94:6

Table 1: Selected results for the asymmetric PKR of symmetric alkynes.

In the later case, it was hypothesized that the PNSO ligand was not behaving as hemi-labile and the olefin was coordinating to the cobalt atom with the sulfur still bond to it.

However, the asymmetric PKR of dissymmetric internal alkynes remained unexplored at the beginning of this study. Taking into account the remarkable reactivity we had discovered in the PKR of internal trifluoromethyl alkynes, we considered interesting to explore the asymmetric versions of the PKR of these substrates, since having the corresponding PK adducts in its optically enriched form would allow us to access the regioisomeric PK adducts of terminal alkynes as single enantiomers, adding value to our approach.

6.2 Ligand screening

One of the most interesting trifluoromethyl alkynes in hand was 1-methyl-4-(3,3,3-trifluoroprop-1-yn-1-yl)benzene (**50d**), since its enentiomerically pure PK adduct would grant us access to enantiopure α-cuparenone.

Once chosen the alkyne, we began our study by selecting a series of PNSO and a PNP ligand, all of them developed in the group[3, 4] (Figure 2).

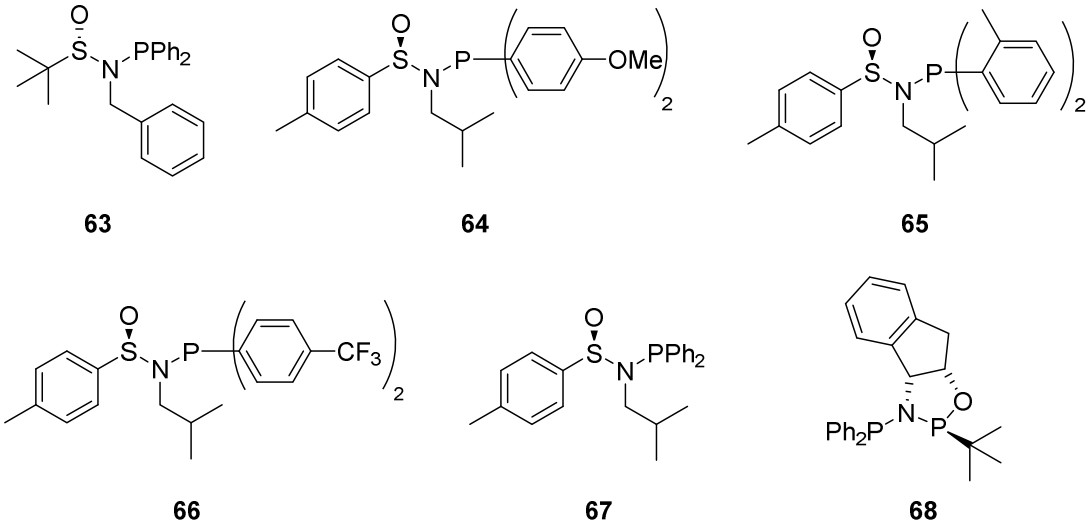
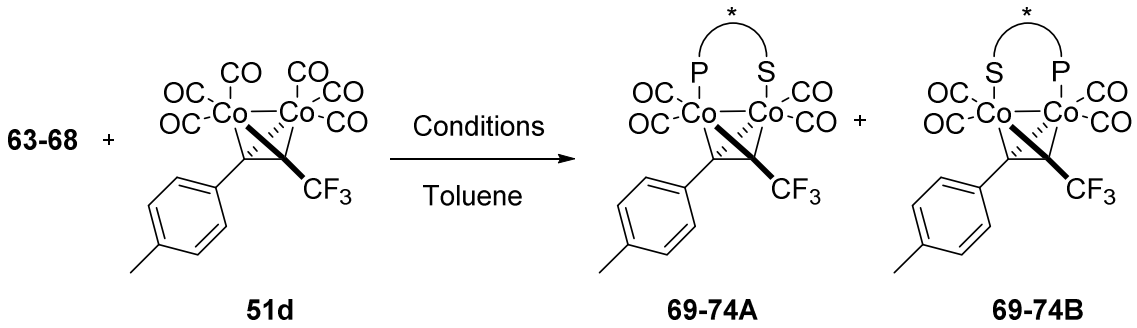


Figure 2: Selected ligands.

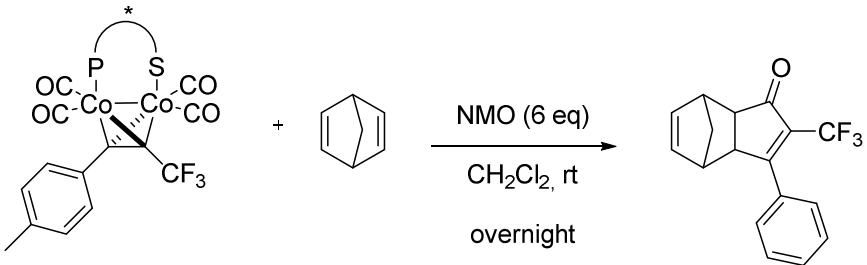
Except for **I**, all these ligands were stored as borane-protected phosphines. The deprotection and complexation of the free ligands to the dicobalt complex was done as a *one-pot* procedure. In a Schlenk tube, cobalt complex **51d** was dissolved in anhydrous toluene, and then the ligand and DABCO were added as solids. The system was heated up and the reaction was allowed to proceed until no starting cobalt complex could be detected by TLC and no evolution in the diastereomeric ratio could be detected by TLC or NMR (Table 2).



Entry	Ligand	Conditions	Complex	Yield[a]	dr[c]
1	**63**	70-75°C, vacuum cycles	**69**	-[b]	-
2	**64**	DABCO (1.6 eq), 65°C	**70**	80%	1.1:1
3	**65**	DABCO (2.6 eq), 65°C	**71**	-[b]	-
4	**66**	DABCO (2.6 eq), 65°C	**72**	54%	1.4:1
5	**67**	DABCO (1.6 eq), 65°C	**73**	87%	1.5:1
6	**68**	DABCO (4 eq), 85°C	**74**	39%	1.2:1

Table 2: Complexation of **51d** with the selected ligands. a: isolated yield (both diastereomers). b: complex decomposed upon isolation. c: determined by ^{1}H-MNR of the reaction crudes.

The diastereomeric ratio corresponding to the complexation was almost non-existent in all of the cases. However, both diastereomers could be separated by careful column chromatography. In all cases, the most apolar cobalt complex (the major one, from now on referred as **A** diastereomer) could be separated from the most polar cobalt complex (from now on, **B** diasteromer) and isolated as a single diastereomer. Once with the diasteromerically pure major complexes in hand, we submitted them to the NMO-promoted PKR with norbornadiene (Table 3).



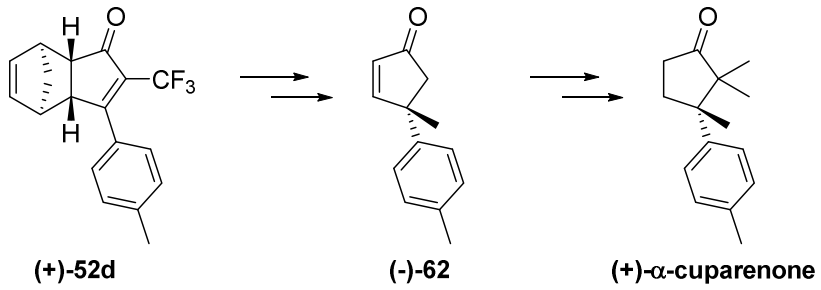
70-74A **exo-52d**

Entry	Complex	Yield	ee	Rotation
1	**70A**	80%	92%	+
2	**72A**	17%	8%	+
3	**73A**	67%	88%	+
4	**74A**	-[a]	-	

Table 3: PKR of complexes **70-74A**. a: complex decomposed before PKR.

We were happy to see that, in spite of the low diastereoselectivity in the complexation, the yields and enantiomeric excesses provided by complexes **70A** and **73A** (with ligands **64** and **67**, respectively) were excellent. Given that that the enantiomeric excess obtained with ligand **64** was higher we decided to carry out the rest of our experiments with it.

The absolute configuration of **(+)-52d**, was determined by chemical correlation with the known key intermediate for the synthesis of α-cuparenone **62**. The synthesis was carried out as we discussed in Chapter 6. Once determined the sign of the optical rotation of intermediate **62**, we could define the absolute configuration of **(+)-52d** (Scheme 1).



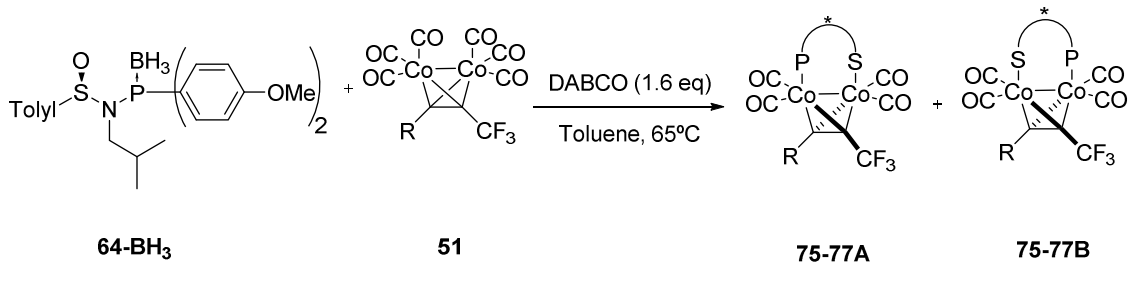
Scheme 1: Determination of the absolute stereochemistry of **(+)-52d** by chemical correlation.

6.3 Alkyne scope

Once selected a suitable ligand for the PKR of internal dissymmetric trifluoromethyl alkynes, we continued to study the scope of alkynes in the aforementioned reaction.

We selected three additional alkynes apart from **50d**: **50b** (R=*p*-MeOPh), **50j** (R=$C_{11}H_{23}$), **50m** (R=*p*-ClPh) and **50n** (R=*p*-BrPh).

The three corresponding dicobalthexacarbonyl complexes (**51b, 51j** and **51m**) were allowed to react with ligand **64** under the same reaction conditions that we used for **51d** (Table 4).



Entry	SM	R	Complex	Yield[a]	dr[b]
1	**51b**	4-methoxyphenyl	**75**	96%	1:1
2	**51j**	undecyl	**76**	45%	1:1
3	**51m**	4-chlorophenyl	**77**	50%	1.4:1
4	**51n**	4-bromophenyl	**78**	75%	1:1

Table 4: Formation of combalt complexes **75-78**. a: isolated yield (both diastereomers). b: determined by ^{1}H-MNR of the reaction crudes.

As it happened before, we found that the complexation yields were moderate to excellent, but the diastereoselectivities were marginal. The resulting complexes were separated by column chromatography in order to obtain one single diastereomer of each. For all the complexes, we could only isolate the most apolar one pure (***75-77A***).

The NMR spectra of all these complexes (**70**, **75**, **76** and **77**) presented remarkable similarities. For instance, the peaks corresponding to the methyl groups of the isobutyl moiety always appeared at lower chemical shifts in the case of the most apolar complexes. Furthermore, the ^{19}F and ^{31}P chemical shifts of the complex pairs were basically identical. Given these similarities, we thought it reasonable to assume that all the **A** complexes corresponded to the same diastereomer, and so would the **B** diastereomers (Figure 3).

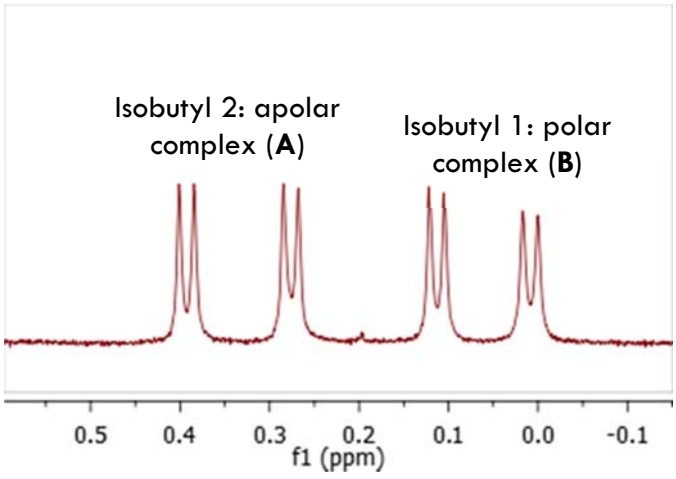
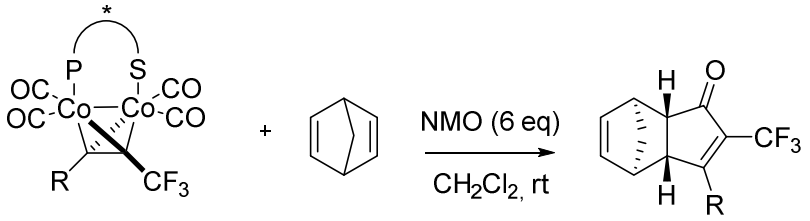


Figure 3: NMR signals of the CH_3 isobutylic protons in a 1:1 mixture of diastereomeric cobalt complexes.

Once the pure complexes were isolated, we submitted them to the PKR with nornornadiene (Table 4).



75-77A **(+)-52**

Entry	Complex	Product	Yield	ee	Rotation
1	**75A**	**52b**	90%	91%	+
2	**76A**	**52j**	-[a]	-	
3	**77A**	**52m**	30%	92%	+
4	**78A**	**52n**	57%	90%	+

Table 5: Asymmetric PKR of complexes ***75-78A***. a: complex decomposed before PKR occurred.

As we had observed in the preparation of **(+)-52d,** the enantiomeric excess was remarkable for the reactions of ***75***, ***77*** and ***78,*** and it was paired with an excellent yield in the first case. Regarding ***76,*** the cobalt complex decomposed before yielding the final product. Even though the thermally activated PKR was attempted, the reaction didn't occur. Concerning ***77***, the cobalt complex also turned to be quite unstable and, even though it could be handled, it decomposed rapidly. This factor may be the explanation to the low yield it provided.

In spite of the poor stability of ***77,*** we were able to obtain a single structure of the major, most apolar complex ***77A*** and confirm its structure (Figure 4).

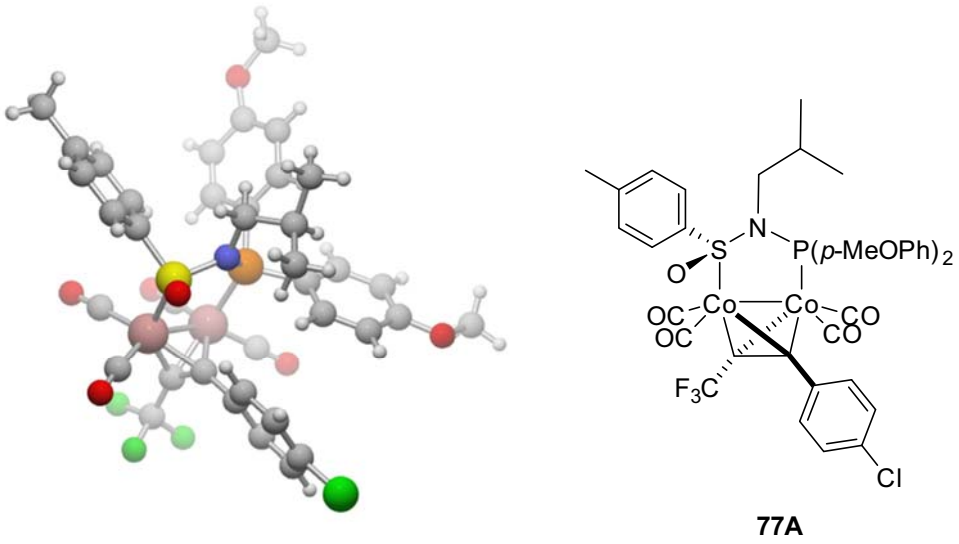
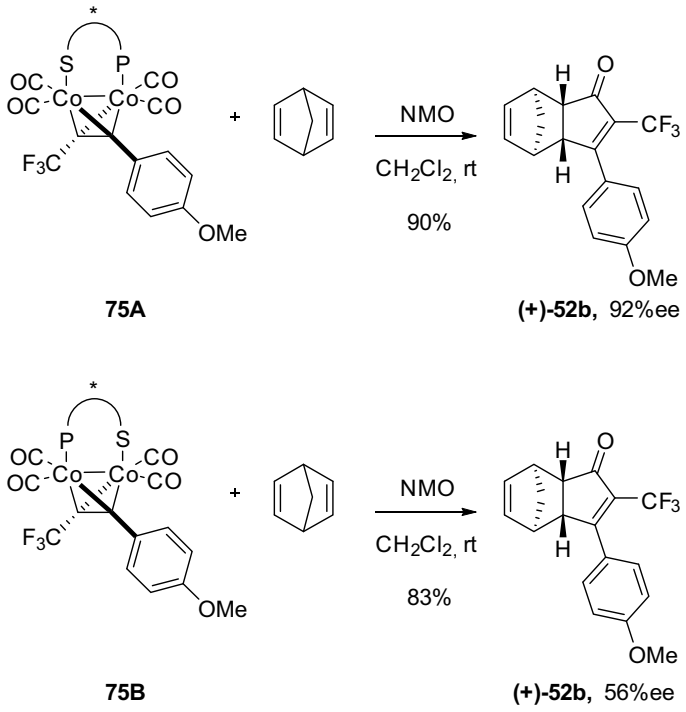


Figure 4: Crystal structure of the major diastereomer of **77**.

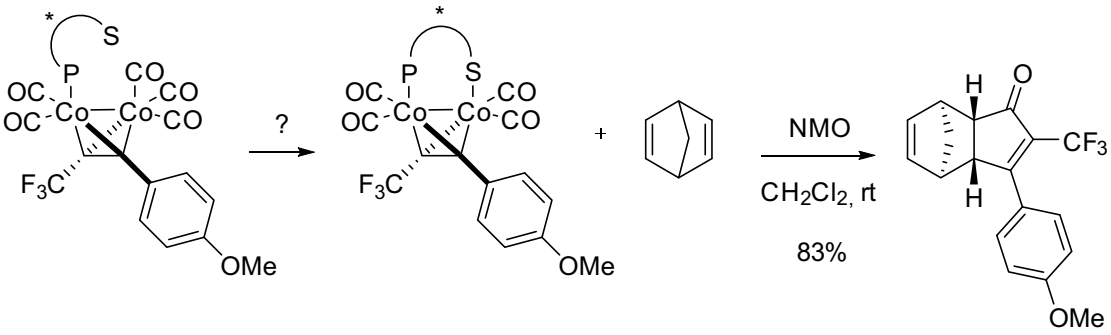
Diastereomeric Co-alkyne tetracarbonyl PNSO complexes have been reported to yield enantiomeric PK adducts[5], and this behavior has been reasoned from a mechanistic point of view, as we explained in Chapter 2. We assumed that the same results would be obtained with our substrates. However, the outcome of the PKR of the minor diastereomer of ***75*** was striking (Scheme 2).



Scheme 2: Asymmetric PKR of complexes **75A** and **75B**.

Instead of obtaining **(-)-52b,** we obtained the same enantiomer as when we carried out the reaction with the major isomer of ***75*** (***75A***), even though the enantiomeric excess was lower. The result was the same when using a mixture of both isomers of ***75.***

We considered the possibility that ***75B*** and ***75A*** were not diastereomers. We could be dealing with the pentacarbonyl complex corresponding to the open structure of ***75A***. This complex could then close in the reaction media to lead to ***75A,*** which would explain that we got the same enantiomer of **52d** when starting from two different cobalt complexes (Scheme 3).



Scheme 3: Revised proposed structure of ***75B***.

Our group had performed a study on the IR spectra of tetracarbonyl cobalt complexes bond to PNSO ligands[6], and had established that their CO stretching bands had a characteristic shape common to all of them. The study of the CO stretching bands of the two isomers of ***75*** revealed that we had two tetracarbonylic complexes.

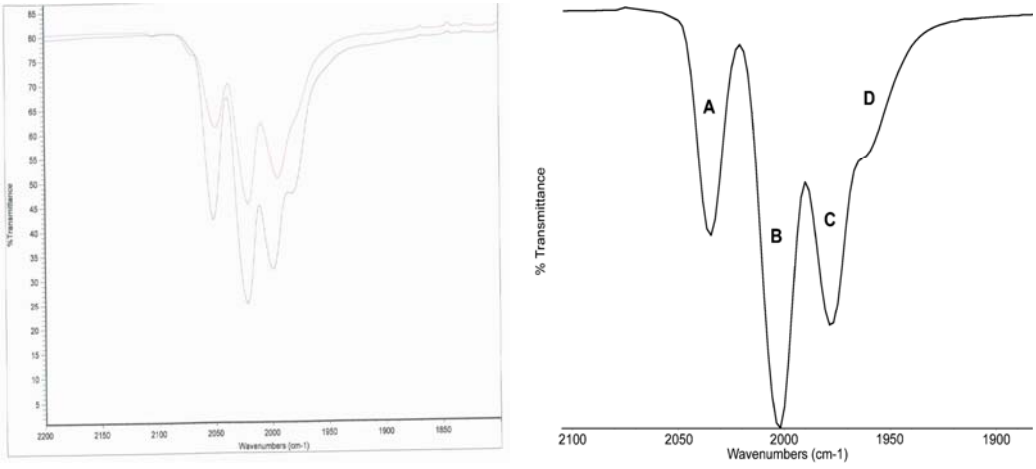


Figure 5: CO stretching bands for the two isomers of ***75*** (left) and theoretical bands for tetracarbonylcomplexes (right).

To further confirm the structural relationship between **75A** and **75B**, we exposed a mixture of the two isomers of **75** to carbon monoxide and monitored the evolution of the reaction by ^{19}F-NMR. If we were truly dealing with two diastereomeric tetracarbonyl complexes, they should both open to yield two different pentacarbonyl complexes. As we expected, that is what we observed (Figure 6).

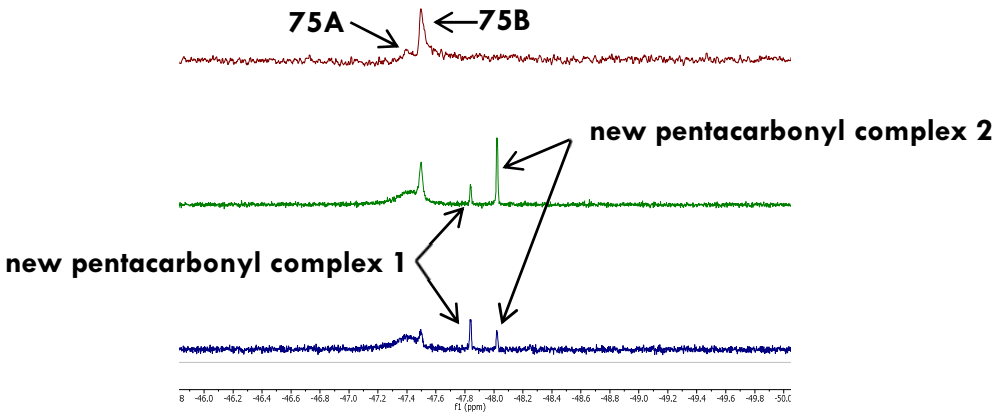
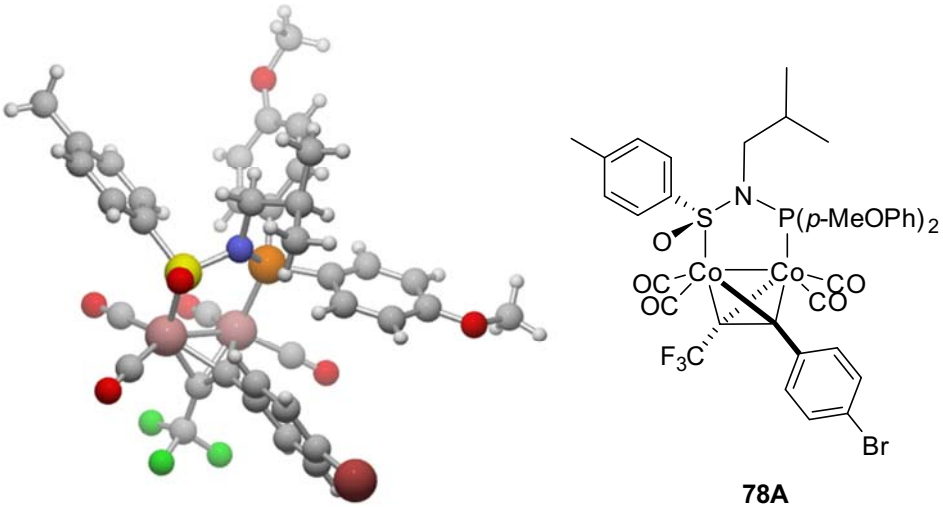
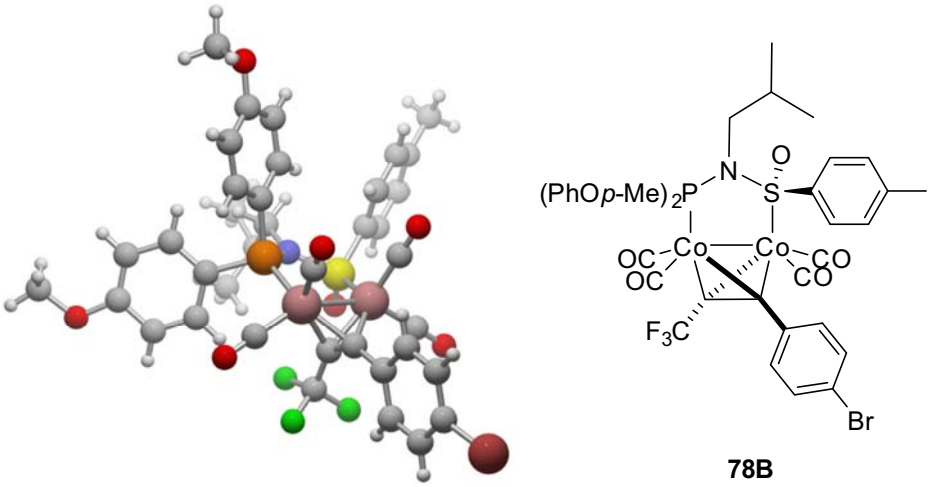


Figure 6: ^{19}F-NMR spectra of a 1:1 mixture of **75A** and **75B** upon exposure to CO. The red spectrum corresponds to the mixture without CO; green and blue spectra were acquired after CO exposition. The two new signals in the green and blue spectra correspond to the two new pentacarbonyl cobalt complexes formed.

Finally, we were able to crystalize both diastereomeric complexes of 78 and to finally confirm that we were indubitably dealing with diastereomeric complexes (Figure 7).



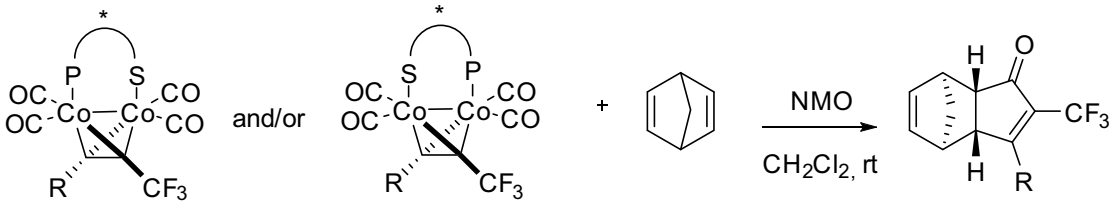
78A



78B

Figure 7: Crystal structures of **78A** and **78B**.

All the experimental evidence pointed out at the fact that we had two diastereomeric tetracarbonylic complexes with a PNSO ligand that, against all odds, yielded the same enantiomer of the corresponding PK adduct. Even though we couldn't observe an equilibration event, the possibility that one diastereomer converts to the other in the sine of the reaction, before the product formation, can't be ruled out. The same behavior was observed for all the remaining PNSO complexes (Table 6).



A **B** **(+)-52**

Entry	Complex	R	Yield 52	ee 52	Rotation
1	**74A**	tolyl	80%	92%	+
2	**74A'+74B' (1:1)**[a]	tolyl	59%	70%	–
3	**77A**	4-chlorophenyl	30%	92%	+
4	**77A+77B (6.8:1)**	4-chlorophenyl	63%	85%	+
5	**77A+77B (1:1)**	4-chlorophenyl	60%	73%	+

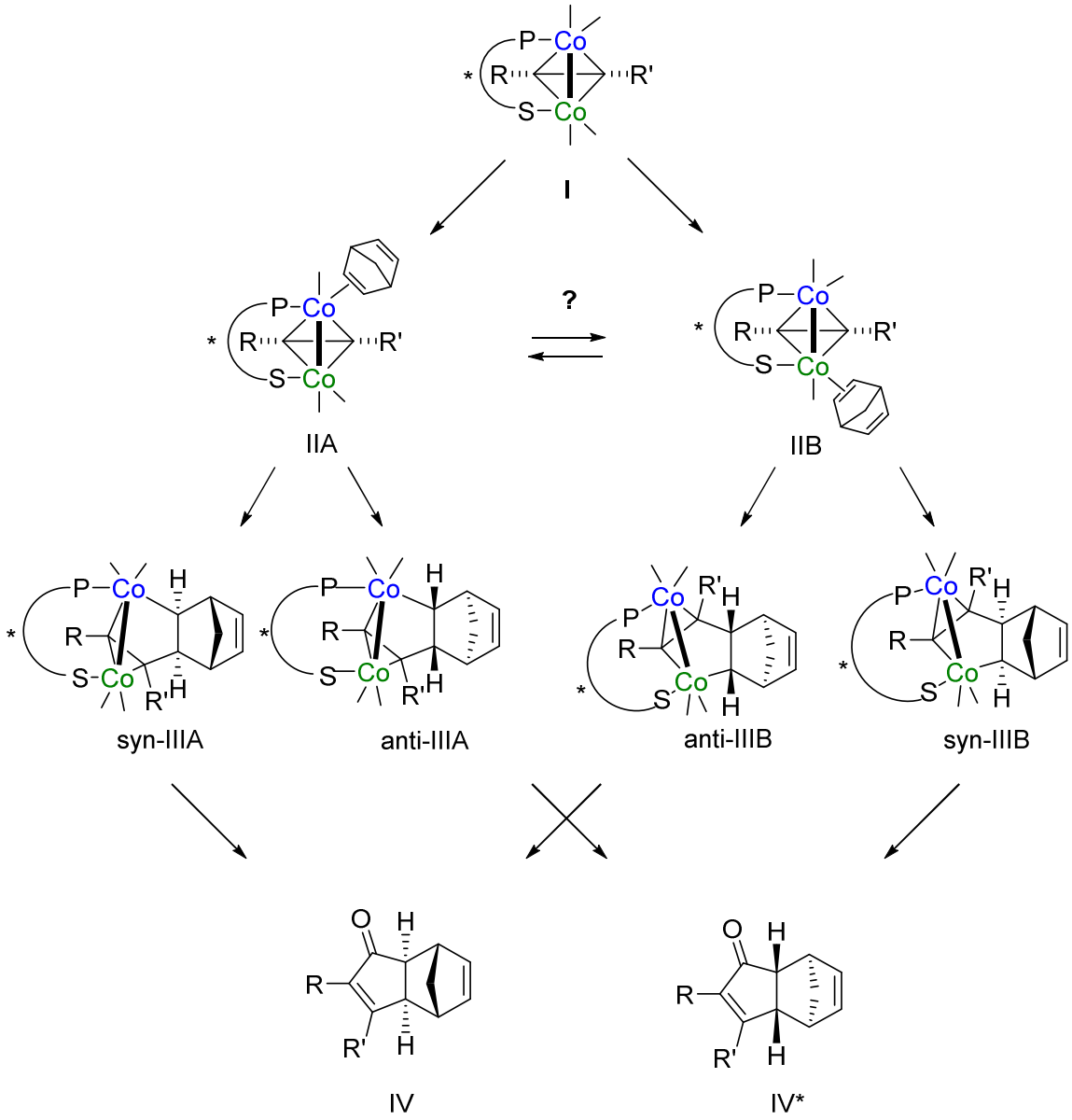
6	**75A**	4-methoxyphenyl	90%	91%	+
7	**75B**	4-methoxyphenyl	83%	56%	+
8	**75A+75B (1:1)**	4-methoxyphenyl	61%	73%	+
9	**75A+75B (1.3:1)**	4-methoxyphenyl	63%	71%	+
10	**78A**	4-bromophenyl	57%	90%	+
11	**78B**	4-bromophenyl	42%	28%	+
12	**78A+78B (1.3:1)**	4-bromophenyl	71%	73%	+

Table 6: PKRs with pure complexes and with mixtures of diastereomers. a: PNSO complex of ligand **64** with the *R* sulfinamide.

6.4 Mechanistic considerations

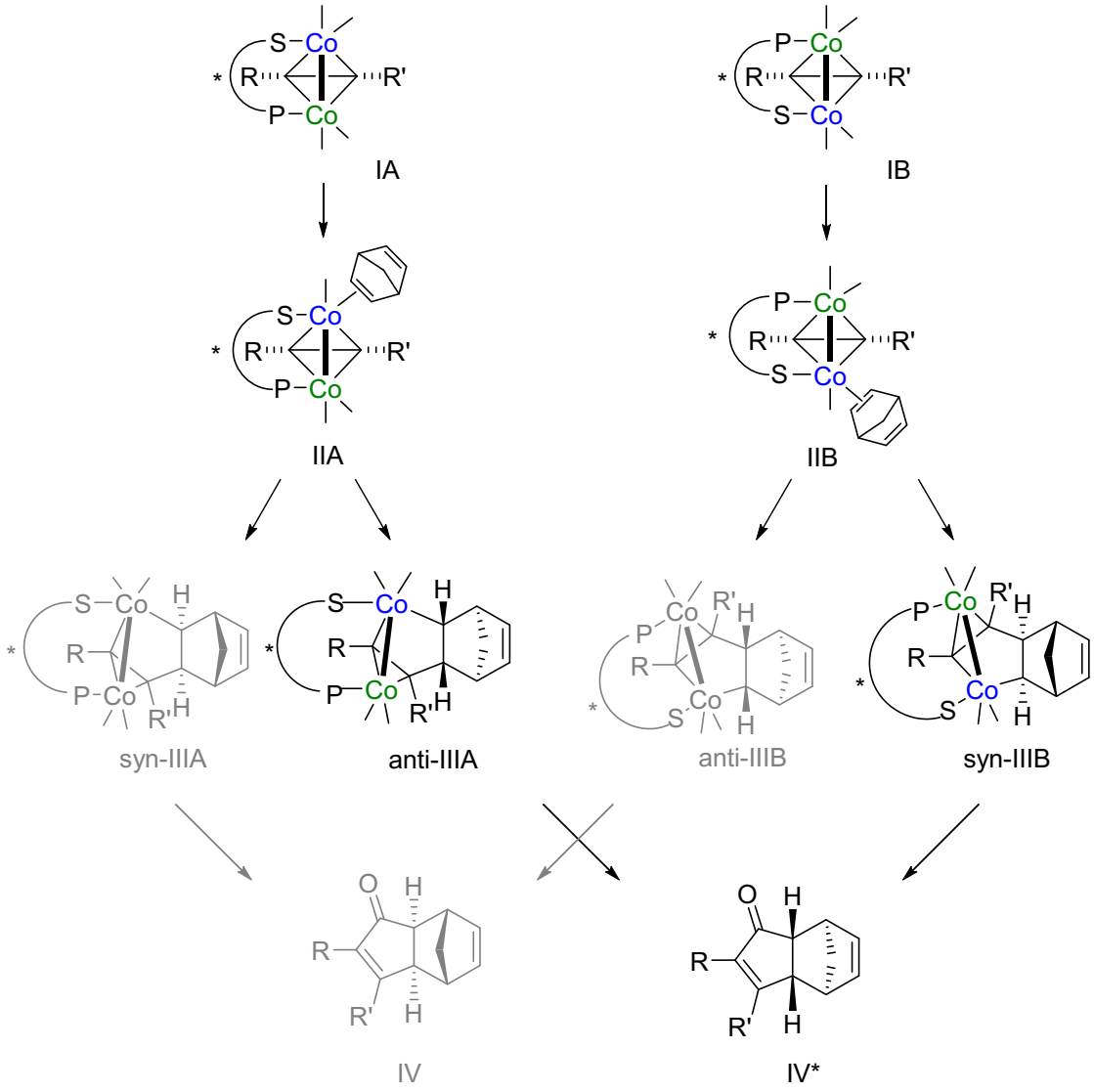
In Chapter 2, we discussed the origin of enantioselectivity in the asymmetric PKR. Based on the mechanism proposed by Magnus[7], we illustrated the pathways that lead to each of the enantiomers of a PK adduct in the reaction of a terminal alkyne with norbornadiene.

The absolute configuration of the final products is established during the insertion of the alkene in the preferred, less hindered Co-C bond. Norbornadiene can insert this bond with two orientations: one of them will lead to the *syn* cobaltacycle (where the norbornadiene bridge and the PNSO ligand are in the same plane) and the other, to the *anti* cobaltacycle (where the norbornadiene bridge and the PNSO ligand are in opposite planes). The *anti* cobaltacycles have been described to be more stable than the *syn* cobaltacycles[8], and are therefore the preferential species to be formed during the insertion event. The *anti* cobaltacycle corresponding to the coordination of norbornadiene with one of the cobalt atoms and the *syn* cobaltacycle resulting of the reaction of norbornadiene with the other cobalt atom lead to the same enantiomer (Scheme 4).



Scheme 4: Origin of enantioselectivity in the PKR.

In our case, two diastereomeric Co-alkyne PNSO complexes were leading to the same enantiomer, and we looked for an explanation in the reaction mechanism. Taking into account that it is accepted that the coordination of norbornadiene is more favorable with the cobalt atom bond to sulfur instead of the cobalt atom bond to phosphorous, the possible routes to the same enantiomer from two diastereomeric complexes are shown in Scheme 5:



Scheme 5: Possible pathways to form the same PK adduct from two diastereomeric PNSO-Co complexes.

As it can be seen in Scheme 5, **IV*** can be obtained from *anti*-IIIA and *syn*-IIIB. That's to say, a unique enantiomer can be formed by two diasteromeric complexes as long as, in one case, the *syn* cobaltacycle is more stable than the *anti* one.

In order to check whether this was our case or not, we calculated the equilibrium geometries for the four possible cobaltacycles. However, we could only conclude that the *anti* cobaltacycles were preferred to the *syn* cobaltacycles. We are currently carrying out a more thorough computational study on this topic, in collaboration with Professor Helaja's group in Helsinki. At the moment of writing this Thesis we still can't provide any conclusive result. We hope to be able to report a plausible explanation to the behavior of the studied complexes in due term.

6.5 Conclusions

We have explored the asymmetric PKR of internal dissymmetric fluorinated alkynes, synthesizing a selected group of PK adducts in their optically enriched form.

1) We have explored a series of PNSO and PNP ligands in order to find the best ligand for our PKRs. Ligand **64** gave the best complexation yields and enantiomeric ratios, even though there was no selectivity in the complexation reaction.
2) Once selected a PNSO ligand, we studied the asymmetric PKR of a series of internal dissymmetric fluorinated alkynes, obtaining good yields and excellent enantiomeric excesses in all cases, although there was no diastereoselectivity in the complexation reaction.
3) We have detected, for the first time, a case where two diastereomeric PNSO-tetracarbonyldicobalt-alkyne complexes yielded the same enantiomer.
4) We have proposed a mechanistic rationalization for this event and carried out preliminary calculations to find a reasonable explanation. However our results so far are inconclusive and we have established collaboration with Professor Helaja's group in Helsinki to try to shed some light in the mechanism.

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7. Conclusions

1) We have designed and tested a new synthetic methodology to access α, β-disubstituted cyclopentenones from the PK adduct of norbornadiene and *N*-Boc-propargylamine. We have assayed a series of conjugate addition reactions on the staring enone, unraveling a great tolerance to a big range of reaction conditions and functional groups. Deprotection of the Boc group followed by permethylation of the free amine has yielded an exocyclic enone on which more conjugate additions were performed. After a retro Diels-Alder reaction we have been able to uncover the desired 4,5-disubstituted enones.
2) We have explored the use of chiral amines as alternative source of chirality to PNSO ligands in our methodology for the synthesis of 4,5-disubstituted cyclopentenones. Unfortunately, all the auxiliaries we have studied gave very poor selectivities and the diastereomers were, in general, impossible to separate.
3) We have applied our new methodology to the synthesis of a natural phytoprostane derivative: 13-*epi*-12-oxo Phytodienoic acid methyl ester. It has been prepared both in its racemic and optically enriched forms, proving the validity of our methodology. The enantioenriched product has been prepared starting from the optically active PK adduct of norbornadiene and *N*-Boc-propargylamine, which has been obtained *via* an asymmetric PKR with one of the PNSO ligands developed in the group.
4) We have explored the reactivity and regioselectivity of the PKR of dissymmetric fluorinated alkynes with norbornadiene, norbornene and ethylene. We have detected that, in all cases, the preferred regioselectivity is for the α-trifluoromethylated PK adducts. The selectivities have been total in the case of norbornadiene and ethylene and very high for norbornene, although in the later case mixtures of regioisomers have been obtained. This fact suggests that the trifluoromethyl group sterics overcome its strong electronegativy and the PKR is ruled mainly by steric factors.
5) We have tested the reactivity of these novel α-trifluoromethyl PK adducts and uncovered an unprecedented tandem conjugate addition/des-

trifluoromethylation reaction that has allowed us to access the unknown β regioisomeric PK adducts of terminal alkynes.

6) We have applied the synthesis of β-regioisomeric PK adducts of terminal alkynes to the formal synthesis of a natural product: α-cuparenone.

7) We have explored the asymmetric PKR of internal dissymmetric fluorinated alkynes. We have explored a series of PNSO and PNP ligands, reaching the conclusion that the poorly hemilabile *N*-phosphino-*p*-tolylsulfinamide ligands are the most suitable for these reactions. We have also synthesized a selected group of PK adducts in their optically enriched form. These reactions constitute the first example of asymmetric PKR of internal and dissymmetrical alkynes.

8) We have observed that for the asymmetric PKR of internal trifluoromethylated alkynes both diastereomers of the PNSO-tetracarbonyldicobalt-alkyne complex yielded the same enantiomer. This event was unprecedented, and we have proposed a mechanistic rationalization for this event and carried out a theoretical study on it.

8. Experimental section

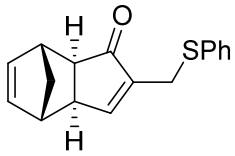
8.1 Methods and materials

Non-aqueous reactions were carried out under nitrogen atmosphere and with flame-dried glassware unless indicated otherwise. Dry tetrahydrofuran, ether and dichloromethane were obtained using a Solvent Purification System (SPS). Dry toluene and dry DMF were purchased directly from Aldrich. Other solvents, such as nitromethane, were used directly as purchased, with no further purification. Lithium derivatives such as MeLi or BuLi were titrated previous to their use with diphenylacetic acid. Commercially available Grignard reagents were used without titration. Magnesium was activated previous to its use and stored in a desiccator. Acetylene was purified before it was used by exposing to two traps: one of them was at -78°C to retain water, and the other one contained H_2SO_4 to eliminate humidity. Other commercially available reagents were used with no further purification. All reactions were monitored by TLC analysis using Merck 60 F_{254} silica gel on aluminum sheets. Silica gel chromatography was performed by using 35-70 μm silica or an automated chromatography system (Combiflash®, Teledyne Isco) with hexanes/ethyl acetate gradients as eluent unless noted otherwise. For reactions under CO pressure, special Schlenk pressure tubes were used. They were attached to a steel cylinder through a steel pipe system bearing a three way valve that allowed the system to be purged. For big scale reactions, a 200mL Miniclave Büchi reactor was used. Reactions under microwaves were done in a CEM Discover Microwave Reactior at the Unitat de Química Combinatòria of the PCB.

NMR spectra were recorded at room temperature on a Varian Mercury 400 or a Bruker 300. ^{1}H and ^{13}C-NMR spectra were referenced to the residual peaks of the deuterated solvent. ^{19}F and ^{31}P-NMR spectra were referenced by the spectrometer without any external pattern. The following abbreviations were used to define the multiplicities: s, singlet; d, doublet; t, triplet; q, quadruplet; p, quintuplet; m, multiplet; br s, broad signal. The chemical shifts (δ) are expressed in ppm and the coupling constants (*J*), in hertz (Hz). IR spectra were recorded in a Thermo Nicolet Nexus FT-IR apparatus, either by preparing a KBr pastille or by depositing a film of the product on a NaCl window. Absorptions are given in wavenumbers (cm^{-1}). Melting points were recorded in a Büchi B-540 apparatus. Mass spectrometry analysis was performed as high resolution ESI analysis at the Mass Spectrometry Core Facility from the IRB Barcelona.

8.2 CHAPTER 3

(*3aR*,4S*,7R*,7aR)-2-((Phenylthio)methyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (2a)**



In a flask with a magnetic stirrer $Co_2(CO)_8$ (634 mg, 1.85 mmol, 1.1 eq.) was dissolved in 5 mL of hexanes. The system was put under nitrogen and phenylpropargyl thioeter (0.23 mL, 1.68 mmol, 1 eq.) was added with a syringe. The system was allowed to stir for 40 minutes, and the solvent was then removed under vacuum. The newly formed complex (300 mg, 0.69 mmol, 1 eq.) was dissolved in 5 mL of anhydrous toluene under nitrogen atmosphere, and norbornadiene (0.70 mL, 6.90 mmol, 10 eq.) was added *via* syringe. The system was heated up to 60 °C and allowed to react for 4h. After this time, the crude was purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarity. The final product was isolated as a yellow oil (74 mg, 40%).

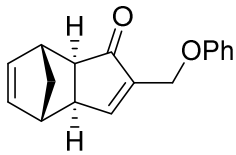
IR (film) $\nu_{max.}$ = 2973, 1699, 1480, 1324 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.08 (dt, *J* = 9.4 and 1.5 Hz, 1H), 1.31 (dt, *J* = 9.4 and 1.6 Hz, 1H), 2.31 (dt, *J* = 5.0 and 1.0 Hz, 1H), 2.58 (br s, 1H), 2.68 (m, 1H), 2.91 (br s, 1H), 3.62-3.72 (m, 2H), 6.19 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.25 (dd, *J* = 5.6 and 3.0 Hz, 1H), 7.16-7.32 (m, 6H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 28.0 (CH_2), 41.4 (CH_2), 43.2 (CH), 43.9 (CH), 47.9 (CH), 52.9 (CH), 126.7 (CH), 129.1 (CH), 129.9 (CH), 135.8 (C), 137.3 (CH), 138.7 (CH), 146.1 (C), 161.5 (CH), 208.3 (C) ppm.

HRMS (ESI) calculated for $C_{17}H_{17}OS$ 269.1000, found 269.0988 $[M+H]^+$.

(*3aR*,4S*,7R*,7aR)-2-(Phenoxymethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (2b)**



In a flask with a magnetic stirrer $Co_2(CO)_8$ (879 mg, 2.57 mmol, 1.1 eq.) was dissolved in 10 mL of hexanes. The system was put under nitrogen and phenylpropargyl eter (0.30 mL, 2.34 mmol, 1 eq) was added with a syringe. The system was allowed to stir for 1h, and the solvent was then removed under vacuum. The residue was put under nitrogen and dissolved in 15 mL of anhydrous toluene, and norbornadiene (2.4 mL, 23.4 mmol, 10 eq) was added *via* syringe. The system was heated up to 70 °C and allowed to react for 3h. After this time, the crude was purified by silica gel chromatography using mixtures of

hexanes/AcOEt of increasing polarity. The final product was isolated as a white solid (419 mg, 71%).

Mp: 85-87 °C.

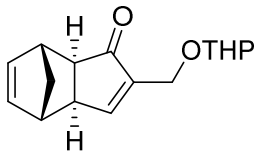
IR (KBr) $\nu_{max.}$ = 2975, 1694, 1489, 1239 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.26 (m, 1H), 1.41 (dt, *J* = 9.4 and 1.5 Hz, 1H), 2.39 (dt, *J* = 5.0 and 1.4 Hz, 1H), 2.72 (s, 1H), 2.83 (m, 1H), 2.96 (s, 1H), 4.72 (t, *J* = 1.8 Hz, 2H), 6.22 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.30 (dd, *J* = 5.6 and 3.1 Hz, 1H), 6.91-6.98 (m, 3H), 7.26-7.31 (m, 2H), 7.54 (dt, *J* = 3.0 and 1.7 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 41.5 (CH_2), 43.1 (CH), 43.8 (CH), 48.5 (CH), 53.3 (CH), 62.0 (CH_2), 114.7 (2 CH), 121.3 (CH), 129.7 (2CH), 137.3 (CH), 138.7 (CH), 146.3 (C), 158.4 (C), 161.2 (CH), 208.4 (C) ppm.

HRMS (ESI) calculated for $C_{17}H_{17}O_2$ 253.1229, found 253.1227 $[M+H]^+$.

(*3aR*,4S*,7R*,7aR)-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (2c)**



In a flask with a magnetic stirrer $Co_2(CO)_8$ (268 mg, 0.78 mmol, 1.1 eq) was dissolved in 5 mL of hexanes. The system was put under nitrogen and tetrahydropyranylpropargyl eter (0.10 mL, 0.71 mmol, 1 eq) was added with a syringe. The system was allowed to stir for 1h, and the solvent was then removed under vacuum. The residue was put under nitrogen and dissolved in 5 mL of anhydrous toluene, and norbornadiene (0.72 mL, 7.10 mmol, 10 eq) was added *via* syringe. The system was heated up to 70 °C and allowed to react for 4h. After this time, the crude was purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarity. The final product was isolated as a pale yellow oil (159 mg, 86%).

IR (film) $\nu_{max.}$ = 2937, 2872, 1694 cm^{-1}.

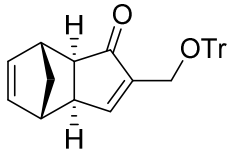
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.27 (m, 1H), 1.40 (dq, *J* = 9.4 and 1.6 Hz, 1H), 1.51-1.86(m, 6H), 2.34 (dt, *J* = 5.1 and 1.4 Hz, 1H), 2.72 (s, 1H), 2.79 (m, 1H), 2.93 (s, 1H), 3.52 (m, 1H), 3.87 (m, 1H), 4.14 (ddt, *J* = 14.5, 11.2 and 1.7 Hz, 1H), 4.42 (ddt, *J* = 14.2, 6.2 and 1.8 Hz, 1H), 4.66 (m, 1H), 6.21 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.30 (dd, *J* = 5.7 and 3.1 Hz, 1H), 7.45 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 19.6 (CH_2), 19.8 (CH_2) ^{*Rotamer}, 25.5 (CH_2), 30.6 (CH_2), 30.7 (CH_2) ^{*Rotamer}, 41.5 (CH_2), 43.1 (CH), 43.8 (CH), 43.8 (CH) ^{*Rotamer}, 48.3 (CH), 53.2

(CH), 61.1 (CH_2), 61.2 (CH_2) *Rotamer, 62.4 (CH_2), 62.7 (CH_2) *Rotamer, 98.7 (CH), 99.1 (CH) *Rotamer, 137.3 (CH), 137.3 (CH) *Rotamer, 138.6 (CH), 147.7 (C), 147.7 (C) *Rotamer, 160.5 (CH), 160.5 (CH) *Rotamer, 208.6 (C) ppm.

HRMS (ESI) calculated for $C_{16}H_{21}O_3$ 261.1483, found 261.1485 $[M+H]^+$.

(*3aR*,4S*,7R*,7aR)-2-((trityloxy)methyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (2d)**



In a flask with a magnetic stirrer was dissolved $Co_2(CO)_8$ (323 mg,0.94 mmol, 1.1 eq) of in 5 mL of hexanes. The system was put under nitrogen and trityl propargyl eter (262 mg, 0.86 mmol, 1 eq) was added as a solid. The system was allowed to stir for 1h, and the solvent was then removed under vacuum. The residue was put under nitrogen and dissolved in 5 mL of anhydrous toluene, and norbornadiene (0.53 mL, 5.30 mmol, 10 eq) was added *via* syringe. The system was heated up to 70 °C and allowed to react for 4h. After this time, the crude was purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarity. The final product was isolated as a white solid (189 mg, 85%).

Mp: 117-179 °C.

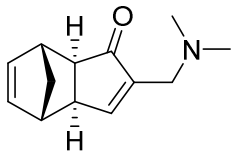
IR (KBr) $\nu_{max.}$ = 2975, 1688, 1481, 1450, 1103, 701 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.21 (d, *J* = 9.3 Hz, 1H), 1.38 (dt, *J* = 9.4 and 1.7 Hz, 1H), 2.30 (dt, *J* = 5.2 and 1.3 Hz, 1H), 2.74 (m, 1H), 2.80 (m, 1H), 2.87 (m, 1H), 3.87 (qt, *J* = 14.9 and 2.1 Hz, 2H), 6.19 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.30 (dd, *J* = 5.6 and 3.1 Hz, 1H), 7.21-7.31 (m, 9H), 7.40-7.45 (m, 6H), 7.62 (q, *J* = 2.1 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 41.5 (CH_2), 43.1 (CH), 43.7 (CH), 48.4 (CH), 53.3 (CH), 59.1 (CH_2), 127.3 (CH), 128.1 (CH), 128.7 (CH), 137.2 (CH), 138.6 (CH), 143.9 (C), 148.4 (C), 159.5 (CH), 208.6 (C) ppm.

HRMS (ESI) calculated for $C_{30}H_{26}O_2Na$ 441.1831, found 441.1836 $[M+Na]^+$.

(*3aR*,4S*,7R*,7aR)-2-((Dimethylamino)methyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (2e)**



In a flask provided with a magnetic stirrer a solution of *N,N*-dimethylpropargylamine (0.10 mL, 1 mmol, 1 eq.) in hexanes (4 mL) was placed under nitrogen atmosphere. Then, $Co_2(CO)_8$ (418 mg, 1.1 mmol, 1.1 eq.) was added. The reaction was stirred for 1h at room temperature. Norbornadiene (1.07 mL, 10 mmol, 10 eq.) was added with a syringe. The mixture was stirred at 60 °C for 3 h. The reaction mixture was allowed to cool and then was acidified with HCl 1N. The organic phase was extracted several times with water; the combined aqueous layers were washed once with DCM. Then, the aqueous phase was treated with NaOH 1 N and extracted with DCM. The combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo to afford the desired product (177 mg, 87%) as a yellow oil with no further purification required.

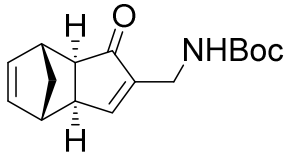
IR (film) $\nu_{max.}$= 2972, 1696, 1455, 1012, 699 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ= 1.23 (m, 1H), 1.39 (dt, *J* = 9.5 and 1.5 Hz, 1H), 2.24 (s, 6H), 2.33 (dt, *J* = 5.0 and 1.4 Hz, 1H), 2.71 (br s, 1H), 2.77 (br s, 1H), 2.92 (br s, 1H), 3.05 (q, *J* = 1.6 Hz, 2H), 6.20 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.31 (dd, *J* = 5.6 and 3.1 Hz, 1H), 7.38 (dt, *J* = 2.6 and 1.3 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ= 41.5 (CH_2), 43.1 (CH), 43.8 (CH), 45.8 (CH_3), 48.1 (CH), 53.0 (CH), 53.9 (CH_2), 137.3 (CH), 138.6 (CH), 147.3 (C), 161.9 (CH), 209.5 (C) ppm.

HRMS (ESI) calculated for $C_{13}H_{18}NO$ 204.1388, found 204.1397 $[M+H]^+$.

***tert*-Butyl (((*3aR*,4S*,7R*,7aR**)-1-oxo-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-2-yl)methyl)carbamate (2f)**



<u>Stoichiometric, thermally activated reaction:</u>

In a round bottom flask and under nitrogen, $Co_2(CO)_8$ (1.25 g, 3.3 mmol, 1.1 eq.) was dissolved in 10 mL of hexanes. *N*-Boc-propargylamine (466 mg, 3 mmol, 1 eq.) was then added, and the mixture was stirred for 45 minutes at room temperature. After this time, norbornadiene (3.24 mL, 30 mmol, 10 eq.) was added, and the system was heated up to 60 °C. After 15h, the reaction reached completion. The solvent was removed under vacuum, and the crude was purified by flash chromatography using mixtures of hexanes/AcOEt of increasing polarity. The product was as a yellow oil that solidified on standing (524 mg, 60%).

Catalytic reaction:

In a 200 mL Büchi pressure reactor, was dissolved *N*-Boc-propargylamine (1.30 g, 9 mmol, 1eq.) in 40 mL of anhydrous toluene. Norbornadiene (3.7 mL, 43 mmol, 5 eq.) and *N*-Boc-propargylamine triphenylphosphine pentacarbonyldicobalt (290 mg, 0.43 mmol, 0.05 eq.) were added. The reactor was loaded with 2 bars of CO and heated up to 80 °C for 48h. After this time, the reactor was emptied and the system was stirred in the open air to oxidize the rests of cobalt. After 2h, the crude was filtered on silica and the solvent was removed. The crude was then purified by flash chromatography using mixtures of hexanes/AcOEt of increasing polarity. The product was obtained as a yellow oil (2.0 g, 85%) that solidified on standing.

Mp: 161-163 °C.

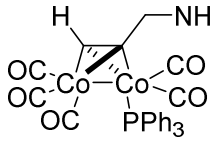
IR (KBr) $\nu_{max.}$ = 3356, 2976, 1694, 1516 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.21 (d, *J* = 9.5 Hz, 1H), 1.39 (d, *J* = 9.4 Hz, 1H), 1.43 (s, 9H), 2.32 (dt, *J* = 5.1 and 1.3 Hz, 1H), 2.71 (m, 1H), 2.76 (m, 1H), 2.92 (m, 1H), 3.81-3.96 (m, 2H), 5.02 (br s, 1H), 6.21 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.29 (dd, *J* = 5.6 and 3.1 Hz, 1H), 7.35 (s, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 28.5 (CH_3), 36.3 (CH_2), 41.3 (CH_2), 43.0 (CH), 43.8 (CH), 48.0 (CH), 53.0 (CH), 79.6 (C), 137.2 (CH), 138.6 (CH), 147.1 (C), 155.9 (C), 160.8 (CH), 209.5 (C) ppm.

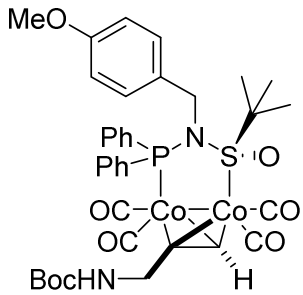
HRMS (ESI) calculated for $C_{16}H_{22}NO_3$ 276.1600, found 276.1600 $[M+H]^+$.

***N*-Boc-propargylamine triphenylphosphine pentacarbonyldicobalt**



In a round bottom flask equipped with a magnetic stirrer $Co_2(CO)_8$ (148 mg, 0.43 mmol, 1 eq.) was put under nitrogen and dissolved in 5 mL of anhydrous toluene. A solution of PPh_3 (114 mg, 0.43 mmol, 1 eq.) in anhydrous toluene (5 mL) were then added *via* canula. The system was protected from the light and stirred for 45 minutes at room temperature. *N*-Boc-propargylamine (50 mg, 0.43 mmol, 1 eq.) was added to the crude complex in one portion, and the reaction was then heated up to 65 °C. Vacuum cycles were performed in order to displace the expelled CO. The solution was stirred until the complete consumption of the starting material was observed by TLC, and the crude complex was used directly in the following reactions with no further purification.

Co_2[μ-(BocNHCH$_2$C$_2$H)](CO)$_4$(μ-$C_{24}H_{28}NO_2PS$) (1f-PNSO)



The dicobalthexacarnobyl complex of *N*-Boc-propargylamine (1.68 g, 3.7 mmol, 1.05 eq.) was dissolved in anhydrous toluene (44 mL) in a 100 mL round bottom flask equipped with magnetic a stirrer and a condenser. The system was put under nitrogen atmosphere and the PNSO ligand (1.49 g, 3.5 mmol, 1 eq.) was added. The system was heated up to 65 °C under vacuum for 23h. The solvent was then removed and residue obtained was digested in hexanes/MeOH. The solid obtained was monitored by ^{1}H-NMR, and the process was repeated until one single diastereomer was observed. The final complex was isolated as a red solid (1.99 g, 70%).

IR (film) $\nu_{max.}$ = 3416, 2921, 2037, 2006, 1978 cm^{-1}

^{1}H-NMR (400 MHz, C_6D_6) δ = 1.21 (s, 9H), 1.52 (s, 9H), 3.22 (s, 3H), 4.32-4.39 (m, 2H), 4.57 (dd, *J* = 18.0 and 9.0 Hz, 1H), 4.71-4.78 (m, 1H), 5.30 (d, *J* = 11.0 Hz, 1H), 6.32-6.38 (m, 4H), 6.88-6.98 (m, 6H), 7.45 (br s, 2H), 7.76-7.81 (m, 2H) ppm.

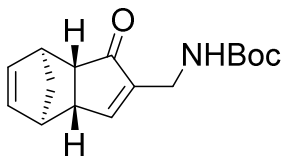
^{13}C-NMR (100 MHz, C_6D_6) δ = 24.4 (CH_3), 28.6 (CH_3), 45.0 (CH_2), 49.5 (d, $^3J_{CP}$ = 5 Hz, CH_2), 54.7 (CH_3), 69.2 (d, $^3J_{CP}$ = 7 Hz, CH), 73.4 (d, $^2J_{CP}$ = 12 Hz, C), 78.8 (C), 108.3 (d, $^2J_{CP}$ = 18 Hz, C), 113.3 (CH), 127.9 (CH), 128.4 (d, $^3J_{CP}$ = 10 Hz, CH), 128.7 (d, $^3J_{CP}$ = 10 Hz, CH), 129.7 (CH), 130.4 (C), 131.3 (CH), 132.0 (d, $^2J_{CP}$ = 12 Hz, CH), 133.94 (d, $^2J_{CP}$ = 16 Hz, CH), 136.3 (d, $^1J_{CP}$ = 35 Hz, C), 136.5 (d, $^1J_{CP}$ = 38 Hz, C), 155.7 (C), 158.3 (C), 199.6 (C), 201.1 (C), 205.1 (C), 208.2 (C) ppm.

^{31}P-NMR (162 MHz, C_6D_6) δ = 115.9 ppm.

HRMS (ESI) calculated for $C_{32}H_{42}Co_2N_2O_4PS$ 699.1261, found 699.1259 $[M+H]^+$.

$[\alpha]_D$ = -22^a (c 0.21, $CHCl_3$).

***tert*-Butyl (((*3aR,4S,7R,7aR*)-1-oxo-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-2-yl)methyl)carbamate ((+)-2f)**



<u>Thermally activated reaction:</u>

In a 250mL round bottom flask with a magnetic stirrer was placed the Co_2[μ-(BocNHCH$_2$C$_2$H)](CO)$_4$(μ-$C_{24}H_{28}NO_2PS$) (2.10 g, 2.60 mmol, 1 eq.). The system was put under nitrogen and the complex was dissolved

in anhydous toluene (130 mL). Norbornadiene (2.7mL, 26 mmol, 10 eq.) wsd added, and the system was heated up to 60 °C for 5h. After this time, the mixture was stirred for 2h in the open air to oxidize the rests of cobalt. The crude was filtered on silica and the solvent was removed under vacuum and purified by flash chromatography using mixtures of hexanes/AcOEt of increasing polarity. The product was obtained as a yellow oil (354 mg, 50% yield, 84-92% ee determined by HPLC*).

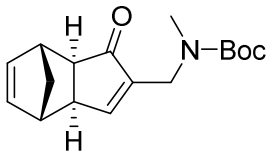
NMO-activated reaction:

In a 100mL round bottom flask with a magnetic stirrer was placed the $Co_2[\mu$-$(BocNHCH_2C_2H)](CO)_4(\mu$-$C_{24}H_{28}NO_2PS)$ (1.97 g, 2.43 mmol, 1 eq.). The system was put under nitrogen and the complex was dissolved in anhydrous dichloromethane (20 mL). Norbornadiene (2.5 mL, 24.3 mmol, 10 eq.) was added, followed by a solution of NMO (1.14 g, 9.72 mmol, 4 eq.) in anhydrous dichloromethane (10 mL). The reaction was stirred at room temperature for 48h. The crude was then filtered on silica to remove the cobalt by-products and it was purified by flash chromatography using mixtures of hexanes/AcOEt of increasing polarity. The desired product was isolated as a yellow oil (350 mg, 52% yield, 84-92% ee determined by HPLC*).

$[\alpha]_D$ = +12[a] (c 0.05, $CHCl_3$)

HPLC*: Chriralpack IA, heptane/EtOH (95:5), 0.5mL/min, λ = 220nm, $t_{R(-)}$ = 28.2 min, $t_{R(+)}$ = 29.3 min.

***tert*-Butyl methyl(((*3aR*,4S*,7R*,7aR**)-1-oxo-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-2-yl)methyl)carbamate (2g)**



In a flask with a magnetic stirrer $Co_2(CO)_8$ (625 mg, 1.64 mmol, 1.1 eq.) and *N*-Boc-*N*-methylpropargylamine (253 mg, 1.50 mmol, 1.0 eq) were dissolved in 3 mL of anhydrous toluene. The system was put under nitrogen and allowed to react for 1h at room temperature. Norbornadiene (1.6 mL, 15.0 mmol, 10 eq) was then added *via* syringe. The system was heated up to 65 °C and allowed to react for 24h. After this time, the crude was purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarity. The final product was isolated as a pale yellow oil (326 mg, 85%).

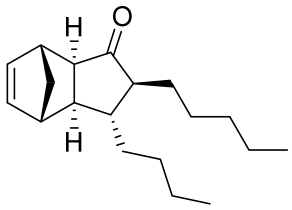
IR (film) $\nu_{max.}$= 2974, 1697, 1481, 1392, 1175, 876 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ= 1.22 (d, *J* = 9.3 Hz, 1H), 1.39-1.50 (m, 10H), 2.34 (d, *J* = 4.9 Hz, 1H), 2.68 (br s, 1H), 2.76 (br s, 1H), 2.85-2.93 (m, 4H), 3.86-4.04 (m, 2H), 6.20 (dd, *J* = 5.7 and 2.9 Hz, 1H), 6.28 (dd, *J* = 5.6 and 3.1 Hz, 1H), 7.20 (br s, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ= 28.6 (CH_3), 35.2 (CH_3), 41.3 (CH_2), 43.1 (CH), 44.8 (CH), 44.6 (CH_2), 48.0 (CH), 53.1 (CH), 79.9 (C), 137.2 (CH), 138.5 (CH), 147.0 (C), 159.7 (CH), 161.0 (C), 209.1 (C) ppm.

HRMS (ESI) calculated for $C_{17}H_{24}NO_3$ 290.1756, found 290.1754 $[M+H]^+$.

(*2S*,3R*,3aR*,4S*,7R*,7aR)-3-Butyl-2-pentyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-one (4)**



a) <u>From **2a**</u>: CuI (77 mg, 0.40 mmol, 2 eq) was put in a round bottom flask with a magnetic stirrer and flame-dried under high vacuum. The system was put under nitrogen and 5 mL of anhydrous ether were added. The suspension was cooled down to -78 °C and a 2.5M solution of BuLi in hexanes (0.32 mL, 0.80 mmol, 1 eq) weas added dropwise. The black suspension was allowed to evolve at low temperature until the Bu_2CuLi was fully formed. Afterwards, a solution of enone **2a** (54 mg, 0.20 mmol, 1 eq.) in 5 mL of anhydrous ether was transferred *via* canula to the cuprate. The system was stirred for one hour at -78 °C and then allowed to warm up to room temperature. The crude was treated with a solution of NH_3/NH_4Cl (1:3) and stirred vigorously in the open air until it reached a deep blue color. The organic layer was separated and the aqueous phase was further extracted with ether. The organic fractions were dried over $MgSO_4$ and filtered. The solvent was removed under vacuum and the crude purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarities. The desired product was isolated as a yellow oil (27 mg, 49%).

b) <u>From **2b**</u>: the same procedure described for **2a** was followed, starting from **2b** (50 mg, 0.80 mmol, 1 eq.) and yielding 31 mg (56%) of the final product.

c) <u>From **2c**</u>: the same procedure described for **2a** was followed, starting from **2c** (133 mg, 0.51 mmol, 1 eq.) and yielding 77 mg (55%) of the final product.

d) <u>From **2e**</u>: the same procedure described for **2a** was followed, starting from **2e** (54 mg, 0.27 mmol, 1 eq.) and yielding 30 mg (40%) of the final product.

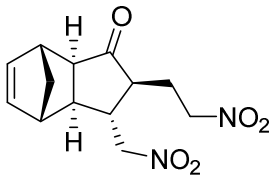
IR (film) $\nu_{max.}$ = 2949, 2930, 2847, 1732, 1457 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.88 (t, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 9.1 Hz, 1H), 1.25-1.60 (m, 15H), 1.67-1.74 (m, 1H), 1.89 (ddd, *J* = 8.7, 5.2 and 2.8 Hz, 1H), 2.17 (s, 1H), 2.29 (dd, *J* = 9.2 and 1.5 Hz, 1H), 2.70 (s, 1H), 3.12 (s, 1H), 6.13 (dd, *J* = 5.7 and 3.0 Hz, 1H), 6.19 (dd, *J* = 5.7 and 3.0 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.3 (CH_3), 14.3 (CH_3), 22.7 (CH_2), 23.3 (CH_2), 26.9 (CH_2), 27.9 (CH_2), 29.9 (CH_2), 32.4 (CH_2) 36.7 (CH_2), 44.9 (CH), 44.9 (CH_2), 45.0 (CH), 47.3 (CH), 48.4 (CH), 54.6 (CH), 59.6 (CH), 137.7 (CH), 138.6 (CH), 219.2 (C) ppm.

HRMS (ESI) calculated for $C_{19}H_{31}O$ 275.2369, found 275.2371 $[M+H]^+$.

(*2S*,3R*,3aR*,4S*,7R*,7aR)-2-(2-Nitroethyl)-3-(nitromethyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-one (5)**



a) From **2a**: 68mg (0.25 mmol, 1 eq) of **2a** were dissolved in 10mL of nitromethane in a round bottom flask with a magnetic stirrer. TBAF·$3H_2O$ (8 mg, 0.025 mmol, 0.1 eq) were added, and the reaction was allowed to progress at room temperature for 24h. The solvent was then removed under reduced pressure and the crude was purified by chromatography on silica gel using mixtures of hexanes/AcOEt of increasing polarities to isolate 61mg of final product as a yellow oil (86%).

b) From **2b**: the same procedure described above was followed, starting from **2b** (48 mg, 0.19 mmol, 1 eq) and using TBAF·$3H_2O$ (6 mg 0.02 mmol, 0.1 eq) in 10 mL of nitromethane. The reaction yielded 53 mg (quantitative) of the desired product after purification.

c) From **2e**: **2e** (163 mg, 0.80 mmol, 1 eq) was dissolved in 5 mL of nitromethane and heated up to 50 °C for 2h and at 80 °C for 3 more hours. After this time, the solvent was removed in vacuo and the crude purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarities to isolate 103 mg of final product as a yellow oil (46%).

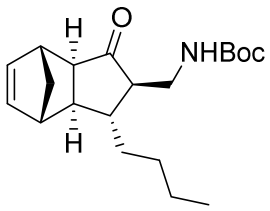
IR (film) $\nu_{max.}$ = 2962, 1726, 1553, 1380 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.04 (d, *J* = 9.5 Hz, 1H), 1.52 (dt, *J* = 9.8 and 1.8 Hz, 1H), 2.12-2.25 (m, 4H), 2.5 (m, 2H), 2.80 (s, 1H), 3.21 (br s, 1H), 4.55 (dd, *J* = 12.0 and 8.0 Hz, 1H), 4.64-4.71 (m, 3H), 6.19 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 25.6 (CH_2), 43.6 (CH), 44.9 (CH), 45.0 (CH_2), 45.2 (CH), 47.4 (CH), 52.7 (CH), 54.4 (CH), 72.7 (CH_2), 79.1 (CH_2), 137.6 (CH), 138.3 (CH), 214.5 (C) ppm.

HRMS (ESI) calculated for $C_{13}H_{17}N_2O_5$ 281.1137, found 281.1123 $[M+H]^+$.

***tert*-Butyl (((*1R*,2R*,3aR*,4R*,7S*,7aR**)-1-butyl-3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-2-yl)methyl)carbamate (6)**



CuI (303 mg, 1.58 mmol, 2 eq) was put in a round bottom flask with a magnetic stirrer and flame-dried under high vacuum. The system was put under nitrogen and 15 mL of anhydrous ether were added. The suspension was cooled down to -78 °C and a 2.5M solution of BuLi in hexanes (1.27 mL, 3.16 mmol, 4 eq) was added dropwise. The black suspension was allowed to evolve at low temperature until the Bu_2CuLi was fully formed. Afterwards, a solution of enone **2f** (219 mg, 0.79 mmol, 1 eq) in anhydrous ether (15 mL) was transferred *via* canula. The system was stirred for one hour at -78 °C and then allowed to warm up to room temperature. The crude was treated with a solution of NH_3/NH_4Cl (1:3) and stirred vigorously in the open air until it reached a deep blue color. The organic layer was separated and the aqueous phase was further extracted with ether. The organic fractions were dried over $MgSO_4$ and filtered. The solvent was removed and the crude purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarities. The desired product was isolated as a yellow oil in a 71% yield (188 mg).

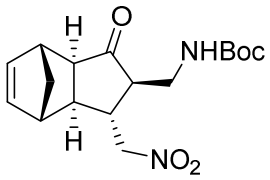
IR (film) $\nu_{max.}$ = 3379, 1713, 1502, 1159 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.93 (t, *J* = 6.9 Hz, 3H), 1.05 (dt, *J* = 9.3 and 1.5 Hz, 1H), 1.35-1.85 (m, 17H), 1.94 (m, 1H), 2.32 (dt, *J* = 9.4 and 1.6 Hz, 1H), 2.39 (br s, 1H), 2.72 (s, 1H), 3.13 (s, 1H), 3.17 (dd, *J* = 13.4 and 6.7 Hz, 1H), 3.37-3.43 (m, 1H), 5.17 (t, *J* = 5.7 Hz, 1H), 6.13 (dd, *J* = 5.7 and 3.0 Hz, 1H), 6.20 (dd, *J* = 5.7 and 3.0 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.2 (CH_3), 23.1 (CH_2), 28.5 (3 CH_3), 29.8 (CH_2), 36.0 (CH_2), 38.3 (CH_2), 42.1 (CH), 44.7 (CH), 44.9 (CH_2), 47.3 (CH), 48.2 (CH), 54.6 (CH), 60.2 (CH), 79.2 (C), 137.5 (CH), 138.7 (CH), 156.2 (C), 219.3 (C) ppm.

HRMS (ESI) calculated for $C_{20}H_{31}NNaO_3$ 356.2202, found 356.2198 $[M+Na]^+$.

***tert*-Butyl (((*1R*,2R*,3aR*,4R*,7S*,7aR**)-1-(nitromethyl)-3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-2-yl)methyl)carbamate (7)**



2f (53 mg, 0.20 mmol, 1 eq.) was dissolved in 10 mL of nitromethane in a round bottom flask with a magnetic stirrer. TBAF·$3H_2O$ (6 mg, 0.02 mmol, 0.1 eq.) were added, and the reaction was allowed to progress at room temperature for 24h. The solvent was then removed under reduced pressure and the crude was purified by chromatography on silica gel using mixtures of hexanes/AcOEt of increasing polarities to isolate 64 mg of final product as a yellow oil (quantitave).

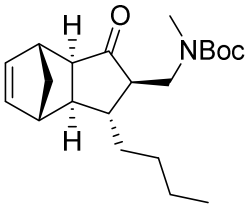
IR (film) $\nu_{max.}$ = 3379, 1732, 1700, 1547, 1502 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.05 (d, *J* = 9.4 Hz, 1H), 1.40-1.48 (m, 10H), 2.25 (m, 2H), 2.43 (m, 1H), 2.61 (m, 1H), 2.80 (s, 1H), 3.19 (br s, 1H), 3.38 (m, 2H), 4.60 (dd, *J* = 12.0 and 8.0 Hz, 1H), 4.84 (dd, *J* = 12.0 and 3.0 Hz, 1H), 4.98 (m, 1H), 6.18 (dq, *J* = 5.7 and 2.9 Hz, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 28.4 (CH_3), 37.0 (CH_2), 40.3 (CH), 44.6 (CH), 44.8 (CH_2), 44.9 (CH), 47.5 (CH), 54.5 (CH), 57.1 (CH), 78.8 (CH_2), 79.9 (C), 137.7 (CH), 138.6 (CH), 156.6 (C), 215.1 (C) ppm.

HRMS (ESI) calculated for $C_{17}H_{25}N_2O_5$ 337.1763, found 337.1765 $[M+H]^+$.

***tert*-Butyl (((*1R*,2R*,3aR*,4R*,7S*,7aR**)-1-butyl-3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-2-yl)methyl)(methyl)carbamate (8)**



CuI (65 mg, 0.34 mmol, 2 eq.) was put in a round bottom flask with a magnetic stirrer and flame-dried under high vacuum. The system was put under nitrogen and 5 mL of anhydrous THF were added. The suspension was cooled down to -78 °C and a 2.5M solution of BuLi in hexanes (0.30 mL, 0.68 mmol, 4 eq.) was added dropwise to the suspension. The black suspension was allowed to evolve at low temperature until the Bu_2CuLi was fully formed. Afterwards, a solution of enone **2g** (50 mg, 0.17 mmol, 1 eq.) in anhydrous THF (4 mL) was transferred *via* canula. The system was stirred for one hour at -78 °C and then allowed to warm up to room temperature. The crude was treated with a solution of NH_3/NH_4Cl (1:3) and stirred vigorously in the open air until it reached a deep blue color. The organic layer was separated and the aqueous phase was further extracted with ether. The organic fractions were dried over $MgSO_4$ and filtered. The solvent was removed and the crude purified by silica gel chromatography

using mixtures of hexanes/AcOEt of increasing polarities. The desired product was isolated as a colorless oil in a 89% yield (54 mg).

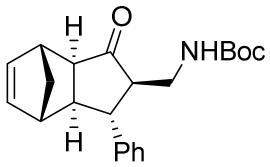
IR (film) $\nu_{max.}$ = 2962, 2917, 2853, 1720, 1707 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ= 0.94 (t, *J* = 6.9 Hz, 3H), 1.03-1.60 (m, 17H), 1.75 (m, 1H), 1.93 (m, 1H), 2.33 (m, 1H), 2.50 (br s, 1H), 2.73 (s, 1H), 2.86 (d, *J* = 7.0 Hz, 3H), 3.13 (s, 1H), 3.32-3.61 (m, 2H), 6.14 (m, 1H), 6.21 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ= 14.4 (CH_3), 23.3 (CH_2), 28.7 (3xCH_3), 29.9 (CH_2), 30.0 (CH_2)^{*Rotamer}, 35.3 (CH_3), , 35.6 (CH_3)^{*Rotamer}, 36.8 (CH_2), 36.9 (CH_2)^{*Rotamer}, 44.2 (CH), 44.3 (CH)^{*Rotamer}, 45.0 (CH_2), 45.4 (CH), 47.5 (CH), 47.7 (CH_2), 47.9 (CH_2)^{*Rotamer}, 48.7 (CH), 54.9 (CH), 58.5 (CH), 58.9 (CH)^{*Rotamer}, 79.5 (C), 79.9 (C)^{*Rotamer}, 137.6 (CH), 138.6 (CH), 138.7 (CH)^{*Rotamer}, 159.9 (C), 156.1 (C)^{*Rotamer}, 218.1 (C) ppm, 218.5 (C)^{*Rotamer} ppm.

HRMS (ESI) calculated for $C_{21}H_{33}NO_3$ 347.2458, found 347.2460 $[M+H]^+$.

***tert*-Butyl (((*2R*,3R*,3aR*,4S*,7R*,7aR**)-1-oxo-3-phenyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-2-yl)methyl)carbamate (9)**



In a three-neck round bottom flask flame-dried, with a magnetic stirrer and an addition funnel were placed magnesium (340 mg, 14 mmol, 35 eq.) and a little iodine crystal. The system was put under nitrogen and a solution of phenyl bromide (1.34 mL, 12 mmol, 30 eq.) in anhydrous THF (10 mL) were added dropwise with an addition funnel. Once the addition was complete, the reaction was stirred for 1h at 40 °C.

At the same time, CuI (10 mg, 0.04 mmol, 0.1 eq.) were suspended in anhydrous THF (5 mL) in a Shlenk type flask previously flame-dried under vacuum. The suspension was cooled down to -78 °C and the Grignard reagent was added to it *via* canula. The temperature was allowed to rise gradually to 0 °C, and the system was then cooled down to -50 °C. Once at this temperature, **2f** (100 mg, 0.36 mmol, 1 eq.) dissolved in anhydrous THF (2 mL) were added with a canula. The temperature was allowed to rise slowly for 2h. The crude was treated with a solution of NH_3/NH_4Cl (1:3) and stirred vigorously in the open air until it reached a deep blue color. The organic layer was separated and the aqueous phase was further extracted with ether. The organic fractions were dried over $MgSO_4$ and filtered. The solvent was removed and the crude purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarities. The desired product was isolated as a yellow oil in a 77% yield (98 mg).

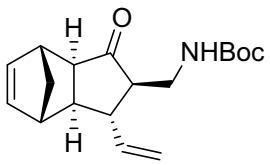
IR (film) $\nu_{max.}$ = 2969, 1726, 1502, 1169 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ= 1.20-1.54 (m, 12 H), 2.39 (t, *J* = 8.3 Hz, 1 H), 2.51-2.62 (m, 2H), 2.84 (s, 1H), 2.93-3.01 (m, 1H), 3.24 (m, 2H), 5.04 (br s, 1H), 6.12 (dd, *J* = 5.7 and 3.0 Hz, 1H), 6.17 (dd, *J* = 5.7 and 3.0 Hz, 1H), 7.31-7.40 (m, 5H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 28.6 (CH_3), 38.2 (CH_2), 44.9 (CH_2), 45.0 (CH), 47.1 (CH), 49.5 (CH), 49.8 (CH), 54.7 (CH), 61.7 (CH), 79.3 (C), 127.2 (CH), 127.9 (2 CH), 129.1 (2 CH), 137.7 (CH), 138.8 (CH), 143.7 (C), 156.2 (C), 217.9 (C) ppm.

HRMS (ESI) calculated for $C_{22}H_{27}NO_3$ 353.1988, found 353.1991 $[M+H]^+$.

***tert*-Butyl (((*2R*,3R*,3aR*,4S*,7R*,7aR**)-1-oxo-3-vinyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-2-yl)methyl)carbamate (10)**



CuI (15 mg, 0.08 mmol, 0.1 eq.) were put in a round bottom flask with a magnetic stirrer and flame-dried under high vacuum. The system was put under nitrogen and the CuI was suspended in anhydrous ether (15 mL). The suspension was cooled down to -78 °C and a 1.0M solution of vinyl magnesium bromide in THF (1.58 mL, 1.58 mmol, 2 eq.) was added dropwise. The black suspension was allowed to evolve at low temperature until the cuprate was formed. A solution of enone **2f** (218 mg, 0.76 mmol, 1 eq.) in anhydrous ether (15 mL) was then transferred *via* canula. The system was stirred at -78 °C until no starting material could be detected by TLC and then allowed to warm up to room temperature. The crude was treated with a solution of NH_3/NH_4Cl (1:3) and stirred vigorously in the open air until it reached a deep blue color. The organic layer was separated and the aqueous phase was further extracted with ether. The organic fractions were dried over $MgSO_4$ and filtered. The solvent was removed and the crude purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarities. The desired product was isolated as a yellow oil in a 20% yield (48 mg).

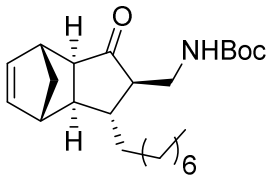
IR (film) $\nu_{max.}$ = 3410, 2958, 1718, 1170 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.10 (d, *J* = 9.1 *Hz,* 1H), 1.42 (s, 9H), 1.46 (m, 1H), 2.01 (m, 1H), 2.11 (m*,* 1H), 2.35 (m, 1H), 2.60 (m, 1H), 2.79 (s, 1H), 3.18 (m, 2H), 3.36 (m, 1H), 5.15 (m, 2H), 5.87 (ddd, *J* = 16.9, 10.0 and 8.1 Hz, 1H), 6.15 (dd, *J* = 5.7 and 2.9 Hz, 1H), 6.19 (dd, *J* = 5.7 and 3.0 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 28.5 (CH_3), 37.8 (CH_2), 44.5 (CH), 45.0 (CH_2), 46.4 (CH), 46.9 (CH), 47.7 (CH), 54.0 (CH), 59.2 (CH), 79.3 (C), 116.4 (CH_2), 137.6 (CH), 138.6 (CH), 140.2 (CH), 156.1 (C), 217.6 (C) ppm.

HRMS (ESI) calculated for $C_{18}H_{26}NO_3$ 304.1907, found 304.1907 $[M+H]^+$.

***tert*-Butyl (((*1R*,2R*,3aR*,4R*,7S*,7aR**)-1-octyl-3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-2-yl)methyl)carbamate (11)**



In a three-neck round bottom flask flame-dried, with a magnetic stirrer, an addition funnel and a condenser were placed magnesium (334 mg, 14.0 mmol, 35 eq.) and a little iodine crystal. The system was put under nitrogen and bromooctane (2 mL, 12.0 mmol, 30 eq.) was added dropwise with the addition funnel. Once the addition was complete, 10 mL of dry THF were added to the reaction mixture and it was stirred for 1h at 40 °C.

At the same time, CuI (4 mg, 0.02 mmol, 0.1 eq.) were suspended in 5 mL of anhydrous THF in a Shlenk type flask previously flame-dried under vacuum. The suspension was cooled down to -78 °C and the Grignard reagent was added to it *via* canula. The temperature was allowed to rise gradually until a clear and transparent solution was obtained, and the system was then cooled down to -65 °C. Once at this temperature, a solution of **2f** (50mg, 0.18 mmol, 1 eq) in anhydrous THF (2 mL) was added with a canula. The temperature was allowed to rise slowly until no starting material could be detected by TLC. The crude was treated with a solution of NH_3/NH_4Cl (1:3) and stirred vigorously in the open air until it reached a deep blue color. The organic layer was separated and the aqueous phase was further extracted with ether. The organic fractions were dried over $MgSO_4$ and filtered. The solvent was removed and the crude purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarities. The desired product was isolated as a yellow oil in a 74% yield (52 mg).

IR (film) $\nu_{max.}$ = 2971, 2853, 1713, 1502, 1361, 1169 cm^{-1}.

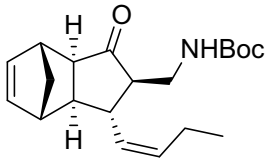
^{1}H-NMR (400 MHz, $CDCl_3$) δ= 0.89 (m, 3H), 1.06 (d, *J* = 9.2 Hz, 1H), 1.20-1.84 (m, 25H), 1.94 (dd, *J* = 9.1 and 5.5 Hz, 1H), 2.33 (m, 1H), 2.39 (br s, 1H), 2.73 (s, 1H), 3.13 (s, 1H), 3.18 (m, 1H), 3.39 (m, 1H), 5.17 (br s, 1H), 6.14 (dd, *J* = 3.0 and 6.0 Hz, 1H), 6.21 (dd, *J* = 3.0 and 60. Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ= 14.3 (CH_3), 22.9 (CH_2), 27.7 (CH_2), 28.6 (3 CH_3), 29.6 (CH_2), 29.8 (CH_2), 30.1 (CH_2), 32.1 (CH_2), 36.4 (CH_2), 38.4 (CH_2), 42.1 (CH), 44.8 (CH),

45.0 (CH_2), 47.3 (CH), 48.3 (CH), 54.7 (CH), 60.3 (CH), 79.3 (C), 137.6 (CH), 138.7 (CH), 156.2 (C), 219.3 (C) ppm.

HRMS (ESI) calculated for $C_{24}H_{39}NO_3$ 389.2918, found 389.2930 $[M+H]^+$.

***tert*-Butyl (((*1R,2R,3aR,4R,7S,7aR*)-1-((Z)-but-1-en-1-yl)-3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-2-yl)methyl)carbamate (13)**



CuI (348 mg, 1.83 mmol, 5 eq.) was placed in a three-neck round bottom flask with a magnetic stirrer. The flask was flame-dried under vacuum and put under nitrogen, and the CuI was suspended in anhydrous THF (15 mL). It was cooled down to -78 °C and a 0.5M solution of EtLi in benzene (7 mL, 2.66 mmol, 10 eq.) was added dropwise. The temperature was allowed to rise up until the solution became deep blue. It was cooled down to -78 °C again and acetylene (previously dried by bubbling it though concentrated H_2SO_4) was bubbled through the cupprate solution until it turned deep green. A solution of **2f** (100 mg, 0.36 mol, 1 eq.) in anhydrous THF (10 mL) was added to the mixture with a canula. The system was stirred for 2h, until no starting material could be detected by TLC. The crude was treated with a solution of NH_3/NH_4Cl (1:3) and stirred vigorously in the open air until it reached a deep blue color. The organic layer was separated and the aqueous phase was further extracted with ether. The organic fractions were dried over $MgSO_4$ and filtered. The solvent was removed and the crude purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarities. The desired product was isolated as a yellow oil in a 86% yield (103 mg).

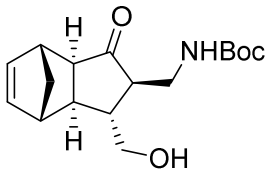
IR (film) $\nu_{max.}$ = 2963, 2924, 2868, 1726, 1489 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ= 1.01 (dt, *J* = 2.8 and 7.6 Hz, 3H), 1.15 (d, *J* = 9.0 Hz, 1H), 1.26 (s, 2H), 1.42 (s, 9H), 2.01-2.11 (m, 2H), 2.29-2.36 (m, 2H), 2.57 (br s, 1H), 2.74 (s, 1H), 3.07-3.19 (m, 2H), 3.31 (br s, 1H), 5.17 (br s, 1H), 5.29-5.60 (m, 2H), 6.16 (br s, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ= 14.8 (CH_3), 21.1 (CH_2), 28.6 (3 CH_3), 29.9 (CH_2), 41.3 (CH), 44.3 (CH), 45.1 (CH_2), 46.5 (CH), 47.7 (CH), 54.0 (CH), 59.8 (CH), 79.2 (C), 131.6 (CH), 134.1 (CH), 137.6 (CH), 138.6 (CH), 156.0 (C), 217.6 (C) ppm.

HRMS (ESI) calculated for $C_{20}H_{29}NO_3$ 331.2147,found 331.2148 $[M+H]^+$.

tert-Butyl (((*1R*,2R*,3aR*,4R*,7S*,7aR)-1-(hydroxymethyl)-3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-2-yl)methyl)carbamate (14)**



2f (300 mg, 1.10 mmol, 1 eq.) and benzophenone (200 mg, 1.10 mmol, 1 eq.) were disolved in anhydrous methanol (50 mL) in a round bottom flask, and a nitrogen flow was bubbled though the solution for 45 minutes. After this time, the flask was irradiated at 350 nm in a Rayonet © photochemical reactor for 3h. After this time, the solvent was evaporated and the crude purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarities. The final product was isolated as a colorless oil (248 mg, 73%).

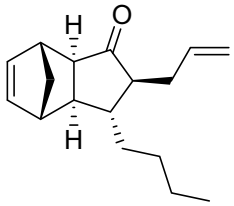
IR (film) $\nu_{max.}$ = 3385, 2975, 2936, 2873, 1713, 1688, 1515, 1169 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.06 (d, *J* = 9.2 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 1H), 1.41 (m, 11H), 1.70 (m, 1H), 1.99 (t, *J* = 8.1 Hz, 1H), 2.34 (dt, *J* = 9.3 and 1.5 Hz, 1H), 2.67 (m, 1H), 2.77 (s, 1H), 3.16 (s, 1H), 3.34-3.48 (m, 2H), 3.73 (dd, *J* = 7.2 and 10.8 Hz, 1H), 3.96 (dd, *J* = 4.8 and 10.8 Hz, 1H), 6.15 (dd, *J* = 3.2 and 5.6 Hz, 1H), 6.20 (dd, *J* = 2.8 and 5.6 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 28.5 (CH_3), 38.5 (CH_2), 43.3 (CH), 44.5 (CH), 45.0 (CH_2), 45.1 (CH), 47.6 (CH), 54.3 (CH), 58.6 (CH), 66.3 (CH_2), 80.0 (C), 137.6 (CH), 138.8 (CH), 157.3 (C), 218.1 (C) ppm.

HRMS (ESI) calculated for $C_{17}H_{26}NO_4$ 308.18563, found 308.18555 $[M+H]^+$.

(*2S*,3R*,3aR*,4S*,7R*,7aR)-2-Allyl-3-butyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-one (15)**



6 (95 mg, 0.28 mmol, 1 eq.) was placed in a round bottom flask provided with a magnetic stirrer and dissolved in the commercially available 1.25M solution of HCl/MeOH (5 mL). The mixture was stirred for 24h at room temperature. The solvent was removed under vacuum and the remaining solid was dissolved in 10 mL of DMF in a round bottom flask. MeI (0.09 mL, 1.40 mmol, 5 eq.) and $NaHCO_3$ (120 mg, 1.40 mmol, 5 eq.) were added in one portion and the mixture was stirred for 17h at room temperature. The crude was treated with water and dichloromethane. The organic layer was separated and further washed with water, dried over $MgSO_4$, filtered and evaporated. The remaining residue was dissolved in 5 mL of anhydrous ether and transferred *via* canula to an ethereal solution of divynil lithium cuprate (0.55 mmol, 2

eq.) prepared as described in the procedure to synthesize **5g**. Upon consumption of the starting material, the crude was treated with a solution of NH_3/NH_4Cl (1:3) and stirred vigorously in the open air until it reached a deep blue color. The organic layer was separated and the aqueous phase was further extracted with ether. The organic fractions were dried over $MgSO_4$ and filtered. The solvent was removed and the crude purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarities. The desired product was isolated as a yellow oil in a 30% yield (20 mg).

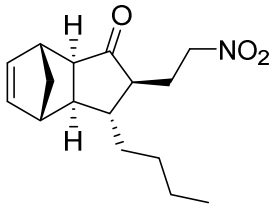
IR (film) $\nu_{max.}$ = 3052, 2971, 2847, 1726 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.94 (t, *J* = 7.0 Hz, 3H), 1.05 (d, *J* = 9.0 Hz, 1H), 1.25-1.38 (m, 7H), 1.69-1.74 (m, 1H), 1.91 (m, 1H), 2.32 (m, 4H), 2.71 (s, 1H), 3.13 (s, 1H), 4.99-5.07 (m, 2H), 5.75 (m, 1H), 6.14 (dd, *J* = 5.7 and 3.0 Hz, 1H), 6.20 (dd, *J* = 5.7 and 3.0 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.2 (CH_3), 23.1 (CH_2), 29.7 (CH_2), 32.0 (CH_2), 36.2 (CH_2), 43.8 (CH), 45.0 (CH_2), 45.0 (CH), 47.2 (CH), 48.4 (CH), 54.4 (CH), 59.0 (CH), 116.9 (CH_2), 135.9 (CH), 137.6 (CH), 138.6 (CH), 218.1 (C) ppm.

HRMS (ESI) calculated for $C_{17}H_{25}O$ 245.1900, found 245.1900 $[M+H]^+$.

***(2S*,3R*,3aR*,4S*,7R*,7aR*)*-3-Butyl-2-(2-nitroethyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-one (16)**



In a round bottom flask provided with a magnetic stirrer **6** (140mg, 0.37 mmol, 1 eq.) was dissolved in the commercially available 1.25M solution of HCl/MeOH (5 mL). The mixture was stirred for 24h at room temperature. The solvent was removed under vacuum. The remaining solid was dissolved in 10 mL of DMF, and MeI (0.20 mL, 3.20 mmol, 9 eq.) and $NaHCO_3$ (267 mg, 3.18 mmol, 10 eq.) were added. The mixture was stirred for 17h at room temperature. The crude was treated with water and dichloromethane. The organic layer was separated and further washed with water, dried over $MgSO_4$, filtered and evaporated. The remaining residue was dissolved in 10 mL of nitromethane and TBAF·$3H_2O$ (20 mg, 0.06 mmol, 0.2 eq.) was added. The solution was stirred at 75 °C for 2h, the solvent was removed under vacuum and the crude purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarities to isolate 84 mg of the final product as a colorless oil (82%).

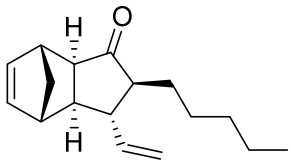
IR (film) $\nu_{max.}$ = 2956, 2930, 1726, 1547 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.96 (t, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 9.2 Hz, 1H), 1.24-1.56 (m, 7H), 1.69-1.75 (m, 1H), 1.96 (m, 1H), 2.05-2.21 (m, 2H), 2.30-2.36 (m, 2H), 2.73 (s, 1H), 3.14 (s, 1H), 4.55-4.70 (m, 2H), 6.14 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.21 (dd, *J* = 5.6 and 3.0 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.2 (CH_3), 23.1 (CH_2), 29.7 (CH_2), 32.0 (CH_2), 36.2 (CH_2), 43.8 (CH), 45.0 (CH_2), 45.0 (CH), 47.2 (CH), 48.4 (CH), 54.4 (CH), 59.0 (CH), 116.9 (CH_2), 135.9 (CH), 137.6 (CH), 138.6 (CH), 218.1 (C) ppm.

HRMS (ESI) calculated for $C_{16}H_{24}NO_3$ 278.17507, found 278.17558 $[M+H]^+$.

***(2S*,3R*,3aR*,4S*,7R*,7aR*)*-2-Pentyl-3-vinyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-one (17)**



In a round bottom flask provided with a magnetic stirrer was dissolved **10** (39 mg, 0.13 mmol, 1 eq.) in the commercially available 1.25M solution of HCl/MeOH (5 mL). The mixture was stirred for 24h at room temperature. The solvent was removed under vacuum and the remaining solid was dissolved in 10 mL of DMF, and MeI (0.04 mL, 0.65 mmol, 5 eq.) and $NaHCO_3$ (54 mg, 0.65 mmol, 5 eq.) were added. The mixture was stirred for 17h at room temperature. The crude was treated with water and dichloromethane. The organic layer was separated and further washed with water, dried over $MgSO_4$, filtered and evaporated. The remaining residue was dissolved in 5 mL of anhydrous ether and transferred *via* canula to an ethereal solution of dibutyl lithium cuprate (0.26 mmol, 2 eq.) prepared as described in the procedure to synthesize **5a**. Upon consumption of the starting material, the crude was treated with a solution of NH_3/NH_4Cl (1:3) and stirred vigorously in the open air until it reached a deep blue color. The organic layer was separated and the aqueous phase was further extracted with ether. The organic fractions were dried over $MgSO_4$ and filtered. The solvent was removed and the crude purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarities. The desired product was isolated as a yellow oil in a 25% yield (8 mg).

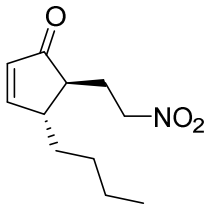
IR (film) $\nu_{max.}$ = 3058, 2924, 2853, 1739 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.87 (m, 3H), 1.11 (d, *J* = 9.1 Hz, 1H), 1.23-1.44 (m, 9H), 1.92-2.05 (m, 2H), 2.31 (dt, *J* = 9.1 and 1.6 Hz, 1H), 2.38 (m, 1H), 2.77 (s, 1H), 3.15 (s, 1H), 5.04-5.10 (m, 2H), 5.84 (ddd, *J* = 16.9, 10.0 and 8.3 Hz, 1H), 6.16 (dq, *J* = 5.7and 3.0 Hz, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.2 (CH_3), 22.6 (CH_2), 26.6 (CH_2), 27.3 (CH_2), 32.2 (CH_2), 44.7 (CH), 44.9 (CH_2), 46.4 (CH), 46.9 (CH), 50.8 (CH), 53.8 (CH), 58.7 (CH), 115.2 (CH_2), 137.7 (CH), 138.4 (CH), 142.1 (CH), 217.4 (C) ppm.

HRMS (ESI) calculated for $C_{34}H_{49}O_2$ 489.3727, found 489.3727 $[2M+H]^+$.

(*4R*,5S)-4-butyl-5-(2-nitroethyl)cyclopent-2-en-1-one (18)**



A microwave vial was purged with nitrogen and equipped with a magnetic stirrer. In it, **17** (30 mg, 0.10mmol, 1 eq.) and maleic anhydride (108 mg, 1.10 mmol, 11 eq.) were dissolved in anhydrous dichloromethane (4 mL). The vial was sealed and the commercially available solution of $MeAlCl_2$ 1M in hexanes (0.06 mL, 0.10 mmol, 1 eq.) was added through the seal. The system was irradiated with microwaves (250W, 110 °C) for 60 sec. The crude was then rapidly mixed with a saturated solution of $NaHCO_3$ and stirred for 20 minutes in the open air. The organic fraction was separated and the aqueous phase was further extracted with Et_2O. The organic layers were dried ($MgSO_4$) and filtered. Solvent removal followed by flash chromatography (hexanes/AcOEt) yielded the product as a colorless oil (14 mg, 67%).

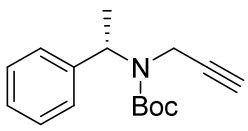
IR (film) $\nu_{max.}$ = 2950, 2924, 2853, 1700, 1553 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.93 (t, *J* = 7.3 Hz, 3H), 1.36-1.40 (m, 6H), 2.03 (m, 1H), 2.17-2.35 (m, 2H), 2.57 (m, 1H), 4.61-4.74 (m, 2H) ,6.13 (dd, *J* = 2.1 and 6.7 Hz, 1H) , 7.62 (dd, *J* = 2.0 and 6.4 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.1 (CH_3), 22.7 (CH_2), 28.5 (CH_2), 29.7 (CH_2), 34.0 (CH_2), 48.2 (CH), 48.4 (CH), 73.2 (CH_2), 132.8 (C), 167.1 (C), 210.4 (C) ppm.

HRMS (ESI) calculated for $C_{11}H_{18}NO_3$ 212.1281, found 212.1283 $[M+H]^+$.

***tert*-butyl *(S)*-(1-phenylethyl)(prop-2-yn-1-yl)carbamate (25)**



To a solution of commercially available *(S)*-1-phenylethan-1-amine (0.11mL, 0.82 mmol, 1.02 eq.) in acetonitrile (1.5 mL) in a round bottom flask provided with a magnetic stirrer was added K_2CO_3 (136 mg, 0.99 mmol, 1.2 eq.) as a solid, followed propargyl bromide (0.07mL, 0.80 mmol, 1 eq.). The system was allowed to stir at room temperature for 2h. Water and AcOEt were added, and the organic fraction was separated and washed with more water. It was dried with $MgSO_4$ and the solvent was removed under vacuum. The crude was purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing

polarity as eluent. The alkylated amine (103 mg, 0.65 mmol, 1 eq.) was dissolved in anhydrous dichloromethane (3 mL) and put under nitrogen. A solution of Boc_2O (118 mg, 0.68 mmol, 1.05 eq.) and DMAP (1.6 mg, 0.01 mmol, 0.02 eq.) of in dry dichloromethane (2 mL) was added to the amine dropwise. The reaction was heated up to 45 °C and allowed to proceed overnight. The solvent was then removed under vacuum and the crude was purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarity to obtain the final product as a colorless oil (68 mg, 37%).

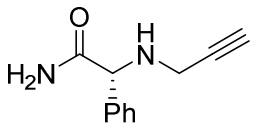
IR (KBr) $\nu_{max.}$ = 3291, 2980, 1791, 1729, 1146 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.42 (s, 9H), 1.58 (d, *J* = 7.1 Hz, 3H), 2.05 (t, *J* = 2.4 Hz, 1H), 3.46 (br s, 1H), 3.91 (br s, 1H), 5.36 (br s, 1H), 7.17-7.30 (m, 5H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 16.7 (CH_3), 27.5 (CH_3), 28.4 (CH_3)^{*Rotamer}, 33.1 (CH_2), 54.8 (CH), 72.0 (CH), 79.1 (C), 80.3 (C), 128.0 (CH), 128.3 (CH), 128.5 (CH), 147.3 (C), 155.1 (C) ppm.

HRMS (ESI) calculated for $C_{16}H_{22}NO_2$ 260.1645, found 260.2646 $[M+H]^+$.

***(R)*-2-phenyl-2-(prop-2-yn-1-ylamino)acetamide (26)**



(R)-2-amino-2-phenylacetamide (123 mg, 0.82 mmol, 1.02 eq.) and K_2CO_3 (136 mg, 0.99 mmol, 1.02 eq.) were suspended in acetonitrile (1.5 mL) in a round-bottom flask provided with a magnetic stirrer. Propargyl bromide (0.07 mL, 0.80 mmol, 1 eq.) was added dropwise to the suspension, and the mixture was allowed to stir for 7h. The solvent was removed under reduced pressure, and the crude was parted into water and AcOEt. The organic layer was further washed with water, dried ($MgSO_4$) and filtered. The solvent was removed under vacuum and the remaining residue was purified by silica gel chromatography with mixtures of hexanes/AcOEt as eluent. The final product was isolated as a white solid (63 mg, 42%), along with the undesired dialkylated amine (29 mg, 16%).

Mp: 143-145 °C.

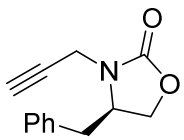
IR (KBr) $\nu_{max.}$ = 3340, 3257, 3154, 2853, 1656 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.26 (t, *J* = 2.4 Hz, 1H), 3.22-3.61 (m, 2H), 4.48 (s, 1H), 5.49 (br s, 1H), 6.62 (br s, 1H), 7.31-7.44 (m, 5H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 36.6 (CH), 65.6 (CH_2), 72.3 (CH), 81.0 (C), 127.7 (CH), 128.5 (CH), 129.0 (CH), 138.2 (C), 174.1 (C) ppm.

HRMS (ESI) calculated for $C_{11}H_{13}N_2O$ 189.1022, found 189.1023 $[M+H]^+$.

***(R)*-4-benzyl-3-(prop-2-yn-1-yl)oxazolidin-2-one (27)**



In a round bottom flask provided with a magnetic stirrer and nitrogen atmosphere NaH (78 mg, 1.97 mmol, 1.2 eq.) was suspended in anhydrous THF (10 mL). *(R)*-4-benzyloxazolidin-2-one (290 mg, 1.64 mmol, 1 eq.) was dissolved in anhydrous THF (3 mL) and transfered *via* canula to the suspension of NaH. The mixture was stirred at room temperature for 30 minutes before adding propargyl bromide (0.28 mL, 3.28 mmol, 2 eq.). The reaction was allowed to progress at room temperature for 24h. The crude was filtered through a celite pad and the solvent was removed in vacuo. The remaining residue was purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarities to yield 215 mg (57%) of the final product as a colorless oil.

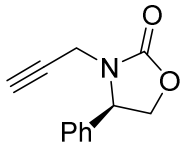
IR (film) $\nu_{max.}$ = 3283, 2917, 1745, 1431, 1246 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.34 (t, *J* = 2.5 Hz, 1H), 2.67-2.73 (m, 1H), 3.24 (dd, *J* = 13.5 and 3.9 Hz, 1H)3.83 (dd, *J* = 17.8 and 2.4 Hz, 1H), 4.03 (m, 1H), 4.18-4.25 (m, 2H), 4.43 (dd, *J* = 17.8 and 2.5 Hz, 1H), 7.18-7.36 (m, 5H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 32.5 (CH_2), 38.3 (CH_2), 56.6 (CH), 67.2 (CH_2), 73.4 (CH), 76.8 (C), 127.3 (CH), 128.9 (CH), 129.0 (CH), 132.3 (C), 157.7 (C) ppm.

HRMS (ESI) calculated for $C_{13}H_{14}NO_2$ 216.1019, found 216.1021 $[M+H]^+$.

***(R)*-4-phenyl-3-(prop-2-yn-1-yl)oxazolidin-2-one (28)**



(R)-4-phenyloxazolidin-2-one (400 mg, 2.46 mmol, 1 eq.) was dissolved in anhydrous THF (20 mL) in a round bottom flask with a magnetic stirrer and nitrogen atmosphere. The solution was cooled down to 0 °C and the commercially available 2.5M solution of BuLi in hexanes (1 mL, 2.50 mmol, 1.02 eq.) was added dropwise. The temperature was allowed to rise up for an hour and, once at room temperature, propargyl bromide (0.32 mL, 2.96 mmol, 1.2 eq.) was added to the solution. The reaction was allowed to progress overnight and the solvent was removed under vacuum. The crude was purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarities. The final product (395 mg, 80%) was isolated as a colorless oil.

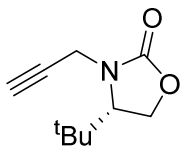
IR (film) $\nu_{max.}$ = 3283, 3033, 2911, 2584, 1752 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.25 (t, *J* = 2.5 Hz, 1H), 3.39 (dd, *J* = 17.7 and 2.0 Hz, 1H), 4.16 (dd, *J* = 8.7 and 7.8 Hz, 1H), 4.41 (dd, *J* = 17.7 and 1.9 Hz, 1H), 4.67 (t, *J* = 8.8 Hz, 1H), 4.97 (dd, *J* = 8.8 and 7.8 Hz, 1H), 7.33-7.45 (m, 5H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 32.0 (CH_2), 59.0 (CH), 69.9 (CH_2), 73.2 (CH), 76.6 (C), 127.2 (CH), 129.3 (CH), 129.4 (CH), 136.6 (C), 157.7 (C) ppm.

HRMS (ESI) calculated for $C_{11}H_{12}NO_2$ 202.0863, found 202.0863.

***(S)*-4-(tert-butyl)-3-(prop-2-yn-1-yl)oxazolidin-2-one (29)**



(S)-4-(tert-butyl)oxazolidin-2-one (100 mg, 0.70 mmol, 1 eq.) was dissolved in anhydrous THF (10 mL) in a round bottom flask with a magnetic stirrer and nitrogen atmosphere. The solution was cooled down to 0 °C and the commercially available 2.5M solution of BuLi in hexanes (0.28 mL, 0.70 mmol, 1 eq.) was added dropwise. The temperature was allowed to rise up for an hour and, once at room temperature, propargyl bromide (0.09 mL, 0.70 mmol, 1.2 eq.) was added to the solution. The reaction was allowed to progress overnight at room temperature and the solvent was removed under vacuum. The crude was purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarities. The final product (120 mg, 94%) was isolated as a yellow oil.

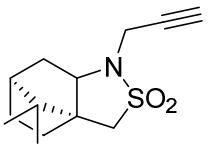
IR (film) $\nu_{max.}$ = 3283, 3244, 2962, 1745 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.00 (s, 9H), 2.34 (t, *J* = 2.5Hz, 1H), 3.73 (dd, *J* = 9.1 and 5.9 Hz, 1H), 3.91 (dd, *J* = 17.9 and 2.4 Hz, 1H), 4.13 (dd, *J* = 9.0 and 5.9 Hz, 1H), 4.17 (t, *J* = 9.1Hz, 1H), 4.54 (dd, *J* = 17.9 and 2.6 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 25.7 (CH_3), 34.3 (C), 35.6 (CH_2), 62.9 (CH), 64.8 (CH_2), 73.8 (CH), 77.3 (C), 159.2 (C) ppm.

HRMS (ESI) calculated for $C_{10}H_{16}NO_2$ 182.1176, found 182.1176 $[M+H]^+$.

(*3aR,6S*)-8,8-dimethyl-1-(prop-2-yn-1-yl)hexahydro-3H-3a,6-methanobenzo[c]isothiazole 2,2-dioxide (30)



(1R)-(+)-2,10-Camphorsultam (100 mg, 0.47 mmol, 1 eq.) was dissolved in anhydrous THF (5 mL) in a round bottom flask with a magnetic stirrer and nitrogen atmosphere. The solution was cooled down to 0 °C and the commercially available 2.5M solution of BuLi in

hexanes (0.19 mL, 0.47 mmol, 1 eq.) was added dropwise. The temperature was allowed to rise up for an hour and, once at room temperature, propargyl bromide (0.06 mL, 0.56 mmol, 1.2 eq.) was added to the solution. The reaction was allowed to progress at room temperature overnight and the solvent was removed under vacuum. The crude was purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarities. The final product (100 mg, 82%) was isolated as a yellow oil.

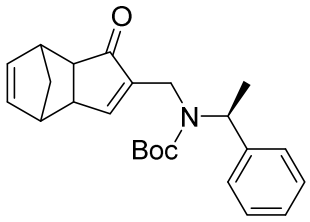
IR (film) $\nu_{max.}$ = 3244, 2969, 2879, 2123, 1310, 1130 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.92 (s, 3H), 1.10 (s, 3H), 1.30-1.34 (m, 1H), 1.46-1.51 (m, 1H), 1.71 (dd, *J* = 12.9 and 2.0 Hz, 1H), 1.86-1.91 (m, 3H), 2.09-2.15 (m, 1H), 2.31 (t, *J* = 2.5 Hz, 1H), 3.13 (s, 2H), 3.30 (dd, *J* = 7.9 and 4.7 Hz, 1H), 3.79 (dd, *J* = 2.5 and 1.8 Hz, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 20.0 (CH_3), 20.4 (CH_3), 26.9 (CH_2), 31.3 (CH_2), 32.1 (CH_2), 34.8 (CH_2), 44.5 (CH), 47.8 (C), 49.3 (CH_2), 49.8 (C), 65.8 (CH), 73.7 (C), 76.8 (CH) ppm.

HRMS (ESI) calculated for $C_{13}H_{20}NO_2S$ 254.1209, found 254.1010 $[M+H]^+$.

***tert*-butyl (((*3aR*,4S*,7R*,7aR**)-1-oxo-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-2-yl)methyl)((*S*)-1-phenylethyl)carbamate (31)**



In a round bottom flask provided with a magnetic stirrer and under nitrogen atmosphere was **25** (68 mg, 0.28 mmol, 1 eq.) in anhydrous toluene (5 mL). $Co_2(CO)_8$ (106 mg, 0.31 mmol, 1.1 eq.) was added as a solid, and the solution was stirred at room temperature for 1.5h. Then, norbornadiene (0.24 mL, 2.80 mmol, 10 eq.) was added to the cobalt complex, and the system was heated up to 70 °C. The reaction was allowed to progress overnight. The crude was filtered through a celite pad, and the solvent removed under vacuum. The crude was purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarities. The final product was isolated as an inseparable 1:1 mixture of diastereomers (95 mg, 90%) as a yellow oil.

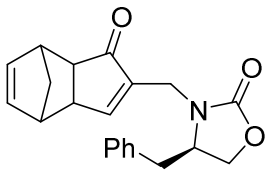
IR (film) $\nu_{max.}$ = 2975, 1694, 1451, 1316 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.16-1.53 (m, 15H), 2.22 (m, 1H), 2.50-2.63 (m, 2H), 2.84 (d, *J*=22.4 *Hz*, 1H), 3.75 (m, 2H), 6.16 (m, 1H), 6.24 (m, 1H), 7.16-7.43 (m, 6H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 17.3 (CH_3), 28.7 (CH_3), 38.9 (CH_2), 41.5 (CH_2), 43.1 (CH), 43.7 (CH), 43.8^{*Diasteromer}(CH), 47.8 (CH), 53.1 (CH), 53.3 (CH), 80.2 (C), 127.4 (CH), 127.5 (CH), 127.6 (CH), 128.5 (CH), 128.6^{*Diasteromer}(CH), 137.1 (CH), 137.2^{*Diasteromer} (CH), 138.6 (CH), 141.4 (C), 148.2 (C), 155.9 (C), 208.6 (C), 208.8^{*Diasteromer} (C) ppm.

HRMS (ESI) calculated for $C_{24}H_{30}NO_3$ 380.2222, found 380.2220 $[M+H]^+$.

(*R*)-4-benzyl-3-(((*3aR*,4S*,7R*,7aR)-1-oxo-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-2-yl)methyl)oxazolidin-2-one (32)**



In a round bottom flask provided with a magnetic stirrer and under nitrogen atmosphere was dissolved **27** (195 mg, 0.84 mmol, 1 eq.) in anhydrous toluene (15 mL). $Co_2(CO)_8$ (289 mg, 0.84 mmol, 1 eq.) was added as a solid, and the solution was stirred at room temperature for 40 minutes. Toluene was removed under reduced pressure and the resulting cobalt complex was re-dissolved in anhydrous dichloromethane (40 mL) under nitrogen. Then, norbornadiene (0.80 mL, 8.40 mmol, 10 eq.) was added to the cobalt complex, followed by a solution of NMO (590 mg, 5.04 mmol, 6 eq.) in dry dichloromethane (5 mL). The reaction was allowed to progress at room temperature for 24h, and the solvent was evaporated. The crude was purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarities. The final product was isolated as an inseparable 1:1 mixture of diastereomers (253 mg, 90%) as a yellow oil.

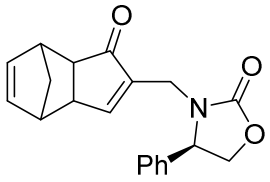
IR (film) $\nu_{max.}$ = 2975, 2937, 1752, 1688 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.19 (m, 1H), 1.42 (m, 1H), 2.35 (m, 1H), 2.62 (ddd, *J* = 12.8, 8.5 and 6.1 Hz, 1H), 2.74 (br s, 1H), 2.81 (m, 1H), 2.95 (br s, 1H), 3.29 (ddd, *J* = 13.5, 9.9 and 3.8 Hz, 1H), 3.84-4.25 (m, 5H), 6.22 (dd, *J* = 5.6 and 3.1 Hz, 1H), 6.31 (dd, *J* = 5.5 and 3.1 Hz, 1H), 7.15-7.35 (m, 5H), 7.53 (d, *J* = 2.3 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 38.3 (CH_2), 38.4 (CH_2)^{*Diasteromer}, 40.0 (CH_2), 40.1 (CH_2)* ^{Diasteromer}, 42.8 (CH_2), 42.9 (CH_2)* ^{Diasteromer}, 44.4 (CH), 44.5 (CH)* ^{Diasteromer}, 45.3 (CH), 45.4 (CH)* ^{Diasteromer}, 49.8 (CH), 49.9 (CH)* ^{Diasteromer}, 54.3 (CH), 54.4 (CH)* ^{Diasteromer}, 58.5 (CH), 58.6 (CH)* ^{Diasteromer}, 68.8 (CH_2), 128.8 (CH), 130.5 (CH), 130.8 (CH), 137.1 (C), 138.6 (CH), 140.12 (CH), 140.2 (CH)* ^{Diasteromer}, 146.6 (C), 159.7 (C), 159.8 (C)* ^{Diasteromer}, 165.2 (CH), 165.3 (CH)* ^{Diasteromer}, 210.6 (C), 210.7 (C)* ^{Diasteromer} ppm.

HRMS (ESI) calculated for $C_{21}H_{22}NO_3$ 336.1594, found 336.1595 $[M+H]^+$.

(*R*)-3-(((*3aR*,4S*,7R*,7aR)-1-oxo-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-2-yl)methyl)-4-phenyloxazolidin-2-one (33)**



In a round bottom flask provided with a magnetic stirrer and under nitrogen atmosphere were dissolved **28** (67 mg, 0.32 mmol, 1 eq.) in anhydrous dichloromethane (5 mL). $Co_2(CO)_8$ (109 mg, 0.32 mmol, 1 eq.) was added as a solid, and the solution was stirred at room temperature for 40 minutes. Then, norbornadiene (0.33 mL, 3.20 mmol, 10 eq.) was added to the cobalt complex, followed by solid NMO (226 mg, 1.93 mmol, 6 eq.). The reaction was allowed to progress at room temperature for 24h, and the solvent was evaporated. The crude was purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarities. The final product was isolated as an inseparable 1:1.5 mixture of diastereomers (86 mg, 83%) as a yellow oil.

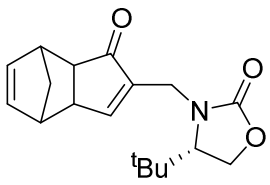
IR (film) $\nu_{max.}$ = 3065, 2969, 1752, 1700 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.19 (d, *J* = 9.4 Hz, 1H), 1.41 (dt, *J* = 9.5 and 1.6 Hz, 1H), 2.22 (dt, *J* = 5.0 and 1.4 Hz, 1H), 2.72 (br s, 2H), 2.90 (s, 1H), 3.53 (dt, *J* = 15.9 and 1.4 Hz, 1H), 4.07 (dt, *J* = 15.9 and 1.2 Hz, 1H), 4.16 (dd, *J* = 8.8 and 6.8 Hz, 1H), 4.62 (t, *J* = 8.8 Hz, 1H), 4.85 (dd, *J* = 8.9 and 6.7 Hz, 1H), 6.20 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.29 (dd, *J* = 5.6 and 3.0 Hz, 1H), 7.30-7.43 (m, 5H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 37.1 (CH_2) , 41.3 (CH_2) , 42.8 (CH), 43.6 (CH), 48.0 (CH), 52.6 (CH), 60.5 (CH), 70.0 (CH_2), 97.0 (C), 127.3 (CH), 129.1 (CH), 129.3 (CH), 136.9 (C), 137.0 (CH), 137.8 (CH), 138.5 (CH), 163.0 (C), 208.6 (C) ppm.

HRMS (ESI) calculated for $C_{20}H_{20}NO_3$ 322.1438, found 322.1440 $[M+H]^+$.

(*S*)-4-(tert-butyl)-3-(((*3aR*,4S*,7R*,7aR)-1-oxo-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-2-yl)methyl)oxazolidin-2-one (34)**



In a round bottom flask provided with a magnetic stirrer and under nitrogen atmosphere was dissolved **29** (52 mg, 0.29 mmol, 1 eq.) in of anhydrous toluene (7 mL). $Co_2(CO)_8$ (99 mg, 0.29 mmol, 1 eq.) was added as a solid, and the solution was stirred at room temperature for 0.5h. Then, norbornadiene (0.30 mL, 2.90 mmol, 10 eq.) was added to the cobalt complex, and the system was heated up to 70 °C. The reaction was allowed to progress for 24h. The solvent removed under vacuum, and the crude was purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing

polarities. The product was isolated as a separable 1:1.6 mixture of diastereomers (70 mg, 85%).

Major diasteromer: white solid.

Mp: 157-159 °C.

IR (KBr) $\nu_{max.}$ = 2969, 2866, 1739, 1688 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.95 (s, 9H), 1.21 (d, *J* = 9.4 Hz, 1H), 1.41 (d, *J* = 9.5 Hz, 1H), 2.33 (d, *J* = 5.0 Hz, 1H), 2.72 (s, 1H), 2.81 (s, 1H), 2.92 (s, 1H), 3.57 (dd, *J* = 9.0 and 4.4 Hz, 1H), 4.00 (d, *J* = 16.4 Hz, 1H), 4.15 (dd, *J* = 9.3 and 4.6 Hz, 1H), 4.20-4.26 (m, 2H), 6.21 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.30 (dd, *J* = 5.6 and 3.1 Hz, 1H), 7.45 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 25.6 (CH_3), 34.9 (C), 40.9 (CH_2), 41.3 (CH_2), 42.8 (CH), 43.6 (CH), 48.1 (CH), 52.9 (CH), 64.7 (CH), 65.1 (CH_2), 137.0 (CH), 138.6 (CH), 145.1 (C), 159.5 (C), 162.4 (CH), 208.8 (C) ppm.

HRMS (ESI) calculated for $C_{18}H_{24}NO_3$ 302.1751, found 302.1753 $[M+H]^+$.

Minor diasteromer: white solid.

Mp: 135-137 °C.

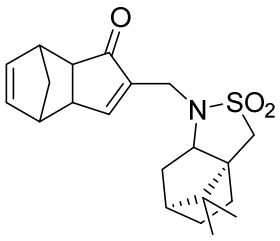
IR (KBr) $\nu_{max.}$ = 2969, 2866, 1758, 1694 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.95 (s, 9H), 1.21 (dt, *J* = 9.4 and 1.5 Hz, 1H), 1.41 (dt, *J* = 9.3 and 1.5 Hz, 1H), 2.33 (dt, *J* = 5.0 and 1.4 Hz, 1H), 2.75 (m, 1H), 2.79 (m, 1H), 2.92 (s, 1H), 3.55 (dd, *J* = 8.7 and 4.4 Hz, 1H), 3.98 (dt, *J* = 16.3 and 1.3 Hz, 1H), 4.13-4.28 (m, 3H), 6.21 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.30 (dd, *J* = 5.6 and 3.1 Hz, 1H), 7.46 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 25.6 (CH_3), 34.9 (C), 40.8 (CH_2), 41.3 (CH_2), 42.9 (CH), 43.6 (CH), 48.1 (CH), 52.7 (CH), 64.6 (CH), 65.1 (CH_2), 137.0 (CH), 138.1 (CH), 145.0 (C), 159.4 (C), 162.6 (CH), 208.8 (C) ppm.

HRMS (ESI) calculated for $C_{18}H_{24}NO_3$ 302.1751, found 302.1754 $[M+H]^+$.

(*3aR*,4S*,7R*,7aR)-2-(((*3aR,6S*)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)methyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (35)**



In a round bottom flask provided with a magnetic stirrer and under nitrogen atmosphere **30** (128 mg, 0.51 mmol, 1 eq.) was dissolved anhydrous toluene (10 mL). $Co_2(CO)_8$ (174 mg, 0.51 mmol, 1 eq.) was added as a solid, and the solution was stirred at room temperature for 45 minutes. Then, norbornadiene (0.53 mL, 5.10 mmol, 10 eq.) was added to the cobalt complex, and the system was heated up to 70 °C. The reaction was allowed to progress for 48h. The solvent removed under vacuum, and the crude was purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarities. The product was isolated as an inseparable 1:1 mixture of diastereomers (87 mg, 46%) that was a colorless oil.

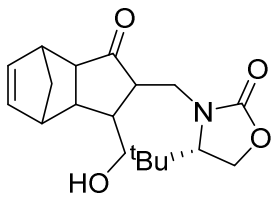
IR (film) $\nu_{max.}$ = 2969, 2866, 1739, 1688 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.89 (s, 3H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.21-1.40 (m, 6H), 1.63 (m, 1H), 1.82-1.88 (m, 3H), 2.29 (dd, *J* = 8.4 and 5.1 Hz, 1H), 2.71 (s, 1H), 2.75 (brs, 1H), 3.06-3.11 (m, 3H), 3.54 (t, *J* = 16.0 Hz, 1H), 3.81 (dd, *J* = 15.8 and 4.6 Hz, 1H), 6.18 (br s, 1H), 2.26 (brs, 1H), 7.59 (s, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 20.0 (CH_3), 20.2 (CH_3), 20.3 (CH_3)*Diastereomer, 26.9 (CH_2), 27.0 (CH_2)* Diastereomer, 32.0 (CH_2), 32.1 (CH_2)* Diastereomer, 35.0 (CH_2), 35.1 (CH_2)* Diastereomer, 36.3 (CH_2), 36.5 (CH_2)* Diastereomer, 41.2 (CH_2), 41.3 (CH_2)* Diastereomer, 42.8 (CH), 43.0 (CH)* Diastereomer, 43.7 (CH), 43.8 (CH)* Diastereomer, 44.4 (CH), 44.5 (CH)* Diastereomer, 47.7 (C), 48.0 (CH), 48.1 (CH)* Diastereomer, 49.7 (C), 49.8 (C)* Diastereomer, 49.9 (CH_2), 50.0 (CH_2)* Diastereomer, 52.6 (CH), 52.7 (CH)* Diastereomer, 67.4 (CH), 67.5 (CH)* Diastereomer, 137.0 (CH), 137.1 (CH)* Diastereomer, 138.5 (CH), 138.6 (CH)* Diastereomer, 144.2 (C), 144.4 (C)* Diastereomer, 164.3 (CH), 164.5 (CH)* Diastereomer, 208.2 (C), 208.3 (C)* Diastereomer ppm.

HRMS (ESI) calculated for $C_{21}H_{27}NO_3SNa$ 396.1604, found 396.1603 $[M+Na]^+$.

(*S*)-4-(*tert*-butyl)-3-(((*1R,*2R**,*3aR**,*4R**,*7S**,*7aR**)-1-(hydroxymethyl)-3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-2-yl)methyl)oxazolidin-2-one (37)**



34 (60 mg, 0.21 mmol, 1 eq) and benzophenone (38 mg, 0.21 mmol, 1 eq) were disolved in anhydrous methanol (15 mL) in a round bottom flask, and a nitrogen flow was bubbled though the solution for 45 minutes. After this time, the flask was irradiated at 350 nm in a Rayonet © photochemical reactor for 2h. After this time, the solvent was evaporated and the crude purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarities. The final product was isolated as a colorless oil (41 mg, 61%).

IR (film) $\nu_{max.}$ = 3434, 2962, 2866, 1728, 1240 cm^{-1}.

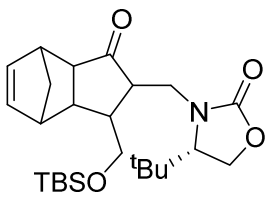
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.98 (s, 9H), 1.06 (d, *J* = 9.2 Hz, 1H), 1.45 (dt, *J* = 9.3 and 1.7 Hz, 1H), 1.52-1.59 (m, 1H), 2.07 (d, *J* = 9.2 Hz, 1H), 2.35 (d, *J* = 9.0 Hz, 1H), 2.77 (s, 1H), 2.87-2.93 (m, 1H), 3.14 (s, 1H), 3.46 (dd, *J* = 14.5 and 3.7 Hz, 1H), 3.60 (dd, *J* = 14.5 and 3.1 Hz, 1H), 3.77-3.85 (m, 2H), 3.93 (dd, *J* = 11.5 and 3.9 Hz, 1H), 4.17-4.26 (m, 2H), 6.15 (dd, *J* = 5.7 and 3.0 Hz, 1H), 6.19 (dd, *J* = 5.7 and 3.0 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 25.7 (CH_3), 35.2 (C), 42.8 (CH), 43.7 (CH_2), 44.7 (CH), 46.4 (CH_2), 44.9 (CH), 46.9 (CH), 53.8 (CH), 56.9 (CH), 64.5 (CH), 65.1 (CH_2), 65.8 (CH_2), 137.2 (CH), 134.8 (CH), 159.8 (C), 217.4 (C) ppm.

HRMS (ESI) calculated for $C_{19}H_{28}NO_4$ 334.2013, found 334.2014 $[M+H]^+$.

$[\alpha]_D$ = -23^a (c 0.80, $CHCl_3$).

(*S*)-4-(*tert*-butyl)-3-(((*1R,*2R**,*3aR**,*4R**,*7S**,*7aR**)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-2-yl)methyl)oxazolidin-2-one**



The free alcohol **X** (360 mg, 1.08 mmol, 1 eq.) was dissolved in anhydrous DMF (5 mL) in a round bottom flask under nitrogen. 2,6-lutidine (0.19 mL, 1.62 mmol, 1.5 eq.) was added to the product, followed by TBDMSOTf (0.37 mL, 1.62 mmol, 1.5 eq.). The mixture was stirred for 5h at room temperature. Water was added to the crude, and the organic components were extracted with dichloromethane. The organic layers were further washed with water, dried with $MgSO_4$ and filtered. The solvent was removed under vacuum and the product was purified by silica gel chromatography using

deactivated silica (SiO_2/NEt_3) and a 6:4 mixture of hexanes/AcOEt as eluent. The final product was recovered as a colorless oil (360 mg, 75%).

IR (film) $\nu_{max.}$ = 2956, 1752, 1415, 1252, 1095, 837 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 0.91 (s, 9H), 1.05 (d, *J* = 9.2 Hz, 1H), 1.43 (m, 1H), 1.69 (m, 1H), 2.18 (m, 1H), 2.28 (m, 1H), 2.78 (br s, 1H), 2.94 (dddd, *J* = 11.3, 6.5, 4.7 and 1.8 Hz, 1H), 3.15 (br s, 1H), 3.50 (dd, *J* = 6.5 and 5.1 Hz, 1H), 3.59 (dd, *J* = 14.8 and 4.7 Hz, 1H), 3.78 (m, 3H), 4.13 (m, 2H), 6.15 (dd, *J* = 5.8 and 3.0 Hz, 1H), 6.20 (dd, *J* = 5.7 and 3.0 Hz, 1H) ppm.

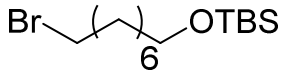
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 3.4 (CH_3), -2.8 (CH_3), 18.3 (C), 18.4 (C), 25.8 (CH_3), 26.1 (CH_3), 42.5 (CH_2), 43.2 (CH), 45.0 (CH_2), 45.6 (CH), 45.7 (CH), 47.8 (CH), 53.5 (CH), 54.8 (CH), 63.8 (CH_2), 64.3 (CH), 65.2 (CH_2), 137.5 (CH), 138.7 (CH), 159.9 (C), 218.0 (C) ppm.

HRMS (ESI) calculated for $C_{25}H_{42}NO_4Si$ 448.2878, found 448.2882 $[M+H]^+$.

$[\alpha]_D$ = $+17^a$ (c 1.40, $CHCl_3$).

8.3 CHAPTER 4

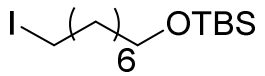
((8-Bromooctyl)oxy)(*tert*-butyl)dimethylsilane (38)



In a 100mL round bottom flask with a magnetic stirrer, 8-bromo-1-octanol (2.53 g, 12 mmol, 1eq.) was dissolved in 20 mL of anhydrous DCM under nitrogen and cooled down to -10 °C. A solution of TBSCl (2.23 g, 15 mmol, 1.25 eq.) in 4 mL of anhydrous DCM and another one of DMAP (25 mg, 0.2 mmol, 0.02 eq.) and imidazole (1.02 g, 15 mmol, 1.25 eq.) in 20 mL of anhydrous DCM were prepared. These solutions were added dropwise *via* canula to the alcohol. The system was allowed to temper and stirred at room temperature for 24h. The solvent was then removed under vacuum and the resulting oil was distilled in a Kugelrohr distiller ($T_{eb,\ 0.2\ Torr}$ = 176 °C). The desired product was isolated as a colorless oil (3.14 g, 81%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ= 0.04 (s, 6H), 0.90 (s, 9H), 1.29-1.36 (m, 6H), 1.39-1.45 (m, 2H), 1.47-1.55 (m, 2H), 1.86 (p, *J* = 7.0 Hz, 2H), 3.41 (t, *J* = 7.0 Hz, 2H), 3.60 (t, *J* = 6.5 Hz, 2H) ppm.

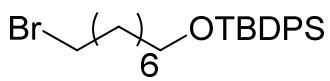
***tert*-Butyl((8-iodooctyl)oxy)dimethylsilane (39)**



In a 100mL round bottom flask equipped with a magnetic stirrer and a condenser ((8-Bromooctyl)oxy)(*tert*-butyl)dimethylsilane (6.20 g, 19 mmol, 1 eq.) was dissolved in acetone (50 mL). KI (16.0 g, 96 mmol, 5 eq.) was added, and the suspension was heated to reflux overnight. The following day, the crude was filtered on celite and the solvent was removed under vacuum. To the crude were added H_2O and Et_2O, and the aqueous layer was further extracted with Et_2O. The organic fractions were dried over Mg_2SO_4, filtered and dried. The product was isolated as a pale yellow oil with no further purification needed (5.80 g, 84%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ= 0.05 (s, 6H), 0.91 (s, 9H), 1.28-1.35 (m, 6H), 1.36-1.45 (m, 2H), 1.48-1.57 (m, 2H), 1.82 (q, *J* = 7.0 Hz, 2H), 3.18 (t, *J* = 7.0 Hz, 2H), 3.61 (t, *J* = 6.5 Hz, 2H) ppm.

((8-Bromooctyl)oxy)(*tert*-butyl)diphenylsilane (40)



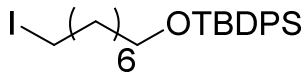
In a 100mL round bottom flask with a magnetic stirrer, 8-bromo-1-octanol (2.53 g, 12 mmol, 1eq.) was dissolved in 20 mL of anhydrous DCM under nitrogen and cooled down to -10 °C. A solution of TBDPSCl (4.12 g, 15 mmol, 1.25 eq.) in 4 mL of anhydrous DCM and another one of DMAP (25 mg, 0.2 mmol, 0.02 eq.) and imidazole (1.02 g, 15 mmol, 1.25 eq.) in 20 mL of anhydrous DCM were prepared. These solutions were added dropwise *via* canula to

the alcohol. The system was allowed to temper and stirred at room temperature for 24h. The solvent was then removed under vacuum and the crude was purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarities as eluent. The desired product was isolated as a colorless oil (5.63 g, 84%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ= 1.05 (s, 9H), 1.26-1.60 (m, 10H), 1.80-1.88 (m, 2H), 3.40 (t, *J* = 6.9 Hz, 2H), 3.65 (t, *J* = 6.5 Hz, 2H), 7.35-7.40 (m, 6H), 7.67 (dd, *J* = 7.9, 1.7 Hz, 4H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ= 19.2 (C), 25.6 (CH_2), 26.9 (CH_3), 28.1 (CH_2), 28.7 (CH_2), 29.1 (CH_2), 32.5 (CH_2), 32.8 (CH_2), 34.0 (CH_2), 63.9 (CH_2), 127.5 (CH), 129.5 (CH), 134.1 (C), 135.6 (CH) ppm.

***tert*-Butyl((8-iodooctyl)oxy)diphenylsilane (40)**

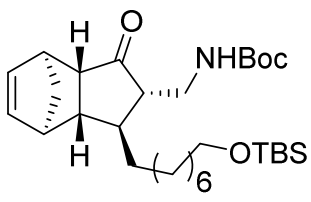


In a 100mL round bottom flask equipped with a magnetic stirrer and a condenser ((8-Bromooctyl)oxy)(*tert*-butyl)diphenylsilane (8.50 g, 19 mmol, 1 eq.) was dissolved in acetone (50 mL). KI (16.0 g, 96 mmol, 5 eq.) was added, and the suspension was heated to reflux overnight. The following day, the crude was filtered on celite and the solvent was removed under vacuum. To the crude were added H_2O and Et_2O, and the aqueous layer was further extracted with Et_2O. The organic fractions were dried over Mg_2SO_4, filtered and dried. The product was isolated as a yellow oil after silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarities as eluent (7.52 g, 80%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ= 1.05 (s, 9H), 1.24-1.58 (m, 10H), 1.72-1.84 (m, 2H), 3.18 (t, *J* = 7.0 Hz, 2H), 3.52 (t, *J* = 6.8 Hz, 2H), 7.35-7.42 (m, 6H), 7.65-7.68 (m, 4H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ= 7.3 (CH_2), 19.2 (C), 26.9 (3xCH_3), 28.5 (CH_2), 28.8 (CH_2), 29.1 (CH_2), 32.5 (CH_2), 32.6 (CH_2), 33.5 (CH_2), 63.9 (CH_2), 127.5 (CH), 129.5 (CH), 134.1 (C), 135.6 (CH) ppm.

***tert*-Butyl (((*1S,2S,3aS,4S,7R,7aS*)-1-(8-((tert-butyldimethylsilyl)oxy)octyl)-3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-2-yl)methyl)carbamate (12)**



<u>From the Grignard reagent of 1-tert-butildimetilsililoxi-8-bromooctane:</u>

In a three neck round bottom flask with a magnetic stirrer, an addition funnel and a condenser were placed magnesium (90

mg, 3.7 mmol, 1.2 eq.) and a little crystal of iodine. The system was put under nitrogen and through the addition funnel was added, very slowly, 1-tert-butildimetilsililoxi-8-bromooctane (1.00 g, 3.1 mmol, 1eq.). Once the reaction started, the 1-tert-butildimetilsililoxi-8-bromooctane left was added along with dry THF. When we finished adding the bromide, more THF was added until we reached a volume of 10 mL. The reaction was heated at 40 °C for 1h.

In a 25 mL Schlenk type flask equipped with a magnetic stirrer and previously dried under vacuum with a hot air gun CuI (14 mg, 0.07 mmol, 0.01 eq.) was suspended in anhydrous THF (5 mL) and cooled down to -78 °C.

The Grignard reagent was transferred *via* canula to the CuI suspension. The system was allowed to warm up slowly until a transparent, colorless solution was obtained. Then, the solution was cooled down again to -65 °C and a solution of **2f** (200 mg, 0.73 mmol, 1 eq.) in anhydrous THF (2 mL) were added *via* canula. The crude acquired a yellowish color that rapidly faded. The reaction was allowed to evolve during 45 minutes at -78 °C, it was taken to room temperature and treated with an NH_4Cl/NH_3 (4:1) solution until the crude turned deep blue. The organic layer was separated and the aqueous layer was further extracted with Et_2O. The organic fractions were dried with Mg_2SO_4, filtered and dried. The crude was purified by flash chromatography, using mixtures of hexanes/AcOEt of increasing polarity. The desired product was obtained as a colorless oil (223 mg, 60%).

Metallating 1-tert-butildimetilsililoxi-8-iodooctane:

The starting iodide (1.07 g, 2.9 mmol, 2 eq.) was dissolved in 5 mL of anhydrous ether in a 25 mL heart-shaped flask and dried with 4Å molecular sieves. This solution was transferred *via* canula to a 25 mL Schlenk flask previously dried with a magnetic stirrer and under nitrogen. The solution was cooled down to -78 °C and a commercially available 1.5M solution of ^tBuLi in pentane (3.9 mL, 5.8 mmol, 4 eq.) was added dropwise. The mixture was stirred for 25 minutes at -78 °C, and then it was allowed to temper over an hour to obtain a transparent, slightly brown solution. The solution was cooled down back to -78 °C and it was transferred *via* canula to a suspension of CuI (276 mg, 1.44 mmol, 1 eq.) in 10 mL of dry ether in a 50 mL Schlenk flask. The -78 °C bath was then changed for a bath at -10 °C. The reaction was stirred for an hour at this temperature, thus obtaining a black, clear solution. The bath was changed again for the -78 °C one, and a solution of **2f** (300 mg, 1.10 mmol, 0.4 eq.) in 5 mL of anhydrous ether and previously dried over 4Å molecular sieves were added *via* canula. After 1h,

the system was allowed to reach room temperature gradually, and then treated with an NH_4Cl/NH_3 (4:1) solution until the crude turned deep blue. The organic layer was separated and the aqueous layer was further extracted with Et_2O. The organic fractions were dried with Mg_2SO_4, filtered and evaporated. The crude was purified by flash chromatography, using mixtures of hexanes/AcOEt of increasing polarity. The desired product was obtained as a colorless oil (372 mg, 65%).

IR (film) $\nu_{max.}$ = 2930, 2847, 1720, 1495 cm^{-1}.

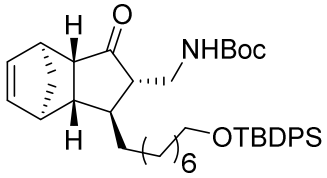
^{1}H-NMR (400 MHz, $CDCl_3$) δ= 0.05 (s, 6H), 0.90 (s, 9H), 1.06 (d, *J* = 9.1 Hz, 1H), 1.21-1.59 (m, 25H), 1.94 (m, 1H), 2.32 (dd, J = 9.4 and 1.5 Hz, 1H), 2.40 (br s, 1H), 2.72 (s, 1H), 3.14 (s, 1H), 3.19 (m, 1H), 3.38 (m, 1H), 3.58-3.66 (m, 2H), 5.17 (br s, 1H), 6.14 (dd, *J = 5.7 and 3.0 Hz*, 1H), 6.21 (dd, *J = 5.7 and 3.0 Hz*, 1H)ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ= -5.3 (CH_3), 18.6 (C), 26.0 (CH_2), 26.2 (3 CH_3), 27.8 (CH_2), 28.6 (3 CH_3), 29.7 (CH_2), 29.9 (CH_2), 30.1 (CH_2), 33.1 (CH_2), 36.4 (CH_2), 38.3 (CH_2), 42.2 (CH), 44.8 (CH), 45.0 (CH_2), 47.3 (CH), 48.3 (CH), 54.7 (CH), 60.3 (CH), 63.6 (CH_2), 79.3 (C), 137.5 (CH), 138.7 (CH), 156.3 (C), 219.3 (C) ppm.

HRMS (ESI) calculated for $C_{30}H_{53}NO_4Si$ 397.3392, found 397.3400 $[M+H]^+$.

$[\alpha]_D$ = $+28^a$ (c 0.67, $CHCl_3$).

***tert*-Butyl (((*1S*,2S*,3aS*,4S*,7R*,7aS**)-1-(8-((tert-butyldiphenylsilyl)oxy)octyl)-3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-2-yl)methyl)carbamate (44)**



tert-Butyl((8-iodooctyl)oxy)diphenylsilane (700 mg, 1.4 mmol, 2 eq.) was dissolved in 5 mL of anhydrous ether in a 25 mL heart-shaped flask and dried with 4Å molecular sieves. This solution was transferred *via* canula to a 25 mL Schlenk flask previously dried with a magnetic stirrer and under nitrogen. The solution was cooled down to -78 °C and a commercially available 1.7M solution of ^{t}BuLi in pentane (1.6 mL, 2.8 mmol, 4 eq.) was added dropwise. The mixture was stirred for 25 minutes at -78 °C, and then it was allowed to temper over an hour to obtain a transparent, slightly brown solution. The solution was cooled down back to -78 °C and it was transferred *via* canula to a suspension of CuI (134 mg, 0.70 mmol, 1 eq.) in 5 mL of dry ether in a 50 mL Schlenk flask. The -78 °C bath was then changed for a bath at -10 °C. The reaction was stirred for an hour at this temperature, thus obtaining a black, clear solution. The bath was changed again for the -78 °C one, and a solution of **2f** (80 mg, 0.30 mmol, 0.3 eq.) in 5 mL of anhydrous ether and previously dried over 4Å molecular

sieves were added *via* canula. After 1h, the system was allowed to reach room temperature gradually, and then treated with an NH_4Cl/NH_3 (4:1) solution until the crude turned deep blue. The organic layer was separated and the aqueous layer was further extracted with Et_2O. The organic fractions were dried with Mg_2SO_4, filtered and evaporated. The crude was purified by flash chromatography, using mixtures of hexanes/AcOEt of increasing polarity. The desired product was obtained as a colorless oil (97 mg, 52%).

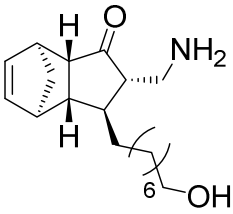
IR (film) $\nu_{max.}$ = 2924, 2847, 1726, 1502 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ= 1.05 (s, 9H), 1.26-1.42 (m, 24H), 1.57 (m, 2H), 1.78 (brs, 1H), 1.94 (m, 1H), 2.32 (d, *J* = 9.3 Hz, 1H), 2.40 (brs, 1H), 2.72 (s, 1H), 3.14-3.19 (m, 2H), 3.40 (m, 1H), 3.66 (t, *J* = 6.5 Hz, 2H), 6.14 (dd, *J* = 5.6, 2.9 Hz, 1H), 6.20 (dd, *J* = 5.6, 2.9 Hz, 1H), 7.35-7.42 (m, 6H), 7.66-7.69 (m, 4H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ= 19.2 (C), 25.8 (CH_2), 26.9 (3xCH_3), 27.5 (CH_2), 28.4 (3xCH_3), 29.4 (CH_2), 29.6 (CH_2), 29.9 (CH_2), 32.6 (CH_2), 36.2 (CH_2), 38.1 (CH_2), 42.0 (CH), 44.5 (CH), 44.7 (CH_2), 47.1 (CH), 48.1 (CH), 54.5 (CH), 60.1 (CH), 64.0 (CH_2), 79.1 (C), 127.5 (CH), 129.5 (CH), 134.2 (C), 135.6 (CH), 137.3 (CH), 138.5 (CH), 156.1 (C), 219.1 (C) ppm.

HRMS (ESI) calculated for $C_{40}H_{58}NO_4Si$ 644.4130, found 644.4136 $[M+H]^+$.

***(2S,3S,3aS,4R,7S,7aS)*-2-(Aminomethyl)-3-(8-hydroxyoctyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-one (43)**



With TFA:

A solution of **12** (95 mg, 0.19 mmol, 1 eq.) in 2 mL of DCM was cooled down to 0 °C in a 5 mL round bottom flask with a magnetic stirrer. TFA (1.5 mL, 19 mmol, 10 eq.) was added dropwise to the solution. The reaction was stirred for 1.5h at 0 °C. The reaction was quenched by the addition of Et_2O and water, and the mixture was treated with a saturated solution of $NaHCO_3$ until it reached pH = 8. The organic layer was then extracted, and the aqueous phase was washed with more Et_2O. The ethereal layers were dried over $MgSO_4$, filtered and dried, thus obtaining 52 mg (90%) of the desired product as a yellow oil.

With HCl/MeOH:

12 (150 mg, 0.29 mmol, 1 eq.) was dissolved in the commercially available 1.25M solution of HCl/MeOH (2 mL, 2.5 mmol, 9eq.) in a 5 mL round bottom flask with a magnetic stirrer. After 4h, the solvent was removed under vacuum and to the crude were added a saturated solution of $NaHCO_3$ and AcOEt. The aqueous layer was further extracted with more AcOEt, and the organic fractions were dried on $MgSO_4$, filtered and dried. The product was obtained quantitatively (88 mg) as a yellow oil.

IR (film) $\nu_{max.}$ = 3340, 2924, 2847, 1720 cm^{-1}.

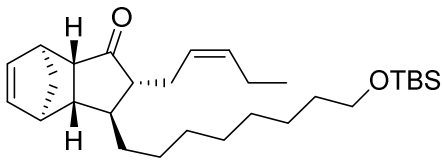
^{1}H-NMR (400 MHz, $CDCl_3$) δ= 1.00 (d, *J* = 9.3 Hz, 1H), 1.24-1.60 (m, 19H), 1.99 (m, 1H), 2.39 (d, *J* = 9.3 Hz, 1H), 2.50 (m, 1H), 2.75 (m, 1H), 3.16 (s, 1H), 3.29 (ddd, *J* = 13.3, 7.9 and 5.0 Hz, 1H), 3.62-3.67 (ddt, *J* = 13.8, 7.4 and 3.5 Hz, 2H), 3.73 (m, 1H), 6.15 (dd, *J* = 5.7 and 3.0 Hz, 1H), 6.22 (dd, *J* = 5.6 and 3.1 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 25.9 (CH_2), 27.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 30.0 (CH_2), 33.0 (CH_2), 36.2 (CH_2), 37.8 (CH_2), 42.6 (CH), 44.7 (CH), 45.0 (CH_2), 47.5 (CH), 48.1 (CH), 54.6 (CH), 58.7 (CH), 63.2 (CH_2), 137.4 (CH), 138.7 (CH), 219.2 (C) ppm.

HRMS (ESI) calculated for $C_{19}H_{31}NO_2$ 305.2434, found 305.2426 $[M+H]^+$.

$[\alpha]_D$ = $+54^a$ (c 0.02, $CHCl_3$).

***(2R,3S,3aS,4R,7S,7aS)*-3-(8-((*tert*-Butyldimethylsilyl)oxy)octyl)-2-((Z)-pent-2-en-1-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-one (47)**



43 (88 mg, 0.29 mmol, 1 eq.) was dissolved in 10 mL of anhydrous DCM in a 50 mL round bottom flask with a magnetic stirrer and under nitrogen, and cooled down to -10 °C. The following solutions were prepared: one of TBSCl (109 mg, 0.73 mmol, 2.5 eq.) in 1 mL of anhydrous DCM and another one of DMAP (9 mg, 0.07 mmol, 0.02 eq.) and imidazole (50 mg, 0.73 mmol, 2.5 eq.) in 3 mL of anhydrous DCM. These solutions were added dropwise *via* canula to the alcohol. The system was allowed to temper and stirred at room temperature for 24h. The solvent was removed under vacuum, and to the crude were added AcOEt and a saturated solution of $NaHCO_3$. The organic layer was separated and washed with water and a saturated solution of NaCl. The organic phases were dried over $MgSO_4$, filtered and the solvent removed, and the product was isolated as a yellow oil (125 mg, 81%) and used with directly in the next reaction.

The crude diprotected product (125 mg, 0.23 mmol, 1 eq.) was dissolved in a round bottom flask with a magnetic stirrer in 5 mL of DMF, and (118mg, 1.40 mmol, 6 eq.) of $NaHCO_3$ and (0.50 mL, 1.40 mmol, 6 eq.) of MeI were added to it. The reaction was stirred at room temperature for 24h. The solvent was eliminated under vacuum and the crude was divided into DCM and H_2O. The organic layer was washed with H_2O, dried with $MgSO_4$ and filtered. The solvent was removed under vacuum, further dried under high vacuum and used immediately.

In a 50 mL Schlenk flask previously dried, with a magnetic stirrer and under nitrogen Z-1-bromobut-ene (283 mg, 1.76 mmol, 14 eq.) was dissolved in 4 mL of anhydrous THF. The solution was cooled down to -78 °C and a commercially available 1.5M solution of ^{t}BuLi in pentane (2.3 mL, 3.52 mmol, 14 eq.) was added dropwise. The solution, initially colorless, turned bright yellow and remained transparent. The mixture was stirred at -78 °C for 30 min, and then was allowed to temper over 45 min. During this time, the yellow coloring faded to pale yellow or even colorless. Temperature was taken to -78 °C again, and the commercially available 0.25M solution of 2-thienyl lithium cyanocuprate in THF (7 mL, 1.76 mmol, 14 eq.) was added dropwise. The solution turned yellow-brownish. It was stirred for 45 min at -78 °C, and then a solution of the crude exocyclic enone (48 mg, 0.12 mmol, 1 eq.) in 5 mL of anhydrous THF and dried with 4Å molecular sieves was added *via* canula. The system was allowed to evolve at -78 °C for 2h, reach room temperature gradually, and then treated with an NH_4Cl/NH_3 (4:1) solution until the crude turned deep blue. The organic layer was separated and the aqueous layer was further extracted with AcOEt. The organic fractions were dried with $MgSO_4$, filtered and dried. The crude was purified by flash chromatography on silica gel, using mixtures of hexanes/AcOEt of increasing polarity. The desired product was obtained as a pale yellow oil (23 mg, 34%).

IR (film) $\nu_{max.}$ = 2930, 2853, 1739, 1457, 1252 cm^{-1}.

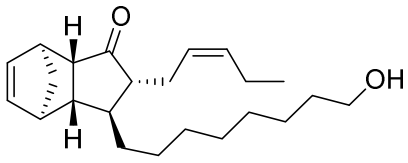
^{1}H-NMR (400 MHz, $CDCl_3$) δ= 0.05 (m, 6H), 0.83-0.92 (m, 10H), 0.96 (m, 3H), 1.07 (m, 1H), 1.24-1.38 (m, 13H), 1.52 (m, 2H), 1.71 (m, 1H), 1.89 (m, 1H), 2.05 (m, 2H), 2.28 (m, 3H), 2.70 (s, 1H), 3.13 (s, 1H), 3.61 (td, *J* = 6.6 and 5.3 Hz, 2H), 5.28 (m, 1H), 5.40 (m, 1H), 6.13 (dd, *J* = 5.7 and 2.9 Hz, 1H), 6.20 (dd, *J* = 5.7 and 2.9 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ= -5.1 (CH_3), 14.4 (CH_3) 18.5 (C), 20.7 (CH_2), 25.1 (CH_2), 25.9 (CH_2), 26.1 (3xCH_3), 27.6 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 30.1 (CH_2), 33.0 (CH_2), 36.8 (CH_2), 44.2 (CH), 45.0 (CH_2), 45.1 (CH), 47.2 (CH), 48.5 (CH), 54.5 (CH), 59.5 (CH), 63.4 (CH_2), 125.9 (CH), 135.5 (CH), 137.7 (CH), 138.6 (CH), 218.4 (C) ppm.

HRMS (ESI) calculated for $C_{29}H_{51}O_2Si$ 459.3653, found 459.3649 $[M+H]^+$.

$[\alpha]_D$ = +22[a] (c 0.19, $CHCl_3$).

***(2R,3S,3aS,4R,7S,7aS)*-3-(8-Hydroxyoctyl)-2-((Z)-pent-2-en-1-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-one**



A solution of **11** (46 mg, 0.17 mmol, 1 eq.) in 0.4 mL of THFwas added dropwise to a mixture of H_2O:AcOH (1.02 mL:2.04 mL) at 0 °C in a 10 mL round bottom flask with a magnetic stirrer. Once finished the addition, the ice-cold bath was withdrawn and the reaction was allowed to temper. After 2.5h, a saturated solution of $NaHCO_3$ was added dropwise to the reaction until it reached pH = 8. The organic layer was extracted, and the aqueous portion was extracted with AcOEt. The organic fractions were dried with Mg_2SO_4 and filtered, and the solvent was removed under vacuum. The crude was purified by flash chromatography on silica gel using mixtures of hexanes/AcOEt of increasing polarities. The product was recovered as a pale yellow oil (35 mg, 84%).

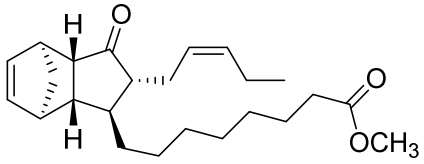
IR (film) $\nu_{max.}$ = 3443, 2924, 2847, 1726, 1457 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ= 0.96 (t, *J* = 7.5 Hz, 3H), 1.07 (d, *J* = 9.1 Hz, 1H), 1.30-1.73 (m, 17H), 1.89 (m, 1H), 2.05 (p, *J* = 7.3 Hz, 2H), 2.25-2.37 (m, 4H), 2.70 (s, 1H), 3.13 (s, 1H), 3.65 (t, *J* = 6.6 Hz, 2H), 5.28 (m, 1H), 5.41 (m, 1H), 6.14 (dd, *J* = 5.8 and 3.0 Hz, 1H), 6.20 (dd, *J* = 5.7 and 3.0 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ= 14.3 (CH_3), 20.7 (CH_2), 25.1 (CH_2), 25.9 (CH_2), 27.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 30.1 (CH_2), 32.9 (CH_2), 36.8 (CH_2), 44.2 (CH), 45.0 (CH), 45.1 (CH_2), 47.2 (CH), 48.4 (CH), 54.4 (CH), 59.4 (CH), 63.2 (CH_2), 125.8 (CH), 133.4 (CH), 137.6 (CH), 138.5 (CH), 218.4 (C) ppm.

HRMS (ESI) calculated for $C_{23}H_{37}O_2$ 345.2788, found 345.2791 $[M+H]^+$.

Methyl 8-((*1S,2R,3aS,4S,7R,7aS*)-3-oxo-2-((Z)-pent-2-en-1-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-yl)octanoate (48)



In a 5 mL round bottom flask equipped with a magnetic stirrer and nitrogen atmosphere was suspended Dess-Martin's periodinane (47 mg, 0.11 mmol, 1.3 eq.) in 1 mL of anhydrous DCM and cooled down to 0 °C. A solution of *(2R,3S,3aS,4R,7S,7aS)*-3-(8-Hydroxyoctyl)-2-((Z)-pent-2-en-

1-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-one (29 mg, 0.08 mmol, 1eq.) in 1 mL of anhydrous DCM was then added dropwise to the suspension. Once the addition was finished, the system was allowed to heat up to room temperature. After 45 min, the crude was treated with H_2O, Et_2O and a saturated solution of Na_2SO_3. The aqueous layer was further extracted with Et_2O. The organic fractions were dried ($MgSO_4$), filtered and evaporated.

The crude aldehyde was dissolved in 1.7 mL of ^tBuOH and 0.6 mL of 2,3-dimethyl-2-butene and the solution was cooled down to 10 °C. To this solution was added, very slowly, a mixture of $NaClO_2$ (45 mg, 0.5 mmol, 5.7 eq.) and NaH_2PO_4 (67 mg, 0.56 mmol, 7 eq.) in 1 mL of water. The reaction was stirred at 10 °C for 10 min. The organic volatile components were removed under vacuum, leaving the water to be extracted with AcOEt. The organic layers were dried ($MgSO_4$), filtered and dried under vacuum.

The crude carboxylic acid obtained was dissolved in a mixture of benzene and MeOH (5 mL : 1.6 mL) and cooled down to 5 °C. Then, the commercially available 2M solution of (Trimetilsilil)diazomethane in hexanes (0.05 mL, 0.10 mmol, 1.2 eq.) was added dropwise. Stirring was kept for 45 min. The crude was dried under vacuum and purified by flash chromatography (hexanes/AcOEt) to furnish 28 mg (quantitative) of the desired product as a colorless oil.

IR (film) $\nu_{max.}$ = 2930, 2847, 1732, 1463, 1431 cm^{-1}.

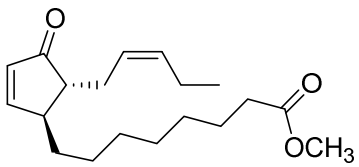
^{1}H-NMR (400 MHz, $CDCl_3$) δ= 0.96 (t, *J* = 7.5 Hz, 3H), 1.07 (d, *J* = 9.1 Hz, 1H), 1.30-1.73 (m, 16H), 1.89 (m, 1H), 2.05 (p, *J* = 7.5 Hz, 2H), 2.25-2.37 (m, 4H), 2.70 (s, 1H), 3.13 (s, 1H), 3.67 (s, 3H), 5.28 (m, 1H), 5.41 (m, 1H), 6.14 (dd, *J* = 5.7, 2.9 Hz, 1H), 6.20 (dd, *J* = 5.7, 3.0 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.2 (CH_3), 20.5 (CH_2), 24.9 (CH_2), 27.4 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 29.8 (CH_2), 34.1 (CH_2), 36.6 (CH_2), 44.0 (CH), 44.8 (CH_2), 44.9 (CH), 47.1 (CH), 48.3 (CH), 51.4 (CH_3), 54.3 (CH), 59.3 (CH), 125.7 (CH), 133.2 (CH), 138.4 (CH), 137.5 (CH), 174.3 (C), 218.2 (C) ppm.

HRMS (ESI) calculated for $C_{24}H_{37}O_3$ 373.2737, found 373.2740 $[M+H]^+$.

$[\alpha]_D$ = $+22^a$ (c 0.75, $CHCl_3$).

Methyl 8-((*1S,5R*)-4-oxo-5-((Z)-pent-2-en-1-yl)cyclopent-2-en-1-yl)octanoate (49)



A microwave vial was purged with nitrogen and equipped with a magnetic stirrer. In it, **48** (20 mg, 0.06 mmol, 1 eq.) and maleic anhydride (88 mg, 0.90 mmol, 15 eq.) were dissolved in 4 mL of anhydrous DCM. The vial was sealed and the commercially available 1M solution of $MeAlCl_2$ in hexanes (0.06 mL, 0.06 mmol, 1 eq.) was added through the seal. The system was irradiated with microwaves (250W, 70 °C) for 60 sec. The crude was then rapidly mixed with a saturated solution of $NaHCO_3$ and stirred for 20 minutes in the open air. The organic fraction was separated and the aqueous phase was further extracted with Et_2O. The organic layers were dried ($MgSO_4$) and filtered. Solvent removal followed by flash chromatography (hexanes/AcOEt) yielded the product as a colorless oil (9.7 mg, 54%).

IR (film) $\nu_{max.}$ = 2924, 2847, 1740, 1700 cm^{-1}.

^{1}H-NMR (600 MHz, $CDCl_3$) δ= 0.96 (t, *J* = 7.5 Hz, 3H), 1.30-1.40 (m, 8H), 1.47-1.52 (m, 2H), 1.60-1.66 (m, 2H), 2.01 (ddd, *J* = 8.1, 4.8 and 2.1 Hz, 1H), 2.05 (pd, *J* = 7.5 and 1.6 Hz, 2H), 2.24-2.33 (m, 3H), 2.43-2.50 (m, 1H), 2.57 (tq, *J* = 7.0 and 2.2 Hz, 1H), 3.67 (s, 3H), 5.27 (m, 1H), 5.45 (m, 1H), 6.12 (dd, *J* = 5.7 and 1.9 Hz, 1H), 7.60 (dd, *J* = 5.7 and 2.5 Hz, 1H) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$) δ = 14.2 (CH_3), 20.6 (CH_2), 24.9 (CH_2), 27.4 (CH_2), 28.2 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.5 (CH_2), 34.0 (CH_2), 34.3 (CH_2), 47.1 (CH), 51.4 (CH_3), 51.5 (CH), 125.1 (CH), 132.8 (CH), 133.9 (CH), 167.4 (CH), 174.2 (C), 211.7 (C) ppm.

HRMS (ESI) calculated for $C_{19}H_{31}O_3$ 307.2268, found 307.2268 $[M+H]^+$.

$[\alpha]_D$ = $+58^a$ (c 0.30, $CHCl_3$).

8.4 CHAPTER 5

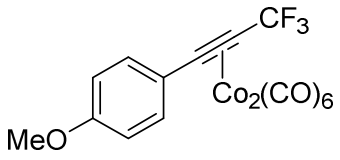
General procedure for the synthesis of the cobalt complexes of trifluoromehtylated alkynes.

Ag_2CO_3 (1.0 mmol, 2 eq.) and phenantroline (1.0 mmol, 2 eq.) were added to a Schlenk tube equipped with a stirring bar and capped with a pressure cap. The tube was softly flamed under high vacuum conditions, and put under nitrogen. In the glove box, CuCl (1.0 mmol, 2 eq.) and ^tBuOK (1.0 mmol, 2 eq.) were added to the mixture. The system was then purged and put under nitrogen, and anhydrous DMF (10 mL) was added. The red-brown solution was stirred at room temperature for 30 minutes. Then, $TMSCF_3$ (2.5 mmol, 5 eq.) was added. The tube was sealed with a glass cap and the system heated at 40 °C during one hour. After this time, the cap was changed for a rubber septum. Then, a solution of the terminal alkyne (0.5 mmol, 1 eq.) in DMF (3 mL) was added to the mixture under continuous stirring and at 40 °C with the help of a syringe pump (addition ratio: 0.5 mL/hour) and allowed to react overnight.

The reaction was quenched by the addition of water and hexanes. While stirring vigorously to the open air, a solution of NH_3/NH_4Cl (1:3) was added. Stirring was kept for half an hour before phase separation. The organic layer was further washed with water, dried with $MgSO_4$ and filtered.

The crude alkyne dissolved in hexanes was mixed with $Co_2(CO)_8$ (0.5 mmol, 1 eq.). The mixture was put under nitrogen and stirred at room temperature. Once the alkyne was completely consumed (30-45 minutes, approximately) the crude was evaporated to dryness and purified by silica gel chromatography with hexanes as eluent.

1-methoxy-4-(3,3,3-trifluoroprop-1-yn-1-yl)benzene hexacarbonyldicobalt (51b)



The general procedure was followed starting from *p*-methoxyphenylacetylene. The cobalt complex was isolated as a burgundy oil (105 mg, 43%).

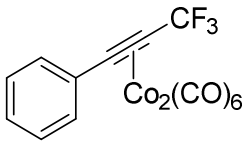
IR (film) $\nu_{max.}$ = 2104, 2070, 2045, 2020, 1599, 1499, 1279 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ = 2.77 (s, 3H), 6.12 (d, *J* =8.7 Hz, 2H), 7.16 (d, *J* = 8.6 Hz, 2H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 54.4 (CH_3), 76.1 (q, $^2J_{CF}$ = 49 Hz, C), 89.4 (C), 114.7 (CH), 127.0 (C), 127.8 (q, $^1J_{CF}$ = 268 Hz, C), 131.1 (CH), 160.4 (C), 197.5 (CO) ppm.

^{19}F-NMR (376 MHz, C_6D_6) δ = -51.68 (s, 3F) ppm.

(3,3,3-trifluoroprop-1-yn-1-yl)benzene hexacarbonyldicolbalt (51c)



The general procedure was followed starting from phenylacetylene. The cobalt complex was isolated as a red oil (126 mg, 55%).

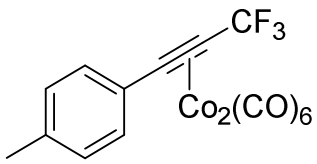
IR (film) $\nu_{max.}$ = 2107, 2070, 2039, 1279, 1141 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ = 6.63-6.68 (m, 3H), 7.31-7.33 (m, 2H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 76.1 (q, $^2J_{CF}$ = 49 Hz, C), 88.8 (C), 127.6 (q, $^1J_{CF}$ = 268 Hz, C), 128.8 (CH), 129.1 (CH), 129.5 (CH), 135.6 (C), 197.2 (CO) ppm.

^{19}F-NMR (376 MHz, C_6D_6) δ = -51.77 (s, 3F) ppm.

1-methyl-4-(3,3,3-trifluoroprop-1-yn-1-yl)benzene hexacarbonyldicobalt (51d)



The general procedure was followed starting from 1-ethynyl-4-methylbenzene. The cobalt complex was isolated as a red oil (211 mg, 91%).

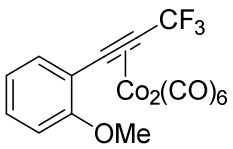
IR (film) $\nu_{max.}$ = 2105, 2068, 2064, 1279, 1141 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ = 1.95 (s, 3H), 6.81 (d, J = 7.9 Hz, 2H), 7.79-7.48 (m, 2H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 20.8 (CH_3), 76.1 (q, $^2J_{CF}$ = 46 Hz, C), 89.3 (C), 127.7 (q, $^1J_{CF}$ = 268 Hz, C), 129.5 (CH), 129.8 (CH), 132.4 (C),139.2 (C), 197.3 (CO) ppm.

^{19}F-NMR (376 MHz, C_6D_6) δ = -51.84 (s, 3F) ppm.

1-methoxy-2-(3,3,3-trifluoroprop-1-yn-1-yl)benzene hexacarbonyldicobalt (51e)



The general procedure was followed starting from o-methoxy phenylacetylene. The cobalt complex was isolated as a red oil (170 mg, 70%).

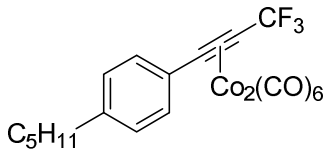
IR (film) $\nu_{max.}$ = 2102, 2051, 2036, 2012, 1617, 1271, 1112 cm^{-1}.

^{1}H-NMR (300 MHz, C_6D_6) δ = 3.30 (s, 3H), 6.31 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 1H), 6.64-6.69 (m, 1H), 6.97-7.02 (m, 1H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 54.5 (CH_3), 79.0 (q, $^2J_{CF}$ = 48 Hz, C), 84.3 (C), 111.7 (CH), 121.7 (CH), 124.2 (C), 126.2 (q, $^1J_{CF}$ = 265 Hz, C), 131.4 (CH), 131.5 (CH), 158.9 (C), 198.9 (CO) ppm.

^{19}F-NMR (282.4 MHz, C_6D_6) δ = -52.21 (s, 3F) ppm.

1-pentyl-4-(3,3,3-trifluoroprop-1-yn-1-yl)benzene hexacarbonyldicobalt (51f)



The general procedure was followed starting from 1-ethynyl-4-pentylbenzene. The cobalt complex was isolated as a red oil (181 mg, 69%).

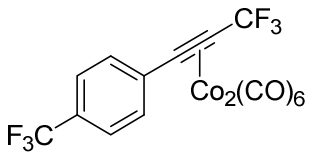
IR (film) $\nu_{max.}$ = 2960, 2934, 2860, 2105, 2037, 1601, 1280 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ = 0.78 (t, *J* = 7.1 Hz, 3H), 1.05-1.20 (m, 4H), 1.32-1.39 (m, 2H), 2.28 (m, 2H), 6.86 (m, 2H), 7.57 (m, 2H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 13.7 (CH_3), 22.4 (CH_2), 30.6 (CH_2), 31.3 (CH_2), 35.6 (CH_2), 76.1 (q, $^2J_{CF}$ = 49 Hz, C), 89.2 (C), 127.7 (q, $^1J_{CF}$ = 268 Hz, C), 129.3 (CH), 129.6 (CH), 132.7 (C), 144.3 (C), 197.3 (CO) ppm.

^{19}F-NMR (376 MHz, C_6D_6) δ = -51.80 (s, 3F) ppm.

1,1,1-trifluoromethyl-4-(3,3,3-trifluoroprop-1-yn-1-yl)benzene hexacarbonyldicobalt (51g)



The general procedure was followed starting from o-methoxy phenylacetylene. The cobalt complex was isolated as a red oil (105 mg, 44%).

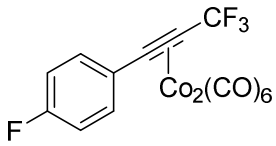
IR (film) $\nu_{max.}$ = 2110, 2070, 2038, 2028, 1616, 1275, 1103 cm^{-1}.

^{1}H-NMR (300 MHz, C_6D_6) δ = 7.08 (br s, 2H), 7.40 (br s, 2H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 77.1 (q, $^2J_{CF}$ = 48 Hz, C), 87.0 (C), 125.1 (q, $^1J_{CF}$ = 270 Hz, C), 127.1 (q, $^3J_{CF}$ = 4 Hz, CH), 128.5 (q, $^1J_{CF}$ = 267 Hz, C), 130.5 (2 CH), 131.2 (q, $^2J_{CF}$ = 33 Hz, C), 140.7 (C), 197.8 (CO) ppm.

^{19}F-NMR (282.4 MHz, C_6D_6) δ = -52.49 (s, 3F), -63.09 (s, 3F) ppm.

1-fluoro-4-(3,3,3-trifluoroprop-1-yn-1-yl)benzene hexacarbonyldicobalt (51h)



The general procedure was followed starting from 1-ethynyl-4-fluorobenzene. The cobalt complex was isolated as a red oil (147 mg, 62%).

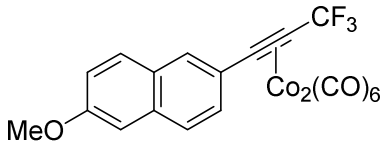
IR (film) $\nu_{max.}$ = 2104, 2076, 2025, 2013, 1610, 1493 cm^{-1}.

^{1}H-NMR (300 MHz, C_6D_6) δ = 6.51-6.59 (m, 2H), 7.35-7.42 (m, 2H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 77.0 (q, $^2J_{CF}$ = 47 Hz, C), 88.5 (C), 117.3 (d, $^2J_{CF}$ = 28 Hz, CH), 128.5 (q, $^1J_{CF}$ = 268 Hz, C), 132.3 (CH), 132.4 (CH), 132.5 (C), 163.7 (d, $^1J_{CF}$ = 249 Hz, C), 198.1 (CO) ppm.

^{19}F-NMR (282.4 MHz, C_6D_6) δ = -110.7 (m, 1F), -52.1 (s, 3F) ppm.

6-methoxy-2-(3,3,3-trifluoroprop-1-yn-1-yl)naphthalene hexacarbonyldicobalt (51i)



The general procedure was followed starting from 2-ethynyl-6-methoxynaphthalene. The cobalt complex was isolated as a red oil (188 mg, 70%).

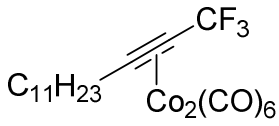
IR (film) $\nu_{max.}$ = 2101, 2064, 2020, 1623, 1209, 1110 cm^{-1}.

^{1}H-NMR (300 MHz, C_6D_6) δ = 3.29 (s, 3H), 6.77 (s, 1H), 7.02 (d, J = 8.9 Hz, 1H), 7.28 (d, J = 8.9 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 8.18 (s, 1H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 55.4 (CH_3), 77.3 (q, $^2J_{CF}$ = 49 Hz, C), 90.5 (C), 106.9 (CH), 120.9 (CH), 128.8 (q, $^1J_{CF}$ = 267 Hz, C), 129.9 (CH), 130.0 (CH), 130.8 (CH), 131.4 (C), 159.0 (C), 198.4 (CO) ppm.

^{19}F-NMR (282.4 MHz, C_6D_6) δ = -51.98 (s, 3F) ppm.

1,1,1-trifluorotetradec-2-yne hexacarbonyldicobalt (51j)



The general procedure was followed starting from tridecyne. The cobalt complex was isolated as a red oil (233 mg, 87%).

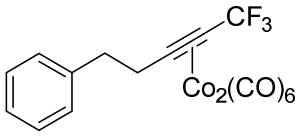
IR (film) $\nu_{max.}$ = 2928, 2857, 2105, 2033, 1602, 1467, 1255 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ = 0.88-1.51 (m, 23H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 13.8 (CH_3), 22.7 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 31.6 (CH_2), 31.9 (CH_2), 32.9 (CH_2), 77.2 (q, $^2J_{CF}$ = 47.0 Hz, C), 98.1 (C), 127.2 (q, $^1J_{CF}$ = 268 Hz, C), 197.7 (CO) ppm.

^{19}F-NMR (376 MHz, C_6D_6) δ = -52.20 (s, 3F) ppm.

(5,5,5-trifluoropent-3-yn-1-yl)benzene hexacarbonyldicobalt (51k)



The general procedure was followed starting from 3-butynylbenzene. The cobalt complex was isolated as a bright orange oil (144 mg, 60%).

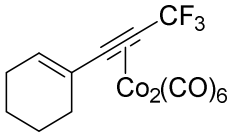
IR (film) $\nu_{max.}$ = 3031, 2928, 2106, 2065, 2033, 1601, 1255, 1140 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ = 2.40 (s, 4H), 6.51 (d, *J* = 6.7 Hz, 2H), 6.67-6.72 (m, 3H) ppm.

^{13}C-NMR (100 MHz, C_6D_6): δ = 34.3 (CH_2), 37.4 (CH_2), 77.2 (q, $^2J_{CF}$ = 49 Hz, C), 96.6 (C), 127.2 (q, $^1J_{CF}$ = 268 Hz, C), 126.3 (CH), 128.1 (CH), 128.6 (CH), 139.6 (C), 197.5 (CO) ppm.

^{19}F-NMR (376 MHz, C_6D_6) δ = -52.03 (s, 3F) ppm.

1-(3,3,3-trifluoroprop-1-yn-1-yl)cyclohexene hexacarbonyldicobalt (51l)



The general procedure was followed starting from o-methoxy phenylacetylene. The cobalt complex was isolated as a red oil (161 mg, 70%).

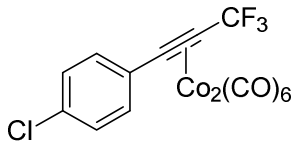
IR (film) $\nu_{max.}$ = 2102, 2066, 2046, 2000, 1585, 1276, 1102 cm^{-1}.

^{1}H-NMR (300 MHz, C_6D_6) δ = 1.25-1.41 (m, 4H), 1.71 (br s, 2H), 2.22 (br s, 2H), 6.34 (s, 1H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 22.3 (CH_2), 23.4 (CH_2), 27.0 (CH_2), 30.7 (CH_2), 77.6 (q, $^2J_{CF}$ = 49 Hz, C), 93.8 (C), 128.6 (q, $^1J_{CF}$ = 267 Hz, C), 133.7 (CH), 134.0 (CH), 198.8 (CO) ppm.

^{19}F-NMR (282.4 MHz, C_6D_6) δ = -52.33 (s, 3F) ppm.

1-chloro-4-(3,3,3-trifluoroprop-1-yn-1-yl)benzene hexacarbonyldicobalt (51m)



The general procedure was followed starting from *p*-chloro phenylacetylene. The cobalt complex was isolated as a red oil (180 mg, 30%).

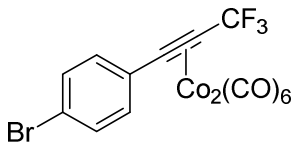
IR (film) $\nu_{max.}$ = 2107, 2071, 2034, 1276, 1144 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ = 6.57 (m, 2H), 7.02 (m, 2H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 29.8 (C), 87.0 (C), 127.5 (q, $^{1}J_{CF}$ = 268 Hz, C), 129.4 (CH), 130.5 (CH), 134.1 (C), 134.7 (C) ppm.

^{19}F-NMR (376 MHz, C_6D_6) δ = -52.81 (s, 3F) ppm.

1-bromo-4-(3,3,3-trifluoroprop-1-yn-1-yl)benzene hexacarbonyldicobalt (51n)



The general procedure was followed starting from *p*-bromo phenylacetylene. The cobalt complex was isolated as a red oil (225 mg, 84%).

IR (film) $\nu_{max.}$ = 2974, 2071, 2041, 1991, 1759 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ = 7.01 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H) ppm.

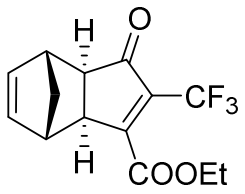
^{13}C-NMR (100 MHz, C_6D_6) δ = 123.0 (C), 130.7 (CH), 132.4 (CH), 134.5 (C), 197.0 (C) ppm.

^{19}F-NMR (376 MHz, C_6D_6) δ = -51.85 (s, 3F) ppm.

General conditions for the Pauson-Khand reaction with norbornadiene.

The cobalt complex corresponding to the desired alkyne was dissolved in anhydrous toluene (3 mL/0.1 mmol complex) in a round bottom flask with a magnetic stirrer and put under N_2. Norbornadiene (10 eq.) was then added, and the system was heated up to 70 °C. The reaction was allowed to progress for 24 hours. After that time, the solvent was removed under reduced pressure. The crude was purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarity.

ethyl *(3aS*,4S*,7R*,7aR*)*-1-oxo-2-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoindene-3-carboxylate (52a)



The general procedure was followed starting from the dicobalt hexacarobnyl complex of ethyl 4,4,4-trifluorobut-2-ynoate (90 mg, 0.20 mmol). The desired product was isolated as a white solid (53 mg, 92%).

Mp: 98-99 °C.

IR (KBr) $\nu_{max.}$ = 2891, 2876, 1728, 1659, 1461, 1352, 1269, 1014, 687cm^{-1}.

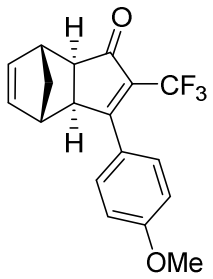
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.38 (t, *J* = 7.2 Hz, 3H), 1.57 (s, 1H), 2.53 (d, *J* = 5.2 Hz, 1H), 2.99 (s, 1H), 3.10 (m, 2H), 4.40 (q, *J* = 6.8 Hz, 2H), 6.28 (dd, *J* = 5.6 and 3.2 Hz, 1H), 6.33 (dd, *J* = 5.6 and 3.2 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 13.9 (CH_3), 41.4 (CH_2), 43.0 (CH), 44.6 (CH), 49.5 (CH), 53.0 (CH), 62.6 (CH_2), 119.6 (q, $^{1}J_{CF}$ = 273 Hz, C), 137.7 (q, $^{2}J_{CF}$ = 33 Hz, C), 138.0 (CH), 138.5 (CH), 164.3 (C), 166.9 (q, $^{3}J_{CF}$ = 3 Hz, C), 200.8 (C) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$) δ = -63.33 (s, 3F) ppm.

HRMS (ESI) calculated for $C_{14}H_{14}F_3O$ 309.0714, found 309.0717 $[M+H]^+$.

***(3aS*,4S*,7R*,7aR*)*-3-(4-methoxyphenyl)-2-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (52b)**



The general procedure was followed starting from cobalt complex **51b** (107 mg, 0.21 mmol). The desired product was isolated as a white solid (54 mg, 81%).

Mp: 122-124 °C.

IR (KBr) $\nu_{max.}$ = 2981, 2937, 1720, 1604, 1514 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.33 (dt, *J* = 9.6 and 1.5 Hz, 1H), 1.45 (dq, *J* = 9.6 and 1.6 Hz, 1H), 2.51 (s, 1H), 2.57 (dt, *J* = 5.6 and 1.3 Hz, 1H), 3.10 (s, 1H), 3.28 (m, 1H), 3.88 (s, 3H), 6.26 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.29 (dd, *J* = 5.6 and 2.8 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H) ppm.

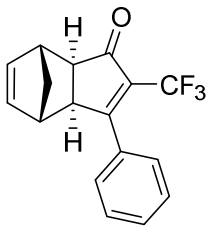
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 41.8 (CH_2), 43.7 (CH), 44.2 (CH), 52.3 (CH), 53.1 (q, $^{4}J_{CF}$ = 1 Hz, CH), 55.4 (CH_3), 114.0 (CH), 121.2 (q, $^{1}J_{CF}$ = 274 Hz, C), 125.5 (C), 129.7

(q, $^5J_{CF}$ = 2 Hz, CH), 131.6 (q, $^2J_{CF}$ = 30 Hz, C), 138.0 (CH), 138.2 (CH), 161.9 (C), 178.3 (q, $^3J_{CF}$ = 3 Hz, C), 202.1 (C) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$) δ = -59.96 (d, *J* = 1.8 Hz, 3F) ppm.

HRMS (ESI) calculated for $C_{18}H_{16}F_3O$ 321.1097, found 321.1099 $[M+H]^+$.

(*3aS*,4S*,7R*,7aR)-3-phenyl-2-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (52c)**



The general procedure was followed starting from cobalt complex **51c** (57 mg, 0.12 mmol). The desired product was isolated as a white solid (27 mg, 77%).

Mp: 125-126 °C.

IR (KBr) $\nu_{max.}$ = 2981, 2911, 1707, 1623 cm^{-1}.

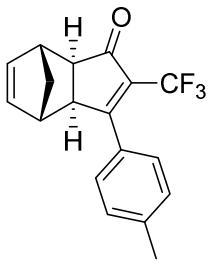
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.35-1.43 (m, 1H), 1.48 (dt, *J* = 9.6 and 1.6 Hz, 1H), 2.53 (s, 1H), 2.60 (dt, *J* = 5.4 and 1.4 Hz, 1H), 3.12 (m, 1H), 3.23 (dd, *J* = 5.2 and 2.4 Hz, 1H), 6.25 (dd, *J* = 5.7 and 3.1 Hz, 1H), 6.29 (dd, *J* = 5.6 and 3.0 Hz, 1H), 7.35-7.38 (m, 2H), 7.45-7.52 (m, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 41.6 (CH_2), 43.2 (CH), 44.3 (CH), 52.9 (CH), 53.2 (q, $^4J_{CF}$ = 1 Hz, CH), 120.9 (q, $^1J_{CF}$ = 274 Hz, C), 127.1 (q, $^3J_{CF}$ = 2 Hz, CH), 128.5 (CH), 130.1 (CH), 133.4 (q, $^2J_{CF}$ = 30 Hz, C), 133.8 (C), 137.9 (CH), 138.2 (CH), 179.0 (q, $^3J_{CF}$ = 3 Hz, C), 202.0 (C) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$) δ = -60.10 (d, *J* = 2.7 Hz, 3F) ppm.

HRMS (ESI) calculated for $C_{17}H_{14}F_3O$ 291.0991, found 291.0993 $[M+H]^+$.

***(3aS*,4S*,7R*,7aR*)*-3-(p-tolyl)-2-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (52d)**



The general procedure was followed starting from cobalt complex **51d** (440 mg, 0.91 mmol). The desired product was isolated as a white solid (265 mg, 95%).

Mp: 97-99 °C

IR (KBr) $\nu_{max.}$ = 2994, 2924, 2866, 1713, 1610, 1361, 1124 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.36 (dt, *J* = 9.7 and 1.5 Hz, 1H), 1.45 (dt, *J* = 9.6 and 1.6 Hz, 1H), 2.43 (s, 3H), 2.51 (m, 1H), 2.58 (dt, *J* = 5.5 and 1.4 Hz, 1H), 3.11 (m, 1H),

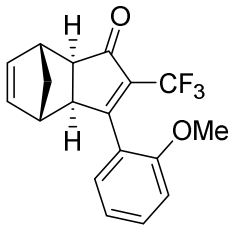
3.24 (ddd, *J* = 4.5, 2.2 and 1.1 Hz, 1H), 6.25 (dd, *J* = 5.5 and 3.0 Hz, 1H), 6.29 (dd, *J* = 5.6 and 2.9 Hz, 1H), 7.27-7.31 (m, 4H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 21.5 (CH_3), 41.6 (CH_2), 43.4 (CH), 44.3 (CH), 53.2 (q, $^4J_{CF}$ = 1 Hz, CH), 121.0 (q, $^1J_{CF}$ = 274 Hz, C), 127.4 (q, $^5J_{CF}$ = 2 Hz, CH), 139.3 (CH), 130.7 (C), 132.6 (q, $^3J_{CF}$ = 31 Hz, C), 138.0 (CH), 138.2 (CH), 141.2 (C), 179.1 (q, $^4J_{CF}$ = 3 Hz, C), 202.1 (C) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$) δ = -60.11 (d, *J* = 1.9 Hz, 3F) ppm.

HRMS (ESI) calculated for $C_{18}H_{16}F_3O$ 305.1148, found 305.1149 $[M+H]^+$.

***(3aS*,4S*,7R*,7aR*)*-3-(2-methoxyphenyl)-2-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (52e)**



The general procedure was followed starting from cobalt complex **51e** (97 mg, 0.20 mmol). The desired product was isolated as a white solid (47 mg, 74%).

Mp: 93-95 °C.

IR (KBr) $\nu_{max.}$ = 2977, 2931, 1707, 1631 cm^{-1}.

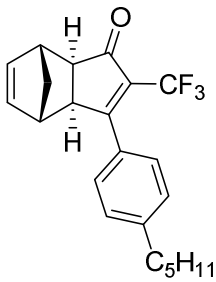
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.44-1.52 (m, 2H), 2.55-2.58 (m, 2H), 3.09-3.10 (m, 1H), 3.22-3.25 (m, 1H), 3.81 (s, 3H), 6.22 (dd, *J* = 5.5 and 3.0 Hz, 1H), 6.27 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.95-7.01 (m, 2H), 7.30-7.13 (m, 1H), 7.38-7.44 (m, 1H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 41.8 (CH_2), 43.0 (CH), 44.4 (CH), 52.8 (CH), 53.2 (CH), 55.5 (CH_3), 110.9 (CH), 120.4 (CH), 123.4 (C), 124.4 (q, $^1J_{CF}$ = 271 Hz, C), 127.4 (CH), 131.1 (CH), 134.8 (q, $^2J_{CF}$ = 31 Hz, C), 137.9 (CH), 138.4 (CH), 155.6 (C), 176.4 (C), 202.5 (C) ppm.

^{19}F-NMR (282.4 MHz, $CDCl_3$) δ = -63.40 (s, 3F) ppm.

HRMS (ESI) calculated for $C_{18}H_{16}F_3O_2$ 321.1102, found 321.1097 $[M+H]^+$.

(*3aS*,4S*,7R*,7aR)-3-(4-pentylphenyl)-2-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (52f)**



The general procedure was followed starting from cobalt complex **51f** (56 mg, 0.23 mmol). The desired product was isolated as a yellow oil (84 mg, quantitative).

IR (film) $\nu_{max.}$ = 2630, 2860, 1726, 1617 1361 cm^{-1}.

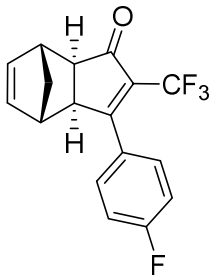
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.91 (t, *J* = 6.9 Hz, 3H), 1.33-1.39 (m, 5H), 1.45 (dp, *J* = 9.5 and 1.6 Hz, 1H), 1.66 (p, *J* = 7.5 Hz, 2H), 2.52 (s, 1H), 2.58 (d, *J* = 5.5 Hz, 1H), 2.67 (m, 2H), 3.11 (s, 1H), 3.25 (m, 1H), 6.25 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.29 (dd, *J* = 5.5 and 2.9 Hz, 1H), 7.27 - 7.32 (m, 4H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.0 (CH_3), 22.5 (CH_2), 30.8 (CH_2), 31.5 (CH_2), 35.8 (CH_2), 41.7 (CH_2), 43.4 (CH), 44.3 (CH), 52.6 (CH), 53.2 (q, $^4J_{CF}$ = 1 Hz, CH), 121.1 (q, $^1J_{CF}$ = 274 Hz, C), 127.4 (q, $^5J_{CF}$ = 2 Hz, CH), 128.6 (CH), 130.8 (C), 132.6 (q, $^3J_{CF}$ = 31 Hz, C), 137.9 (CH), 138.2 (CH), 146.2 (C), 179.1 (q, $^4J_{CF}$ = 3 Hz, C), 202.0 (C) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$) δ = -60.01 (d, *J* = 1.6 Hz, 3F) ppm.

HRMS (ESI) calculated for $C_{22}H_{23}F_3O$ 361.1774, found 361.1776 $[M+H]^+$.

***(3aS*,4S*,7R*,7aR*)*-3-(4-fluorophenyl)-2-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (52g)**



The general procedure was followed starting from cobalt complex **51g** (95 mg, 0.20 mmol). The desired product was isolated as a white solid (50 mg, 81%).

Mp: 84-86 °C.

IR (KBr) $\nu_{max.}$ = 2986, 2922, 1703, 1615, 1603 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.33-1.37 (m ,1H), 1.48 (dt, *J* = 9.6 and 1.5 Hz, 1H), 2.50 (s, 1H), 2.59 (dt, *J* = 5.5 and 1.3 Hz, 1H), 3.02-3.07 (m, 1H), 3.19-3.30 (m, 1H), 6.25 (dd, *J* = 5.5 and 3.0 Hz, 1H), 6.30 (dd, *J* = 5.6 and 2.9 Hz, 1H), 7.14-7.20 (m, 2H), 7.36-7.41 (m, 2H) ppm.

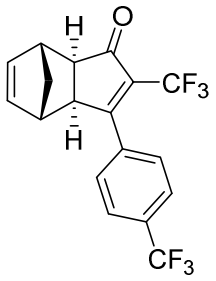
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 41.6 (CH_2), 43.2 (CH), 44.3 (CH), 52.8 (CH), 53.2 (CH), 116.4 (q, $^2J_{CF}$ = 22 Hz, CH), 120.9 (q, $^1J_{CF}$ = 272 Hz, C), 129.4-129.6 (m, CH and C),

133.3 (q, $^2J_{CF}$ = 31 Hz, C), 138.0 (CH), 138.2 (CH), 164.0 (d, $^1J_{CF}$ = 251 Hz, C), 177.6 (q, $^3J_{CF}$ = 3 Hz, C), 201.8 (C) ppm.

^{19}F-NMR (282.4 MHz, $CDCl_3$) δ = -60.57 (d, *J* = 1.9 Hz, 3F), -109.3-(-109.4) (m, 1F) ppm.

HRMS (ESI) calculated for $C_{17}H_{13}F_4O$ 309.0903, found 309.0897 $[M+H]^+$.

***(3aS*,4S*,7R*,7aR*)*-2-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (52h)**



The general procedure was followed starting from cobalt complex **51h** (105 mg, 0.20 mmol). The desired product was isolated as a white solid (50 mg, 70%).

Mp: 88-90 °C.

IR (KBr) $\nu_{max.}$ = 2985, 1711, 1612 cm^{-1}.

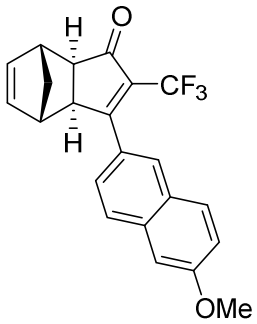
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.37-1.41 (m ,1H), 1.53 (dt, *J* = 9.7 and 1.4 Hz, 1H), 2.53 (s, 1H), 2.63 (dt, *J* = 5.4 and 1.3 Hz, 1H), 3.11-3.16 (m, 1H), 3.18-3.25 (m, 1H), 6.25 (dd, *J* = 5.6 and 3.1 Hz, 1H), 6.31 (dd, *J* = 5.6 and 3.0 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 8.1 Hz, 2H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 41.5 (CH_2), 42.9 (CH), 44.4 (CH), 53.1 (CH), 53.3 (CH), 120.6 (q, $^1J_{CF}$ = 272 Hz, C), 123.6 (q, $^1J_{CF}$ = 270 Hz, C), 125.6 (q, $^2J_{CF}$ = 15 Hz, CH), 127.3 (q, $^3J_{CF}$ = 6 Hz, CH), 132.2 (q, $^2J_{CF}$ = 33 Hz, C), 134.5 (q, $^2J_{CF}$ = 31 Hz, C), 137.4 (C), 138.2 (CH), 138.2 (CH), 177.3 (q, $^4J_{CF}$ = 3 Hz, C), 201.1 (C) ppm.

^{19}F-NMR (282.4 MHz, $CDCl_3$) δ = -60.74 (d, *J* = 2.0 Hz, 3F), -63.43 (s, 3F) ppm.

HRMS (ESI) calculated for $C_{18}H_{13}F_6O$ 359.0871, found 359.0865 $[M+H]^+$.

***(3aS*,4S*,7R*,7aR*)*-3-(2-methoxyphenyl)-2-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (52i)**



The general procedure was followed starting from cobalt complex **51i** (107 mg, 0.20 mmol). The desired product was isolated as a white solid (59 mg, 80%).

Mp: 62-64°C.

IR (KBr) $\nu_{max.}$ = 2973, 2935, 1707, 1620, 1600 cm^{-1}.

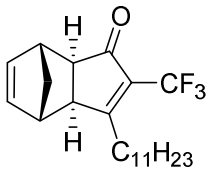
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.40-1.43 (m, 1H), 1.47 (dt, *J* = 9.5 and 1.3 Hz, 1H), 2.52 (s, 1H), 2.63 (dt, *J* = 5.5 and 1.1 Hz, 1H), 3.11-3.16 (m, 1H), 3.35-3.41 (m, 1H), 3.96 (s, 3H), 6.26 (dd, *J* = 5.3 and 2.9 Hz, 1H), 6.31 (dd, *J* = 5.6 and 2.9 Hz, 1H), 7.18-7.26 (m, 2H), 7.42-7.46 (m, 1H), 7.80-7.83 (m, 3H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 41.8 (CH_2), 43.5 (CH), 44.3 (CH), 52.7 (CH), 53.2 (CH), 55.4 (CH_3), 105.7 (CH), 120.0 (CH), 121.1 (q, $^1J_{CF}$ = 272 Hz, C), 126.5 (CH), 127.1 (CH), 127.5 (CH), 128.0 (C), 128.6 (C), 130.3 (CH), 132.7 (q, $^2J_{CF}$ = 34 Hz, C), 135.7 (C), 138.0 (CH), 138.3 (CH), 159.2 (C), 179.0 (C), 202.1 (C) ppm.

^{19}F-NMR (282.4 MHz, $CDCl_3$) δ = -60.27 (d, *J* = 1.8 Hz, 3F) ppm.

HRMS (ESI) calculated for $C_{22}H_{18}F_3O_2$ 371.1259, found 371.1253 $[M+H]^+$.

***(3aS*,4S*,7R*,7aR*)*-2-(trifluoromethyl)-3-undecyl-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (52j)**



The general procedure was followed starting from cobalt complex **51j**(233 mg, 0.42 mmol). The desired product was isolated as a pale yellow oil (122 mg, 79%).

IR (film) $\nu_{max.}$ = 2927, 2855, 1718, 1364 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.87 (m, 3H), 1.26-1.68 (m, 20H), 2.39 (dt, *J* = 5.3 and 1.4 Hz, 1H), 2.41-2.47 (m, 1H), 2.78-2.85 (m, 2H), 2.88 (s, 1H), 3.03 (s, 1H), 6.26 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.31 (dd, *J*=5.6, 3.0 Hz, 1H) ppm.

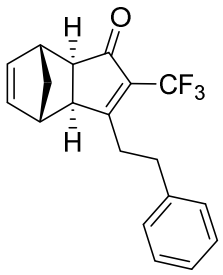
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.1 (CH_3), 22.7 (CH_2), 28.3 (q, $^5J_{CF}$ = 2 Hz, CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.8 (CH_2), 30.5 (q, $^4J_{CF}$ = 2 Hz, CH_2,), 31.9

(CH_2), 41.4 (CH_2), 43.0 (CH), 44.0 (CH), 51.1 (CH), 52.8 (q, $^4J_{CF}$ = 1 Hz, CH), 121.5 (q, $^1J_{CF}$ = 273 Hz, C), 133.2 (q, $^2J_{CF}$ = 31 Hz, C), 137.9 (CH), 138.1 (CH), 184.4 (q, $^3J_{CF}$ = 3 Hz, C), 202.3 (C) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$) δ = -61.10 (s, 3F) ppm.

HRMS (ESI) calculated for $C_{22}H_{32}F_3O$ 369.2400, found 369.2399 $[M+H]^+$.

***(3aS*,4S*,7R*,7aR*)*-3-phenethyl-2-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (52k)**



The general procedure was followed starting from cobalt complex **51k** (103 mg, 0.21 mmol). The desired product was isolated as a colourless oil (50 mg, 77%).

IR (film) $\nu_{max.}$ = 2934, 2860, 1720 cm^{-1}.

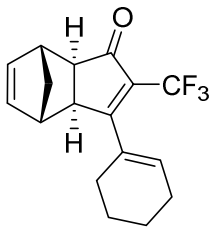
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.26 (m, 1H), 1.46 (m, 1H), 2.38 (dt, *J* = 5.4 and 1.3 Hz, 1H), 2.71-2.78 (m, 2H), 2.84-2.97 (m, 3H), 3.04 (s, 1H), 3.12-3.19 (m, 1H), 6.25 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.29 (dd, *J* = 5.6 and 2.9 Hz, 1H), 7.21 (m, 3H), 7.31-7.34 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 32.4 (q, $^4J_{CF}$ = 2 Hz, CH_2), 34.4 (q, $^3J_{CF}$ = 2 Hz, CH_2), 41.4 (CH_2), 43.0 (CH), 44.1 (CH), 51.5 (CH), 52.9 (q, $^4J_{CF}$ = 1 Hz, CH), 122.8 (q, $^1J_{CF}$ = 272 Hz, C), 126.7 (CH), 128.2 (CH), 137.9 (CH), 138.2 (CH), 133.8 (q, $^2J_{CF}$ = 30 Hz, C), 182.9 (q, $^3J_{CF}$ = 3 Hz, C), 202.1 (C) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$) δ = -61.22 (d, *J* = 1.2 Hz, 3F) ppm.

HRMS (ESI) calculated for $C_{19}H_{18}F_3O$ 319.1304, found 319.1304 $[M+H]^+$.

(*3aS*,4S*,7R*,7aR)-3-(1-cyclohexenyl)-2-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (52l)**



The general procedure was followed starting from cobalt complex **51l** (93 mg, 0.20 mmol). The desired product was isolated as a white solid (35 mg, 60%).

Mp: 115-117 °C.

IR (KBr) $\nu_{max.}$ = 2979, 2952, 2926, 1703, 1608 cm^{-1}.

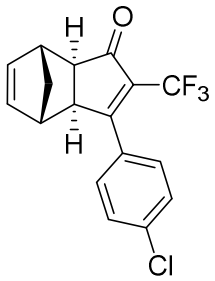
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.23-1.27 (m, 1H), 1.45 (dt, *J* = 9.6 and 1.4 Hz, 1H), 1.59-1.81 (m, 4H), 2.03-2.37 (m, 4H), 2.42 (dt, *J* = 5.5 and 1.3 Hz, 1H), 2.74-2.79 (m, 1H), 2.92-2.97 (m, 1H), 3.02-3.07 (m, 1H), 5.86-5.89 (m, 1H), 6.24-6.31 (m, 2H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 21.5 (CH_2), 22.2 (CH_2), 25.3 (CH_2), 27.2 (CH_2), 41.6 (CH_2), 43.0 (CH), 44.2 (CH), 50.7 (CH), 52.7 (CH), 121.1 (q, $^1J_{CF}$ = 272 Hz, C), 130.8 (q, $^3J_{CF}$ = 2 Hz, C), 131.6 (q, $^2J_{CF}$ = 30 Hz, C), 132.3 (CH), 138.0 (CH), 182.4 (C), 202.4 (C) ppm.

^{19}F-NMR (282.4 MHz, $CDCl_3$) δ = -61.00 (d, *J* = 1.9 Hz, 3F) ppm.

HRMS (ESI) calculated for $C_{17}H_{18}F_3O$ 295.1310, found 295.2304 $[M+H]^+$.

(*3aS*,4S*,7R*,7aR)-3-(4-chlorophenyl)-2-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (52m)**



The general procedure was followed starting from cobalt complex **51m** (83 mg, 0.17 mmol). The desired product was isolated as a white solid (28 mg, 51%).

Mp: 95-97 °C.

IR (KBr) $\nu_{max.}$ = 2986, 1714, 1614, 1362, 1131 cm^{-1}.

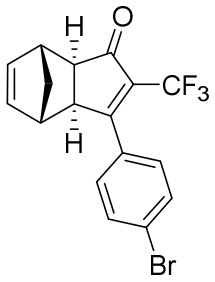
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.35 (dtd, *J* = 9.6, 1.5 and 0.8 Hz, 1H), 1.48 (dt, *J* = 9.7 and 1.5 Hz, 1H), 2.51 (s, 1H), 2.59 (m, 1H), 3.11 (s, 1H), 3.20 (dq, *J* = 4.3 and 2.2 Hz, 1H), 6.25 (dd, *J* = 5.6 and 3.1 Hz, 1H), 6.29 (dd, *J* = 5.6 and 2.9 Hz, 1H), 7.32 (m, 2H), 7.46 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 41.6 (CH_2), 43.1 (CH), 44.3 (CH), 52.8 (CH), 53.2 (q, $^4J_{CF}$ = 1 Hz, CH), 120.8 (q, $^1J_{CF}$ = 274 Hz, C), 128.5 (q, $^5J_{CF}$ = 2 Hz, CH), 129.0 (CH), 132.0 (q, $^2J_{CF}$ = 31 Hz, C), 136.9 (C), 138.0 (CH), 138.2 (CH), 177.3 (q, $^4J_{CF}$ = 3 Hz, C), 201.6 (C) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$) δ = -60.13 (d, *J* = 2 Hz, 3F) ppm.

HRMS (ESI) calculated for $C_{17}H_{14}ClF_3O$ 295.1310, found 295.2304 $[M+H]^+$.

(*3aS*,4S*,7R*,7aR)-3-(4-bromophenyl)-2-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (52n)**



The general procedure was followed starting from cobalt complex **51n** (24 mg, 0.05 mmol). The desired product was isolated as a colorless oil (18 mg, 67%).

IR (KBr) $\nu_{max.}$ = 2979, 1720, 1363, 1195, 1128 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.35 (dt, *J* = 9.6, 1.5 Hz, 1H), 1.49 (dt, *J* = 9.6, 1.5 Hz, 1H), 2.51 (dt, *J* = 2.4, 0.8 Hz, 1H), 2.59 (dt, *J* = 5.5, 1.3 Hz, 1H), 3.12 (dd, *J* = 2.8, 1.3 Hz, 1H), 3.19 (ddq, *J* = 4.3, 2.1, 1.1 Hz, 1H), 6.25 (dd, *J* = 5.6, 3.1 Hz, 1H), 6.30 (dd, *J* = 5.6, 2.9 Hz, 1H), 7.23-7.25 (m, 2H), 7.60-7.64 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 41.5 (CH_2), 43.1 (CH), 44.4 (CH), 52.7 (CH), 53.1 (q, $^4J_{CF}$ = 1 Hz, CH), 120.8 (q, $^1J_{CF}$ = 274 Hz, C), 125.1 (C), 128.5 (q, $^4J_{CF}$ = 2 Hz, CH), 131.9 (CH), 132.5 (C), 133.7 (q, $^2J_{CF}$ = 31 Hz, CH), 138.0 (CH), 138.2 (CH), 177.4 (C), 201.6 (C) ppm.

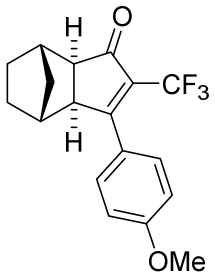
^{19}F-NMR (376 MHz, $CDCl_3$) δ = -60.14 (d, *J* = 2.1 Hz, 3F) ppm.

HRMS (ESI) calculated for $C_{17}H_{14}BrF_3O$ 369.0096, found 369.0100 $[M+H]^+$.

General conditions for the Pauson-Khand reaction with norbornene.

The cobalt complex corresponding to the desired alkyne was dissolved in anhydrous toluene (4 mL/0.1 mmol complex) in a round bottom flask with a magnetic stirrer and put under N_2. Norbornene (10 eq.) was then added, and the system was heated up to 80 °C. The reaction was allowed to progress for 24 hours. After that time, the solvent was removed under reduced pressure. The crude was purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarity.

(*3aS*,4R*,7S*,7aR)-3-(4-methoxyphenyl)-2-(trifluoromethyl)-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-1-one (53b)**



The general procedure was followed starting from cobalt complex **2a** (123 mg, 0.25 mmol) and heated at 80 °C for 96h. The desired products were isolated as colorless oils (35 mg, 51%) and as a 6.4:1 mixture of regioisomers that could be separated by silica gel chromatography.

IR (film) $\nu_{max.}$ = 2960, 2876, 1713, 1604, 1512, 1175, 839 cm^{-1}.

^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1.00 (dp, *J* = 10.8 and 1.4 Hz, 1H), 1.09 (m, 1H), 1.34-1.37 (m, 2H), 1.62-1.64 (m, 2H), 2.00 (s, 1H), 2.45 (dt, *J* = 5.7 and 1.1 Hz, 1H), 2.57 (dd, *J* = 2.6 and 1.4 Hz,1H), 3.12 (ddt, *J* = 5.9, 2.3 and 1.2 Hz, 1H), 3.87 (s, 3H), 6.93-7.02 (m, 2H), 7.37-7.42 (m, 2H) ppm.

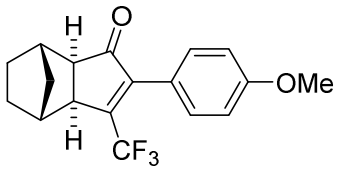
^{13}C-RMN (100 MHz, $CDCl_3$) δ = 28.5 (CH_2), 28.9 (CH_2), 31.6 (CH_2), 36.7 (CH), 39.6 (CH), 52.5 (CH), 54.2 (q, $^4J_{CF}$ = 1 Hz, CH), 55.4 (CH_3), 114.0 (CH), 121.7 (q, $^1J_{CF}$ = 273 Hz, C), 125.7 (C), 129.8 (q, $^5J_{CF}$ = 2 Hz, CH), 130.9 (q, $^2J_{CF}$ = 25 Hz, C), 161.8 (C), 178.3 (q, $^3J_{CF}$ = 3 Hz, C), 203.6 (C) ppm.

^{19}F-RMN (376 MHz, $CDCl_3$) δ = -59.77 (d, *J* = 2.4 Hz, 3F) ppm.

HRMS (ESI) calculated for $C_{18}H_{18}F_3O_2$ 323.1253, found 323.1251 $[M+H]^+$.

<u>Minor regioisomer</u>

(*3aS*,4R*,7S*,7aR)-2-(4-methoxyphenyl)-3-(trifluoromethyl)-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-1-one (54b)**



IR (film) $\nu_{max.}$ = 2958, 1719, 1608, 1512, 1173 cm^{-1}.

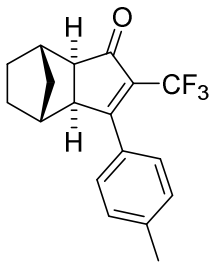
^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1.21-1.07 (m, 2H), 1.46-1.31 (m, 2H), 1.64 (tt, *J* = 12.6 and 4.2 Hz, 1H), 1.84-1.71 (m, 1H), 2.44 (d, *J* = 5.5 Hz, 1H), 2.57-2,51 (m, 2H), 2.92 (d, *J* = 5.5 Hz, 1H), 3.82 (d, *J* = 2.9 Hz, 4H), 6.97-6.89 (m, 2H), 7.27-7.19 (m, 2H) ppm.

^{13}C-RMN (100 MHz, $CDCl_3$) δ = 28.3 (CH_2), 29.0 (CH_2), 31.3 (CH_2), 38.2 (CH), 40.1 (CH), 47.1 (q, $^3J_{CF}$ = 2 Hz, CH), 53.5 (CH), 55.2 (CH_3), 113.6 (CH), 113.7 (q, $^2J_{CF}$ = 14 Hz, C), 128.3 (C), 130.3 (q, $^5J_{CF}$ = 2 Hz, CH), 156.1 (q, $^1J_{CF}$ = 220 Hz, C), 160.3 (C), 208.1 (C) ppm.

^{19}F-RMN (376 MHz, $CDCl_3$) δ = -60.90 (s, 3F) ppm.

HRMS (ESI) calculated for $C_{18}H_{18}F_3O_2$ 323.1253, found 323.1255 $[M+H]^+$.

(*3aS*,4R*,7S*,7aR)-3-(4-tolyl)-2-(trifluoromethyl)-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-1-one (53d)**



The general procedure was followed starting from cobalt complex **2c** (75 mg, 0.15 mmol) and heated at 80 °C for 24h. The desired products were isolated as white solids (36 mg, 87%) and as a 5.9:1 mixture of regioisomers that could be separated by silica gel chromatography.

Mp: 94-96 °C

IR (KBr) $\nu_{max.}$ = 2961, 2874, 1705, 1618, 1364, 1124, 983, 831 cm^{-1}.

^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1.01 (dp, *J* = 10.8 and 1.4 Hz, 1H), 1.12 (dp, *J* = 10.7 and 1.9 Hz, 1H), 1.35 (m, 2H), 1.63 (m, 2H), 2.00 (dd, *J* = 3.0 and 1.5 Hz, 1H), 2.42 (s, 2H), 2.45 (dt, *J* = 5.6 and 1.1 Hz, 1H), 2.60-2.56 (m, 1H), 3.09 (ddd, *J* = 4.9, 3.0 and 1.6 Hz, 1H), 7.31-7.24 (m, 4H) ppm.

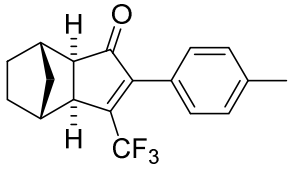
^{13}C-RMN (100 MHz, $CDCl_3$) δ = 21.4 (CH_3), 28.4 (CH_2), 28.9 (CH_2), 31.5 (CH_2), 38.4 (CH), 39.6 (CH), 52.9 (CH), 54.3 (q, $^4J_{CF}$ = *1 Hz*, CH), 121.5 (q, $^1J_{CF}$ = *273 Hz*, C), 127.5 (q, $^5J_{CF}$ = *2 Hz*, CH), 129.2 (CH), 130.9 (C), 132.0 (q, $^2J_{CF}$ = *31 Hz*, C), 141.1 (C), 179.1 (q, $^4J_{CF}$ = *3 Hz*, C), 203.6 (m, C) ppm.

^{19}F-RMN (376 MHz, $CDCl_3$) δ = -59.88 (d, *J* = 2.4 Hz, 3F) ppm.

HRMS (ESI) calculated for $C_{18}H_{18}F_3O$ 307.1304, found 323.1303 $[M+H]^+$.

<u>Minor regioisomer</u>

(*3aS*,4R*,7S*,7aR)-2-(4-tolyl)-3-(trifluoromethyl)-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-1-one (54d)**



Mp: 94-96 °C

IR (KBr) $\nu_{max.}$ = 2958, 1719, 1608, 1512, 1173, 1127 cm^{-1}.

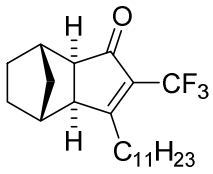
^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1.23-1.08 (m, 2H), 1.39 (m, 2H), 1.70-1.59 (m, 1H), 1.84-1.72 (m, 1H), 2.40-2.35 (m, 3H), 2.45 (d, *J* = 5.5 Hz, 1H), 2.56-2.54 (m, 2H), 2.93 (d, *J* = 5.5 Hz, 1H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H) ppm.

^{13}C-RMN (100 MHz, $CDCl_3$) δ = 21.4 (CH_3), 28.3 (CH_2), 29.0 (CH_2), 31.3 (CH_2), 38.2 (CH), 40.1 (CH), 47.2 (q, $^3J_{CF}$ = 2 Hz, CH), 53.6 (CH), 124.2 (q, $^1J_{CF}$ = 274 Hz, C), 126.0 (C), 128.7 (q, $^5J_{CF}$ = 2 Hz, CH), 128.8 (CH), 139.2 (C), 155.4 (C), 207.9 (C) ppm.

^{19}F-RMN (376 MHz, $CDCl_3$) δ = -60.08 (s, 3F) ppm.

HRMS (ESI) calculated for $C_{18}H_{18}F_3O$ 323.1304, found 323.1306 $[M+H]^+$.

(*3aS*,4R*,7S*,7aR)-2-(trifluoromethyl)-3-undecyl-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-1-one (53j)**



The general procedure was followed starting from cobalt complex **2i** (150 mg, 0.28 mmol) and heated at 80 °C for 19h. The desired product was isolated as a colorless oil (41 mg, 40%).

IR (film) $\nu_{max.}$ = 2927, 2855, 1718, 1638, 1367, 1130 cm^{-1}.

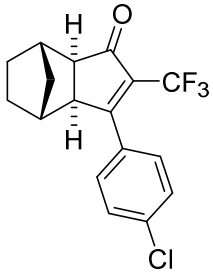
^{1}H-RMN (400 MHz, $CDCl_3$) δ = 0.91-0.86 (m, 3H), 1.06-1.03 (m, 2H), 1.65-1.60 (m, 20H), 1.78-1.70 (m, 1H), 2.28 (d, *J* = 5.5 Hz, 1H), 2.37 (d, *J* = 4.4 Hz, 1H), 2.43 (m, 1H), 2.50 (d, *J* = 4.1 Hz, 1H), 2.70 (dd, *J* = 5.6 and 2.4 Hz, 1H), 2.85-2.75 (m, 1H) ppm.

^{13}C-RMN (100 MHz, $CDCl_3$) δ = 14.1 (CH_3), 22.7 (CH_2), 28.3 (CH_2), 28.51-28.3 (q, $^6J_{CF}$ = *1 Hz*, CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 29.9 (CH_2), 30.5 (q, $^5J_{CF}$ = *2 Hz*, CH_2), 31.5 (CH_2), 31.9 (CH_2), 38.0 (CH), 39.4 (CH), 51.6 (CH), 54.0 (CH), 122.0 (d, $^1J_{CF}$ = *273 Hz*, C), 132.7 (q, $^2J_{CF}$ = 31 Hz, C), 184.6 (q, $^3J_{CF}$ = *3 Hz*, C), 203.9 (C) ppm.

^{19}F-RMN (376 MHz, $CDCl_3$) δ = -61.06 (s, 3F) ppm.

HRMS (ESI) calculated for $C_{22}H_{34}F_3O$ 371.2556, found 371.2559 $[M+H]^+$.

(*3aS*,4R*,7S*,7aR)-3-(4-chlorophenyl)-2-(trifluoromethyl)-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-1-one (53m)**



The general procedure was followed starting from cobalt complex **2m** (100 mg, 0.20 mmol) and heated at 80 °C for 72h. The desired products were isolated as colorless oils (19 mg, 41%) and as a 2.5:1 mixture of regioisomers that could be separated by silica gel chromatography.

IR (film) $\nu_{max.}$ = 2961, 1718, 1365, 1188, 1128 cm^{-1}.

^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1.01-1.10 (m,1H), 1.17-1.08 (m, 1H), 1.41-1.29 (m, 2H), 1.69-1.60 (m, 2H), 2.04-1.98 (m, 1H), 2.48 (dd, *J* = 5.6 and 1.3 Hz, 1H), 2.63-2.57 (m, 1H), 3.09-3.02 (m, 1H), 7.34-7.27 (m, 2H), 7.49-7.41 (m, 1H) ppm.

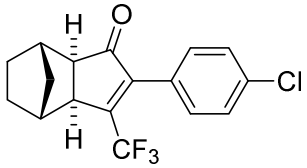
^{13}C-RMN (100 MHz, $CDCl_3$) δ = 28.4 (CH_2), 28.9 (CH_2), 31.5 (CH_2), 38.1 (CH), 40.0 (CH), 53.0 (CH), 54.3 (CH), 121.2 (q, $^{1}J_{CF}$ = 274 Hz, C), 128.7 (q, $^{5}J_{CF}$ = 2 Hz, CH), 128.9 (CH), 132.2 (C), 133.0 (q, $^{2}J_{CF}$ = 31 Hz, C), 136.7 (C), 177.2 (q, $^{4}J_{CF}$ = 3 Hz, C), 203.1 (C) ppm.

^{19}F-RMN (376 MHz, $CDCl_3$) δ = -59.97 (d, *J* = 2.1 Hz, 3F) ppm.

HRMS (ESI) calculated for $C_{17}H_{15}ClF_3O$ 327.0758, found 327.0759 $[M+H]^+$.

Minor regioisomer

***(3aS*,4R*,7S*,7aR*)*-2-(4-chlorophenyl)-3-(trifluoromethyl)-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-1-one (54m)**



IR (film) $\nu_{max.}$ = 2960, 1720, 1492, 1175 cm^{-1}.

^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1.12-1.18 (m, 2H), 1.47-1.34 (m, 2H), 1.69-1.60 (m, 1H), 1.84-1.73 m, 1H), 2.47 (d, *J* = 5.5 Hz, 1H), 2.56 (s, 2H), 2.98-2.91 (m, 1H), 7.21-7.17 (m, 2H), 7.40-7.36 (m, 2H) ppm.

^{13}C-RMN (100 MHz, $CDCl_3$) δ = 28.2 (CH_2), 29.1 (CH_2), 31.3 (CH_2), 38.2 (CH), 40.2 (CH), 47.3 (q, $^{3}J_{CF}$ = 2 Hz, CH), 53.6 (CH), 124.0 (C), 127.4 (C), 128.5 (C), 130.2 (q, $^{5}J_{CF}$ = 2 Hz, CH), 135.4 (C), 207.3 (C) ppm.

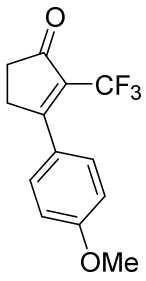
^{19}F-RMN (376 MHz, $CDCl_3$) δ = -60.16 (s, 3F) ppm.

HRMS (ESI) calculated for $C_{17}H_{15}ClF_3O$ 327.0758, found 327.0760 $[M+H]^+$.

General conditions for the Pauson-Khand reaction with ethylene.

The cobalt complex corresponding to the desired alkyne was dissolved in anhydrous toluene (7 mL/0.1 mmol complex) in a pressure flask provided with a manometer and a magnetic stirrer. The system was then loaded with ethylene (6 bars) and heated up at 80-85°C until no starting cobalt complex could be detected by TLC. After that time, the solvent was removed under reduced pressure. The crude was purified by silica gel chromatography using mixtures of hexanes/AcOEt of increasing polarity.

3-(4-methoxyphenyl)-2-(trifluoromethyl)cyclopent-2-en-1-one (55b)



The general procedure was followed starting from cobalt complex 2k (35 mg, 0.07 mmol). The desired product was isolated as a colorless oil (11 mg, 58%).

IR (film) $\nu_{max.}$ = 2934, 1725, 1608, 1513, 1259, 1173 cm^{-1}.

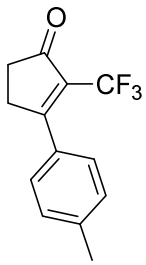
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.69 (m, 2H), 2.87 (m, 2H), 3.83 (s, 3H), 6.94 (m, 2H), 7.25 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 24.7 (q, $^4J_{CF}$ = 2 Hz, CH_2), 30.4 (CH_2), 55.2 (CH_3), 113.7 (CH), 121.0 (C), 122.6 (q, $^1J_{CF}$ = 273 Hz, C), 130.4 (q, $^5J_{CF}$ = 2 Hz, CH), 145.0 (q, $^3J_{CF}$ = 3 Hz, C), 152.6 (q, $^2J_{CF}$ = 34 Hz, C), 160.3 (C), 206.3 (C) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$) δ = -62.76 (s, 3F) ppm.

HRMS (ESI) calculated for $C_{13}H_{15}F_3NO$ 274.1049, found 274.1045 $[M+NH_4]^+$.

3-(*p*-tolyl)-2-(trifluoromethyl)cyclopent-2-en-1-one (55d)



The general procedure was followed starting from cobalt complex 2k (63 mg, 0.13 mmol). The desired product was isolated as a white solid (17 mg, 53%).

Mp: 83-85 °C.

IR (KBr) $\nu_{max.}$ = 2978, 1681, 1594, 1092 cm^{-1}.

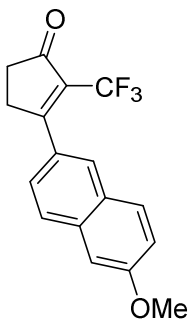
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.38 (s, 3H), 2.70 (m, 2H), 2.87 (m, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J= 8.0 Hz*, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 21.3 (CH_3), 24.08 (CH_2), 34.0 (CH_2), 122.5 (q, $^1J_{CF}$ = 273 Hz, C), 125.9 (C), 128.8 (q, $^5J_{CF}$ = 2 Hz, CH), 128.9 (CH), 139.2 (C), 145.5 (C), 153.4 (C), 206.1 (C) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$) δ = -62.82 (s, 3F) ppm.

HRMS (ESI) calculated for $C_{13}H_{12}F_3O$ 241.0835, found 241.0836 $[M+H]^+$.

3-(6-methoxynaphthalen-2-yl)-2-(trifluoromethyl)cyclopent-2-en-1-one (55i)



The general procedure was followed starting from cobalt complex 2h (61 mg, 0.11 mmol). The desired product was isolated as a yellow oil (14 mg, 41%).

IR (film) $\nu_{max.}$ = 2937, 1722, 1629, 1602, 1124 cm^{-1}.

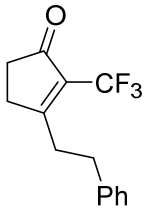
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.74 (m, 2H), 2.93 (m, 2H), 3.93 (s, 3H), 7.17-7.18 (m, 2H), 7.31-7.33 (m, 1H), 7.72 (m, 1H), 7.73-7.77 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 24.9 (q, $^4J_{CF}$ = 2 Hz, CH_2), 34.1 (CH_2), 55.3 (CH_3), 105.6 (CH), 119.2 (CH), 124.0 (C), 126.6 (CH), 126.7 (q, $^5J_{CF}$ = 2 Hz, CH), 128.3 (C), 128.7 (q, $^5J_{CF}$ = 2 Hz, CH), 130.0 (CH), 134.7 (C), 145.6 (q, $^4J_{CF}$ = 3 Hz, C), 153.5 (q, $^2J_{CF}$ = 34 Hz, C), 158.5 (C), 206.1 (C) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$) δ = -62.70 (s, 3F) ppm.

HRMS (ESI) calculated for $C_{17}H_{14}F_3O_2$ 307.0940, found 307.0942 $[M+H]^+$.

3-phenethyl-2-(trifluoromethyl)cyclopent-2-en-1-one (55k)



The general procedure was followed starting from cobalt complex 2k (74 mg, 0.15 mmol). The desired product was isolated as a colorless oil (9 mg, 23%).

IR (film) $\nu_{max.}$ = 2933, 1721, 1236, 1129 cm^{-1}.

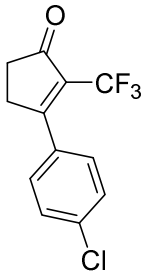
^{1}H-NMR (400 MHz, C_6D_6) δ = 1.45 (m, 2H), 1.59 (m, 2H), 2.35-2.48 (m, 4H), 6.73-6.92 (m, 5H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 24.0 (CH_2), 25.8 (CH_2), 32.8 (CH_2), 34.3 (q, $^4J_{CF}$ = 1 Hz, CH_2), 123.2 (q, $^1J_{CF}$ = 273 Hz, C), 124.7 (C), 125.9 (C), 126.2 (C), 128.2 (CH), 128.3 (CH), 128.4 (CH), 205.4 (q, $^3J_{CF}$ = 20 Hz, C) ppm.

^{19}F-NMR (376 MHz, C_6D_6) δ = -64.40 (s, 3F) ppm.

HRMS (ESI) calculated for $C_{14}H_{14}F_3O$ 285.1461, found 285.1461 $[M+H]^+$.

3-(4-chlorophenyl)-2-(trifluoromethyl)cyclopent-2-en-1-one (55m)



The general procedure was followed starting from cobalt complex 2k (34 mg, 0.07 mmol). The desired product was isolated as a yellow oil (10 mg, 56%).

IR (film) $\nu_{max.}$ = 2917, 1723, 1489, 1257, 1126 cm^{-1}.

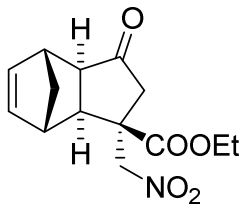
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.71 (m, 2H), 2.90 (m, 2H), 7.21 (m, 2H), 7.39 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 24.9 (CH_2), 34.0 (CH_2), 127.2 (C), 128.5 (CH), 130.3 (CH), 135.5 (C), 205.4 (C) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$) δ = -62.87 (s, 3F) ppm.

HRMS (ESI) calculated for $C_{12}H_9ClF_3O$ 261.0289, found 261.0285 $[M+H]^+$.

ethyl *(1R*,3aR*,4R*,7S*,7aS*)*-1-(nitromethyl)-3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoindene-1-carboxylate (56)



PK adduct **52a** (90 mg, 0.31 mmol, 1 equiv.) was dissolved in nitromethane (5 mL), and TBAF·$3H_2O$ (100 mg, 0.31 mmol, 1 eq.) was added in one portion at room temperature. The reaction mixture was stirred at 90 °C for 3 h. The volume was partially reduced under vacuum and the residue was purified by silica gel chromatography. The product was isolated as a white solid (87 mg, 99%).

Mp: 100-102 °C.

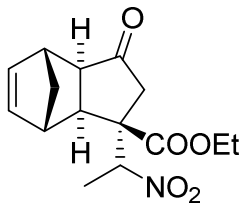
IR (KBr) $\nu_{max.}$ = 2986, 2962, 2890, 1723, 1555, 1372, 1225, 1182, 683 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.35 (t, *J* = 7.2 Hz, 3H), 2.08 (d, *J* = 7.9 Hz, 1H), 1.44-1.47 (m, 2H), 2.42 (dt, *J* = 8.1 and 1.2 Hz, 1H), 2.53 (dd, *J* = 20.4 and 1.2 Hz, 1H), 2.75-2.79 (m, 1H), 3.16-3.21 (d, *J* = 1.2 Hz, 1H), 3.59 (d, *J* = 20.4 Hz, 1H), 4.30 (dq, *J* = 10.8 and 7.2 Hz, 1H), 4.38 (dq, *J* = 10.8 and 7.2 Hz, 1H), 4.41 (d, *J* = 14.8 Hz, 1H), 5.07 (dd, *J* = 14.8 and 1.6 Hz, 1H), 6.21-6.27 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.1 (CH_3), 44.4 (CH_2), 46.2 (CH), 47.4 (CH), 47.8 (CH_2), 49.8 (CH), 49.9 (C), 54.5 (CH), 62.3 (CH_2), 80.8 (CH_2), 138.9 (CH), 139.0 (CH), 170.6 (C), 214.9 (C) ppm.

HRMS (ESI) calculated for $C_{14}H_{18}NO_5$ 280.1185, found 280.1185 $[M+H]^+$.

ethyl (*1R*,3aR*,4R*,7S*,7aS)-1-*((S*)*-1-nitroethyl)-3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoindene-1-carboxylate (58)**



PK adduct **52a** (90 mg, 0.31 mmol, 1 equiv.) was dissolved in nitroethane (5 mL), and TBAF·3H_2O (100 mg, 0.31 mmol, 1 eq.) was added in one portion at room temperature. The reaction mixture was stirred at 90 °C for 3 h. The volume was partially reduced under vacuum and the residue was purified by silica gel chromatography. The product was isolated as a white solid (44 mg, 58%).

Mp: 99-101 °C.

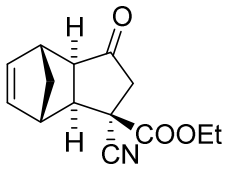
IR (KBr) $\nu_{max.}$ = 2981, 1732, 1546, 1233 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.32 (t, *J=7 Hz*, 3H), 1.38 (t, *J=7 Hz*, 3H*$^{MINOR\ DIASTEREOMER}$), 1.40-1.52 (m, 2H+5H*), 1.53 (d, *J=7 Hz*, 3H), 2.10 (d, *J=8 Hz*, 1H), 2.29 (m, 1H*), 2.41 (m, 1H), 2.48 (d, *J=8 Hz*, 1H*), 2.73 (m, 2H), 2.78 (m, 2H*), 3.98-3.19 (m, 1H+1H*), 3.42 (d, *J=20 Hz*, 1H*), 3.63 (d, *J=20 Hz*, 1H), 4.21-4.40 (m, 2H+2H*), 5.20 (q, *J=7 Hz*, 1H), 5.30 (q, *J=7 Hz*, 1H*), 6.19-6.29 (m, 2H+2H*)* ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.2 (CH_3), 14.4 (CH_3)*, 14.8 (CH_3), 16.6 (CH_3)*, 44.2 (CH)*, 44.5 (CH_2)*, 44.7 (CH), 45.6 (CH_2), 46.8 (CH_2)*, 47.1 (CH_2), 47.4 (CH)*, 47.7 (CH), 51.1 (CH), 51.4 (CH), 53.7 (C), 55.2 (CH)*, 55.6 (CH), 62.4 (CH_2), 62.6 (CH_2)*, 85.5 (CH)*, 87.6 (CH), 139.0 (CH), 139.2 (CH), 139.4 (CH), 170.5 (C)*, 171.3 (C), 215.3 (C)*, 216.4 (C) ppm.

HRMS (ESI) calculated for $C_{15}H_{20}NO_5$ 294.1336, found 294.1336 $[M+H]^+$.

ethyl (*1R*,3aR*,4R*,7S*,7aS)-1-cyano-3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoindene-1-carboxylate (59)**



Adduct **52a** (75 mg, 0.26 mmol, 1 eq.) and KCN (170 mg, 2.60 mmol, 10 eq.) were dissolved in acetonitrile (10 mL). The mixture was heated at 90 °C for 2 h. The solvent was then removed under vacuum, and the crude was purified by silica gel chromatography to afford **Y** as a pale yellow oil (32 mg, 50%).

IR (film) $\nu_{max.}$ = 2917, 2847, 2206, 1745, 1655 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.26 (s, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.57 (d, *J* = 9.7 Hz, 2H), 2.71 (m, 1H), 2.78 (dd, *J* = 7.2 and 1.4 Hz, 1H), 2.96 (d, *J* = 7.1 Hz, 1H), 3.12

(s, 1H), 4.41 (qd, *J* = 7.1 and 1.7 Hz, 2H), 6.17 (dd, *J* = 5.6 and 3.2 Hz, 1H), 6.24 (dd, *J* = 5.7 and 3.0 Hz, 1H) ppm.

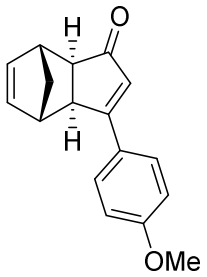
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.3 (CH_3), 29.9 (CH_2), 42.9 (CH_2), 43.9 (CH), 45.7 (CH), 50.3 (CH), 51.9 (CH), 52.1 (C), 63.8 (CH_2), 137.9 (CH), 138.9 (CH), 165.1 (C), 177.0 (C) ppm.

HRMS (ESI) calculated for $C_{14}H_{14}NO_3$ 244.0968, found 244.0958 $[M+H]^+$.

General conditions for the des-trifluoromethylation reaction.

The desired PK adduct was dissolved in nitromethane (3 mL/0.1 mmol) in a round bottom flask with a magnetic stirrer and a condenser and the system was put under nitrogen. Water (5 eq.) and DBU (1 eq.) were then added, and the system was heated to reflux until no starting material could be detected by TLC analysis. Upon completion of the reaction, the solvent was removed under vacuum and the crude was purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarity.

***(3aS*,4S*,7R*,7aR*)*-3-(4-methoxyphenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (57b)**



The general procedure was followed starting from adduct **52b** (35 mg, 0.11 mmol). The reaction proceeded during 1.5h and, after purification, the desired product was obtained as a white solid (18 mg, 64%).

Mp: 126-127 °C

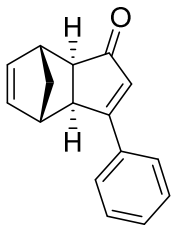
IR (KBr) $\nu_{max.}$ = 2917, 2847, 1681, 1604, 1553, 1508 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.37 (m, 1H), 1.44 (m, 1H), 2.50 (dt, *J* = 5.2 and 1.4 Hz, 1H), 2.82 (s, 1H), 3.01 (s, 1H), 3.28 (d, *J* = 5.4 Hz, 1H), 3.88 (s, 3H), 6.28 (dd, *J* = 5.6 and 2.9 Hz, 1H), 6.36 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.51 (d, *J* = 0.9 Hz, 1H), 6.98 (m, 2H), 7.67 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 42.0 (CH_2), 43.4 (CH), 43.9 (CH), 49.6 (CH), 53.7 (CH), 55.5 (CH_3), 114.3 (CH), 125.9 (C), 129.0 (CH), 129.2 (CH), 137.8 (CH), 137.9 (CH), 162.0 (C), 174.3 (C), 209.0 (C) ppm.

HRMS (ESI) calculated for $C_{17}H_{17}O_2$ 253.1223, found 253.1224 $[M+H]^+$.

***(3aS*,4S*,7R*,7aR*)*-3-phenyl-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (57c)**



The general procedure was followed starting from adduct **52c** (25 mg, 0.09 mmol). The reaction proceeded during 2h and, after purification, the desired product was obtained as a colourless gum (11 mg, 55%).

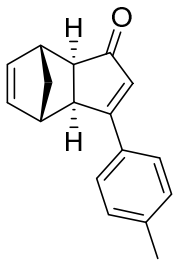
IR (film) $\nu_{max.}$ = 29943060, 2978, 2930, 1688, 1590, 1570 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.37 (dt, *J* = 9.5 and 1.6 Hz, 1H), 1.45 (dq, *J* = 9.4 and 1.6 Hz, 1H), 2.52 (dt, *J* = 5.3 and 1.3 Hz, 1H), 2.82 (s, 1H), 3.02 (s, 1H), 3.33 (dq, *J* = 5.3 and 1.0 Hz, 1H), 6.29 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.37 (dd, *J* = 5.6 and 3.1 Hz, 1H), 6.62 (d, *J* = 1.0 Hz, 1H), 7.46-7.49 (m, 3H), 7.69-7.72 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 42.9 (CH_2), 43.5 (CH), 43.7 (CH), 49.6 (CH), 53.7 (CH), 127.3 (CH), 128.9 (CH), 131.0 (CH), 131.1 (CH), 133.3 (C), 137.7 (CH), 138.0 (CH), 174.7 (C), 209.1 (C) ppm.

HRMS (ESI) calculated for $C_{16}H_{15}O$ 223.1118, found 223.1117 $[M+H]^+$.

***(3aS*,4S*,7R*,7aR*)*-3-(*p*-tolyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (57d)**



The general procedure was followed starting from adduct **52d** (104 mg, 0.34 mmol). The reaction proceeded during 1h and, after purification, the desired product was obtained as a white solid (51 mg, 64%).

With KCN: adduct **52d** (42 mg, 0.14 mmol, 1 eq) was dissolved in acetonitrile (5 mL). KCN (91 mg, 1.40 mmol, 10 eq) was added, the system was put under nitrogen and the heated to reflux for 24h. After this time, the solvent was removed under vacuum and the crude was purified by silica gel chromatography with hexanes/AcOEt of increasing polarity as eluent. The reaction conversion was 76%, and the desired product was isolated in 16% yield (5 mg).

With TBAF: adduct **52d** (25 mg, 0.08 mmol, 1 eq) was dissolved in nitromethane (5 mL). A 1M solutions of TBAF in THF (0.08 mL, 0.08 mmol, 1 eq) was added, the system was put under nitrogen and the heated to reflux until complete conversion was observed (18h). After this time, the solvent was removed under vacuum and the crude was purified by silica gel chromatography with hexanes/AcOEt of increasing polarity as eluent. The desired product was isolated in 20% yield (4 mg).

Mp: 122-124 °C

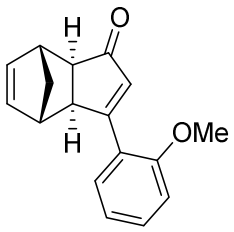
IR (KBr) $\nu_{max.}$ = 3045, 2969, 1681, 1591, 1328, 1188 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.36 (dt, *J* = 9.4 and 1.6 Hz, 1H), 1.43 (dp, *J* = 9.5 and 1.6 Hz, 1H), 2.41 (s, 3H), 2.50 (dt, *J* = 5.3 and 1.4 Hz, 1H), 2.81 (s, 1H), 3.00 (s, 1H), 3.30 (dd, *J* = 5.3 and 1.1 Hz, 1H), 6.28 (dd, *J* = 5.5 and 2.9 Hz, 1H), 6.36 (dd, *J* = 5.6 and 3.1 Hz, 1H), 6.57 (s, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 21.5 (CH_3), 42.0 (CH_2), 43.4 (CH), 43.8 (CH), 49.5 (CH), 53.7 (CH), 127.4 (CH), 129.7 (CH), 130.2 (CH), 130.6 (C), 137.8 (CH), 138.0 (CH), 141.8 (C), 174.7 (C), 209.2 (C) ppm.

HRMS (ESI) calculated for $C_{17}H_{17}O$ 237.1274, found 237.1276 $[M+H]^+$.

***(3aS*,4S*,7R*,7aR*)*-3-(2-methoxyphenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (57e)**



The general procedure was followed starting from adduct **52e** (32 mg, 0.1 mmol). The reaction proceeded during 2h and, after purification, the desired product was obtained as a pale yellow oil (13 mg, 51%).

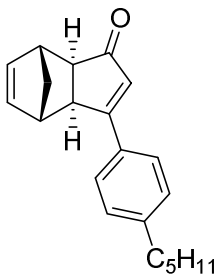
IR (film) $\nu_{max.}$ = 2969, 2939, 1680, 1593, 1551 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.36-1.43 (m, 2H), 2.42-2.44 (m, 1H), 2.71-2.72 (m, 1H), 2.97-3.01 (m, 1H), 3.41-3.44 (m, 1H), 3.90 (s, 3H), 6.90 (d, *J* = 1.0 Hz, 1H), 6.98-7.07 (m, 2H), 7.40-7.45 (m, 1H), 7.60 (dd, *J* = 7.8 and 1.7 Hz, 1H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 42.0 (CH_2), 43.6 (CH), 43.8 (CH), 51.2 (CH), 52.4 (CH), 55.4 (CH_3), 111.5 (CH), 120.5 (CH), 122.5 (C), 129.5 (CH), 132.0 (CH), 135.2 (CH), 137.8 (CH), 138.1 (CH), 159-0 (C), 171.5 (C), 210.8 (C) ppm.

HRMS (ESI) calculated for $C_{17}H_{17}O_2$ 253.1229, found 253.1223 $[M+H]^+$.

***(3aS*,4S*,7R*,7aR*)*-3-(4-pentylphenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (57f)**



The general procedure was followed starting from adduct **52f** (45 mg, 0.14 mmol). The reaction proceeded during 1.5h and, after purification, the desired product was obtained as a pale yellow oil (28 mg, 68%).

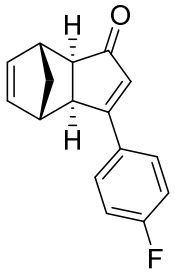
IR (film) $\nu_{max.}$ = 2930, 2854, 1694 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.90 (m, 3H), 1.32-1.44 (m, 6H), 1.63-1.68 (m, 2H), 2.51 (dt, *J* = 5.4 and 1.4 Hz, 1H), 2.66 (m, 2H), 2.83 (s, 1H), 3.01 (s, 1H), 3.31 (d, *J* = 5.5 Hz, 1H), 6.28 (dd, *J* = 5.6 and 2.9 Hz, 1H), 6.37 (dd, *J* = 5.6 and 3.1 Hz, 1H), 6.58 (d, *J* = 0.9 Hz, 1H), 7.27 (m, 2H), 7.62 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.0 (CH_3), 22.5 (CH_2), 30.9 (CH_2), 31.4 (CH_2), 35.9 (CH_2), 42.0 (CH_2), 43.4 (CH), 43.8 (CH), 49.6 (CH), 53.7 (CH), 127.4 (CH), 129.0 (CH), 130.1 (CH), 130.7 (C), 137.8 (CH), 138.0 (CH), 146.8 (C), 174.8 (C), 209.3 (C) ppm.

HRMS (ESI) calculated for $C_{21}H_{24}ONa$ 315.1719, found 315.1720 $[M+Na]^+$.

***(3aS*,4S*,7R*,7aR*)*-3-(4-fluorophenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (57g)**



The general procedure was followed starting from adduct **52g** (31 mg, 0.1 mmol). The reaction proceeded during 2h and, after purification, the desired product was obtained as a pale yellow solid (14 mg, 59%).

Mp: 105-107 °C

IR (KBr) $\nu_{max.}$ = 2977, 2943, 1677, 1601, 1579, 1508 cm^{-1}.

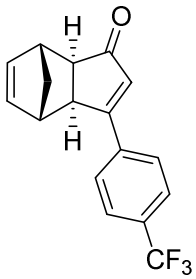
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.33-1.37 (m, 1H), 1.45 (dt, *J* = 9.4 and 1.4 Hz, 1H), 2.52 (dt, *J* = 5.3 and 1.4 Hz, 1H), 2.79 (s, 1H), 3.02 (m, 1H), 3.28 (dq, *J* = 4.4 and 0.8 Hz, 1H), 6.29 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.35 (dd, *J* = 5.6 and 2.9 Hz, 1H), 6.56 (d, *J* = 1.0 Hz, 1H), 7.13-7.19 (m, 2H), 7.66-7.73 (m, 2H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 42.0 (CH_2), 43.4 (CH), 43.6 (CH), 49.7 (CH), 53.8 (CH), 116.1 (d, $^2J_{CF}$ = 22 Hz, 2CH), 129.4 (CH), 129.5 (CH), 129.6 (C), 130.7 (d, $^3J_{CF}$ = 2 Hz, CH), 137.8 (CH), 137.9 (CH) 164.4 (d, $^1J_{CF}$ = 252 Hz, C), 173.4 (C), 209.0 (C) ppm.

^{19}F-NMR (282.4 MHz, $CDCl_3$) δ = -108.1-(-108.2) (m, 1F) ppm.

HRMS (ESI) calcilated for $C_{16}H_{14}FO$ 241.1029, found 223.1023 $[M+H]^+$.

***(3aS*,4S*,7R*,7aR*)*-3-(4-trifluoromethylphenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (57h)**



The general procedure was followed starting from adduct **52h** (36 mg, 0.1 mmol). The reaction proceeded during 3h and, after purification, the desired product was obtained as a pale yellow solid (17 mg, 57%).

Mp: 92-94 °C

IR (film) $\nu_{max.}$ = 2981, 2940, 1677, 1555 cm^{-1}.

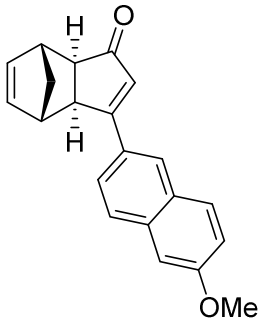
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.26-1.30 (m, 1H), 1.40 (dt, *J* = 9.5 and 1.4 Hz, 1H), 2.49 (dt, *J* = 5.3 and 1.3 Hz, 1H), 2.69-2.74 (m, 1H), 2.97 (m, 1H), 3.27 (dq, *J* = 5.3 and 0.8 Hz, 1H), 6.23 (d, *J* = 5.6 and 2.9 Hz, 1H), 6.31 (d, *J* = 5.6 and 3.1 Hz, 1H), 6.56 (d, *J* = 0.9 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 41.9 (CH_2), 43.4 (CH), 43.6 (CH), 49.7 (CH), 53.8 (CH), 123.7 (q, $^1J_{CF}$ = 271 Hz, C), 125.9 (q, $^3J_{CF}$ = 4 Hz, CH), 127.5 (CH), 132.5 (q, $^2J_{CF}$ = 33 Hz, C), 132.8 (CH), 136.7 (C), 137.8 (CH), 138.0 (CH), 172.8 (C), 208.8 (C) ppm.

^{19}F-NMR (282.4 MHz, $CDCl_3$) δ = -63.40 (s, 3F) ppm.

HRMS (ESI) calculated for $C_{17}H_{14}F_3O$ 291.1000, found 291.0991 $[M+H]^+$.

(*3aS*,4S*,7R*,7aR)-3-[(6-methoxy)-2-naphthyl]-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (57i)**



The general procedure was followed starting from adduct **52i** (37 mg, 0.1 mmol). The reaction proceeded during 2h and, after purification, the desired product was obtained as a pale yellow oil (18 mg, 58%).

IR (film) $\nu_{max.}$ = 2920, 2907, 1680, 1543 cm^{-1}.

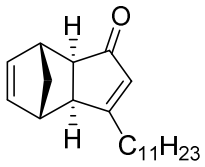
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.41 (dt, *J* = 9.4 and 1.4 Hz, 1H), 1.46 (dt, *J* = 9.3 and 1.3 Hz, 1H), 2.56 (dt, *J* = 5.3 and 1.2 Hz, 1H), 2.90 (s, 1H), 3.04 (s, 1H), 3.43 (dq, *J* =

5.3 and 0.7 Hz, 1H), 3.96 (s, 3H), 6.31 (d, *J* = 5.6 and 3.0 Hz, 1H), 6.43 (d, *J* = 5.6 and 3.3 Hz, 1H), 6.69 (d, *J* = 0.8 Hz, 1H), 7.15-7.26 (m, 2H), 7.70-7.86 (m, 3H), 8.10 (s, 1H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 42.1 (CH_2), 43.4 (CH), 44.0 (CH), 49.5 (CH), 53.8 (CH), 55.4 (CH_3), 105.8 (CH), 119.7 (CH), 127.4 (CH), 127.5 (CH), 130.4 (C), 130.5 (C), 136.1 (C), 137.8 (CH), 138.1 (CH), 159.2 (C), 174.7 (C), 209.2 (C) ppm.

HRMS (ESI) calculated for $C_{21}H_{19}O_2$ 303.1385, found 303.1380 $[M+H]^+$.

***(3aS*,4S*,7R*,7aR*)*-3-undecyl-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (57j)**



The general procedure was followed starting from adduct **52j** (70 mg, 0.19 mmol). The reaction proceeded during 1.75h and, after purification, the desired product was obtained as a colourless oil (35 mg, 61%).

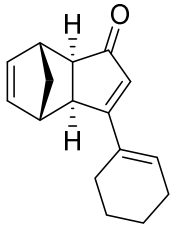
IR (film) $\nu_{max.}$ = 2925, 2853, 1700, 1604, 1546 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.88 (t, *J* = 5.0 Hz, 3H), 1.27-1.41 (m, 17H), 1.58-1.65 (m, 3H), 2.30-2.36 (m, 2H), 2.40-2.44 (m, 1H), 2.71 (d, *J* = 5.1 Hz, 1H), 2.76 (s, 1H), 2.92 (s, 1H), 6.00 (q, *J* = 1.3 Hz, 1H), 6.22 (dd, *J* = 5.6 and 2.9 Hz, 1H), 6.29 (dd, *J* = 5.6 and 3.0 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.0 (CH_3), 22.7 (CH_2), 27.0 (CH_2), 29.3 (CH_2), 29.36 (CH_2), 29.40 (CH_2), 29.5 (CH_2), 29.57 (CH_2), 29.59 (CH_2) 31.3 (CH_2), 32.0 (CH_2), 41.4 (CH_2), 42.2 (CH), 43.2 (CH), 52.4 (CH), 53.3 (CH), 133.1 (CH), 137.6 (CH), 137.8 (CH), 183.9 (C), 209.7 (C) ppm.

HRMS (ESI) calculated for $C_{21}H_{33}O$ 301.2526, found 301.2527 $[M+H]^+$.

***(3aS*,4S*,7R*,7aR*)*-3-(1-cyclohexenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (57l)**



The general procedure was followed starting from adduct **52l** (29 mg, 0.1 mmol). The reaction proceeded during 2h and, after purification, the desired product was obtained as a pale yellow solid (9 mg, 40%).

Mp: 88-90 °C

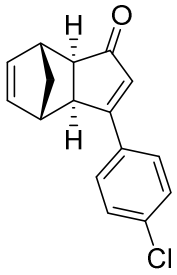
IR (KBr) $\nu_{max.}$ = 2977, 2931, 2912, 1680, 1566 cm^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.28 (dt, *J* = 9.4 and 1.4 Hz, 1H), 1.42 (dt, *J* = 9.3 and 1.5 Hz, 1H), 1.61-1.78 (m, 4H), 2.17-2.32 (m, 4H), 2.38 (dt, *J* = 5.4 and 1.4 Hz, 1H), 2.80 (s, 1H), 2.94 (s, 1H), 3.00 (dd, *J* = 5.4 and 0.8 Hz, 1H), 6.05 (s, 1H) 6.22 (dd, *J* = 5.7 and 3.0 Hz, 1H), 6.29 (d, *J=5.6, 3.0 Hz*, 1H), 6.53-6.57 (m, 1H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 21.6 (CH_2), 22.2 (CH_2), 25.9 (CH_2), 26.4 (CH_2), 42.1 (CH_2), 43.0 (CH), 44.6 (CH), 48.4 (CH), 53.3 (CH), 129.1 (CH), 133.1 (C), 134.9 (CH), 137.6 (CH), 138.0 (CH), 175.6 (C), 209.8 (C) ppm.

HRMS (ESI) calculated for $C_{16}H_{19}O$ 227.1436, found 227.1430 $[M+H]^+$.

***(3aS*,4S*,7R*,7aR*)*-3-(4-chlorophenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (57m)**



The general procedure was followed starting from adduct **52m** (30 mg, 0.09 mmol). The reaction proceeded during 2h and, after purification, the desired product was obtained as a white solid (13 mg, 57%).

Mp: 115-117 °C

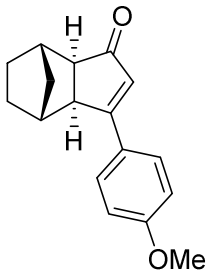
IR (KBr) $\nu_{max.}$ = 2978, 1681, 1594, 1092 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.36 (m, 1H), 1.46 (dp, *J* = 9.5 and 1.6 Hz, 1H), 2.53 (dt, *J* = 5.3 and 1.4 Hz, 1H), 2.78 (s, 1H), 3.02 (s, 1H), 3.28 (m, 1H), 6.29 (dd, *J* = 5.6 and 3.0 Hz, 1H), 6.36 (dd, *J* = 5.6 and 3.1 Hz, 1H), 6.59 (d, *J* = 1.0 Hz, 1H), 7.45 (m, 2H), 7.63 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 42.0 (CH_2), 43.5 (CH_2), 43.6 (CH_2), 49.6 (CH_2), 53.8 (CH_2), 110.0 (C), 128.5 (CH), 129.3 (CH), 131.3 (CH), 131.8 (C), 137.8 (CH), 137.9 (CH), 173.1 (C), 208.8 (C) ppm.

HRMS (ESI) calculated for $C_{16}H_{14}ClO$ 257.0728, found 257.0728 $[M+H]^+$.

(*3aS*,4R*,7S*,7aR)-3-(4-methoxyphenyl)-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-1-one (60b)**



The general procedure was followed starting from adduct **53b** (55 mg, 0.17 mmol). The reaction proceeded during 12h and, after purification, the desired product was obtained as a colorless oil (21 mg, 49%).

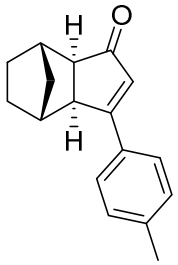
IR (film) $\nu_{max.}$ = 2957, 1678, 1554, 1178 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.96-1.05 (m, 1H), 1.19-1.10 (m, 1H), 1.51-1.31 (m, 2H), 1.74-1.61 (m, 2H), 2.31 (d, *J* = 4.0 Hz, 1H), 2.38 (dt, *J* = 5.5 and 1.2 Hz, 1H), 2.49 (d, *J* = 3.8 Hz, 1H), 3.13 (d, *J* = 5.3 Hz, 1H), 3.87 (s, 3H), 6.53 (d, *J* = 1.0 Hz, 1H), 6.94 (m, 2H), 7.67-7.62 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 28.6 (CH_2), 29.2 (CH_2), 31.8 (CH_2), 38.6 (CH), 39.1 (CH), 50.2 (CH), 55.2 (CH), 55.4 (CH), 114.3 (CH), 126.0 (C), 128.1 (CH), 129.4 (CH), 161.9 (C), 174.6 (C), 210.5 (C) ppm.

HRMS (ESI) calculated for $C_{17}H_{19}O_2$ 255.1380, found 255.1378 $[M+H]^+$.

(*3aS*,4R*,7S*,7aR)-3-(4-tolyl)-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-1-one (60d)**



The general procedure was followed starting from adduct **53d** (77 mg, 0.24 mmol). The reaction proceeded during 12h and, after purification, the desired product was obtained as a colorless oil (16 mg, 28%).

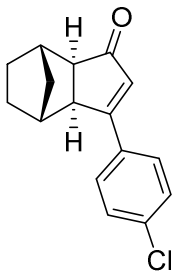
IR (film) $\nu_{max.}$ = 2957, 1688, 1591, 1193 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.97-1.02 (m, 1H), 1.17-1.11 (m, 1H), 1.50-1.33 (m, 2H), 1.76-1.63 (m, 2H), 2.32-2.29 (m, 1H), 2.39 (d, *J* = 5.5 Hz, 1H), 2.41 (s, 3H), 2.50-2.48 (m, 1H), 3.17-3.14 (m, 1H), 6.59 (d, *J* = 1.1 Hz, 1H), 7.28-7.24 (m, 2H), 7.60-7.56 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 21.5 (CH_3), 28.6 (CH_2), 29.2 (CH_2), 31.8 (CH_2), 38.7 (CH), 39.0 (CH), 50.2 (CH), 55.2 (CH), 127.6 (CH), 129.3 (CH), 129.6 (CH), 130.7 (C), 141.6 (C), 175.0 (C), 210.7 (C) ppm.

HRMS (ESI) calculated for $C_{17}H_{19}O$ 239.1430, found 239.1430 $[M+H]^+$.

(*3aS*,4R*,7S*,7aR)-3-(4-chlorophenyl)-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-1-one (60m)**



The general procedure was followed starting from adduct **53m** (19 mg, 0.06 mmol). The reaction proceeded during 12h and, after purification, the desired product was obtained as a colorless oil (4 mg, 30%).

IR (film) $\nu_{max.}$ = 2954, 1677, 1593, 1092 cm^{-1}.

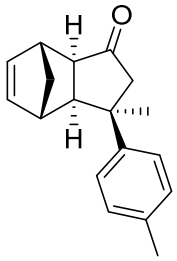
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.99-1.06 (m, 1H), 1.16-1.09 (m,1H), 1.50-1.33 (m, 2H), 1.77-1.60 (m, 2H), 2.30-2.25 (m, 1H), 2.40 (dt, *J* = 5.5 and 1.2 Hz, 1H), 2.50 (d, *J* = 4.1 Hz, 1H), 3.14 (d, *J* = 5.4 Hz, 1H), 6.60 (d, *J* = 1.1 Hz, 1H), 7.45-7.41 (m, 2H), 7.62-7.59 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 28.6 (CH_2), 29.2 (CH_2), 31.8 (CH_2), 38.8 (CH), 50.2 (CH), 55.2 (CH), 128.8 (CH), 129.2 (CH), 130.5 (CH), 131.9 (C) 137.1 (C), 173.4 (C), 210.3 (C) ppm.

HRMS (ESI) calculated for $C_{16}H_{16}ClO$ 259.0884, found 259.0884 $[M+H]^+$.

<u>Formal synthesis of α-cuparenone</u>

(*3R*,3aS*,4S*,7R*,7aR)-3-methyl-3-(p-tolyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-one (61)**

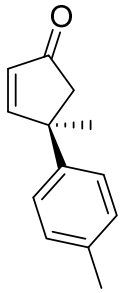


Adduct **57d** (30 mg, 0.13 mmol, 1 eq) and $Ni(acac)_2$ (1.7 mg, $6.5\cdot10^{-3}$ mmol, 5 mol%) were dissolved in anhydrous THF (1 mL) in a round bottom Schlenk flask with a magnetic stirrer and under inert atmosphere. The solution was cooled down to 0 °C and a 2M solution of $AlMe_3$ in toluene (0.07 mL, 0.14 mmol, 1.1 eq) was added dropwise. The solution, initially pale yellow, became brown. The system was allowed to slowly warm up to room temperature (over 2h). Hexanes (1 mL) and a saturated solution of NH_4Cl (1 mL) were added cautiously. The mixture was stirred for 0.5h. Water and AcOEt were added

and the phases were separated. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was eliminated under vacuum. The crude was purified by silica gel chromatography with hexanes/AcOEt of increasing polarity. The desired product was obtained as a yellow oil (20 mg, 67%), along with some minor impurities.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.14 (dp, *J* = 9.6 and 1.6 Hz, 1H), 1.33 (m, 1H), 1.37 (d, *J* = 1.7 Hz, 3H), 2.36 (s, 3H), 2.43 (dt, *J* = 18.2 and 1.4 Hz, 1H), 2.51 (dp, *J* = 7.3 and 1.4 Hz, 1H), 2.55 (m, 1H), 3.06 (br s, 1H), 3.17 (dd, *J* = 18.2 and 1.2 Hz, 1H), 6.17 (dd, *J* = 5.6 and 2.9 Hz, 1H), 6.23 (dd, *J* = 5.7 and 3.2 Hz, 1H), 7.12-7.21 (m, 4H) ppm.

***(R*)*-4-methyl-4-(p-tolyl)cyclopent-2-enone (62)**



61 (26 mg, 0.10 mmol, 1 eq.) was dissolved in anhydrous dichloromethane (5 mL) in a microwave vial with a magnetic stirrer and under nitrogen atmosphere. Maleic anhydride (152 mg, 1.55 mmol, 15 eq.) was added as a solid, followed by a 1M solution of $MeAlCl_2$ in hexanes (0.10 mL, 0.10 mmol, 1 eq.). The system was irradiated with microwaves (100 °C, 250W) over three periods of 60 seconds, in between of which an additional equivalent of $MeAlCl_2$ was added. The crude was then rapidly mixed with a saturated solution of $NaHCO_3$ and stirred for 20 minutes. The organic fraction was separated and the aqueous phase was further extracted with dichloromethane. The organic layers were dried ($MgSO_4$) and filtered. The solvent was removed and the product was purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarity. The desired product was obtained as a colourless oil (16 mg, 80%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.61 (s, 3H), 2.33 (s, 3H), 2.54 (d, *J* = 18.6 Hz, 1H), 2.64 (d, *J* = 18.6 Hz, 1H), 6.19 (d, *J* = 5.6 Hz, 1H), 7.15 (s, 4H), 7.66 (d, *J* = 5.6 Hz, 1H) ppm.

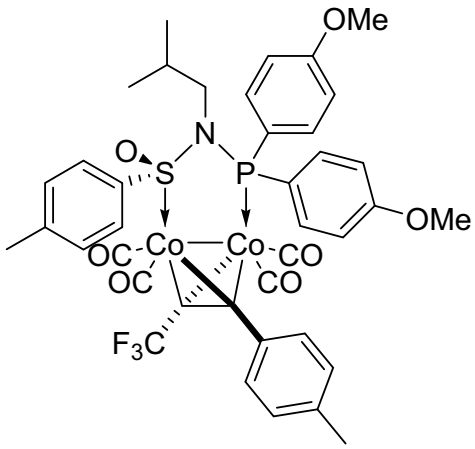
HPLC*: Chriralpack IA, heptane/EtOH (70:30), 0.5mL/min, λ=220nm, t_R(+)=10.9 min, t_R(-) =14.7 min.

8.5 CHAPTER 6

General procedure for the preparation of μ(PNSO)-alkyne-tetracarbonyldicobalt complexes.

The desired dicobalthexacarbonyl-alkyne complex (1.05 eq.) was dissolved in anhydrous toluene (1.5 mL/0.1mmol) under nitrogen atmosphere in a Shlenck type flask. The desired ligand (1 eq.) and DABCO (1.6 to 4 eq.) were added as solids and the system was heated up to 65 or 85 °C. Once the staring ligand could not be detected by TLC and no evolution in the cobalt complexes formed could be observed by TLC or NMR the heating was turned off and the crude was allowed to reach room temperature. The solvent was removed under vacuum and the remaining residue purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarities.

70A



The general procedure was followed starting from **51d** (85 mg, 0.18 mmol), **64-BH$_3$** (80 mg, 0.17 mmol) and DABCO (31 mg, 0.27 mmol, 1.6 eq.). The reaction was allowed to progress for 7h at 65 °C. We obtained a mixture of diastereomers (1.1:1 mixture, 118 mg, 80% global yield) of which the major one could be separated (red oil).

IR (film) $\nu_{max.}$ = 2963, 2052, 2022, 1998, 1595, 1501 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ = 0.01 (d, *J* = 6.7 Hz, 3H), 0.11 (d, *J* = 6.6 Hz, 3H), 0.75 (br s, 1H), 1.84 (s, 3H), 1.98 (s, 3H), 2.79 (ddd, *J* = 15.7, 9.6 and 6.6 Hz, 1H), 3.14 (s, 3H), 3.18 (s, 3H), 3.66 (ddd, *J* = 15.4, 6.0 and 2.6 Hz, 1H), 6.72 (dt, *J* = 8.7 and 2.2 Hz, 4H), 6.88 (dd, *J* = 13.6 and 8.0 Hz, 4H), 7.70 (dd, *J* = 10.5 and 8.5 Hz, 2H), 7.82 (dd, *J* = 10.4 and 8.5 Hz, 2H), 7.99 (d, *J* = 7.8 Hz, 2H), 8.14 (d, *J* = 8.1 Hz, 2H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 18.2 (CH_3), 19.6 (CH_3), 20.7 (CH_3), 20.9 (CH_3), 25.4 (q, $^2J_{CF}$ = 261 Hz, C), 26.7 (CH), 34.6 (q, $^3J_{CF}$ = 204 Hz, C), 52.5 (d, $^3J_{CP}$ = 5 Hz, CH_2), 54.4 (CH_3), 54.5 (CH_3), 113.9 (d, $^3J_{CP}$ = 11 Hz, CH), 114.28 (d, $^3J_{CP}$ = 11 Hz, CH), 125.9 (CH), 126.0 (C), 127.7 (q, $^1J_{CF}$ = 237 Hz, C), 129.3 (CH), 129.4 (CH), 129.5 (CH), 132.8

(q, $^2J_{CP}$ = 15 Hz, CH), 136.0 (d, $^2J_{CP}$ = 16 Hz, CH), 136.9 (C), 137.2 (C), 142.5 (C), 146.7 (d, $^1J_{CP}$ = 13 Hz, C), 166.9 (C), 162.4 (C), 201.6 (CO), 202.7 (CO) ppm.

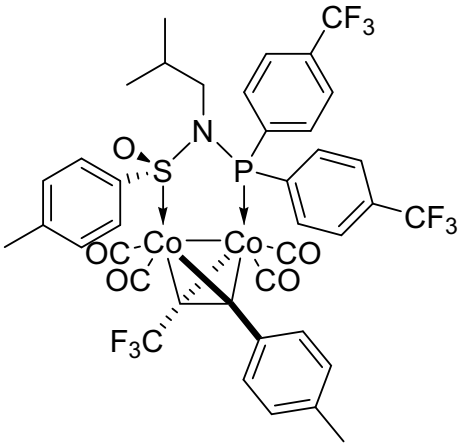
^{19}F-NMR (376 MHz, C_6D_6) δ = -47.47 (s, 3F) ppm.

^{31}P-NMR (121 MHz, C_6D_6) δ = 113.4 (s, 1P) ppm.

HRMS (ESI) calculated for $C_{39}H_{38}Co_2F_3NO_7PS$ 870.0717, found 870.0719 $[M+H]^+$.

$[\alpha]_D$ = $+31^a$ (c 2.80, $CHCl_3$).

72A



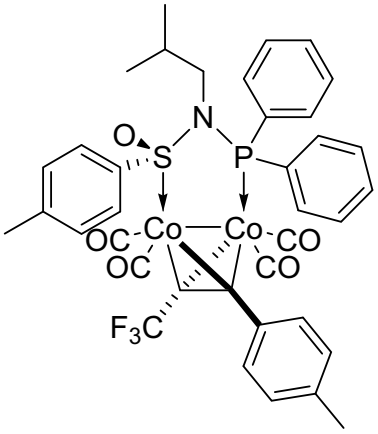
The general procedure was followed starting from **51d** (65 mg, 0.13 mmol), **66-BH$_3$** (65 mg, 0.12 mmol) of and DABCO (23 mg, 0.21 mmol, 1.6 eq.). The reaction was allowed to progress for 2h at 65 °C, and one additional equivalent of DABCO (13 mg) was added to the mixture. The reaction was stopped after an additional period of 0.5h. We obtained a mixture of diastereomers (1.4:1 mixture, 61 mg, 54% global yield) of which the major one could be separated (red oil).

IR (film) $\nu_{max.}$ = 2965, 2918, 2054, 2024, 2000, 1595, 1501 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ = 0.01 (d, *J* = 6.6 Hz, 3H), 0.15 (d, *J* = 6.6 Hz, 3H), 1.52-1.59 (m, 1H), 1.88 (s, 3H), 1.93 (s, 3H), 2.71 (dt, *J* = 14.7 and 5.4 Hz, 1H), 2.91 (ddd, *J* = 14.7, 8.6 and 4.7 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 2H), 7.18-7.25 (m, 6H), 7.55 (dd, *J* = 10.5 and 8.1 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.1 Hz, 2H) ppm.

^{19}F-NMR (376 MHz, C_6D_6) δ = -62.88 (s, ar-CF_3), -62.78 (s, ar-CF_3), -47.82 (3F, CF_3) ppm.

73A



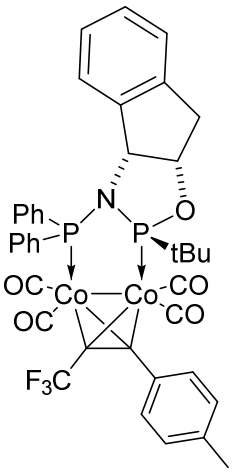
The general procedure was followed starting from **51d** (95 mg, 0.20 mmol), **67-BH$_3$** (76 mg, 0.19 mmol) and DABCO (37 mg, 0.30 mmol, 1.6 eq.). The reaction was allowed to progress for 4.5h at 65 °C. We obtained a mixture of diastereomers (1.5:1 mixture, 133 mg, 87% global yield) of which the major one could be separated (red oil).

IR (film) $\nu_{max.}$ = 2964, 2053, 2023, 1998, 1276, 1129 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ = 0.01 (d, *J* = 6.7 Hz, 3H), 0.15 (d, *J* = 6.6 Hz, 3H), 1.97 (s, 3H), 2.11 (s, 3H), 2.87 (ddd, *J* = 15.5, 9.5 and 6.5 Hz, 1H), 3.73 (ddd, *J* = 15.3, 6.2 and 2.8 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 7.08-7.21 (m, 6H), 7.72-7.89 (m, 2H), 7.93 (ddd, *J* = 10.8, 8.1 and 1.5 Hz, 2H), 8.10 (d, *J* = 8.0 Hz, 2H), 8.22 (d, *J* = 8.3 Hz, 2H) ppm.

^{19}F-NMR (376 MHz, C_6D_6) δ = -47.51 (s, 3F) ppm.

74A



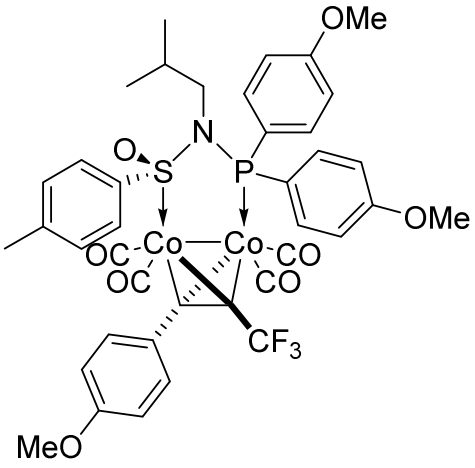
The general procedure was followed starting from **51d** (66 mg, 0.14 mmol), **68-BH$_3$** (62 mg, 0.19 mmol) and DABCO (63 mg, 0.57 mmol, 4 eq.). The reaction was allowed to progress for 5.5h at 85 °C. We obtained a mixture of diastereomers (1.2:1 mixture, 39 mg, 39% global yield) of which the major one could be separated (red oil).

IR (film) $\nu_{max.}$ = 2925, 2038, 2009, 1984, 1275, 1040 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ = 0.68 (d, *J* = 15.3 Hz, 9H), 1.72 (s, 3H), 2.67 (dd, *J* = 16.4 and 8.0 Hz, 1H), 3.36 (dd, *J* = 16.4 and 7.4 Hz, 1H), 4.71 (p, *J* = 7.3 Hz, 1H), 5.03 (d, *J* = 6.8 Hz, 1H), 5.82 (m, 1H), 6.10 (d, *J* = 7.7 Hz, 1H), 6.27-6.44 (m, 4H), 6.66 (d, *J* = 8.0 Hz, 2H), 6.89-6.98 (m, 6H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.75 (m, 2H) ppm.

^{19}F-NMR (376 MHz, C_6D_6) δ = -45.94 (d, *J* = 2.2 Hz, 3F) ppm.

75B



The general procedure was followed starting from **51b** (82 mg, 0.16 mmol), **64-BH$_3$** (75 mg, 0.16 mmol) and DABCO (29 mg, 0.26 mmol, 1.6 eq.). The reaction was allowed to progress for 4h at 65 °C. We obtained a mixture of diastereomers (1.1:1 mixture, 137 mg, 96% global yield) of which the minor one could be separated (red oil).

IR (film) $\nu_{max.}$ = 2962, 2927, 2051, 2021, 1999, 1595, 1098 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ = 0.30 (d, *J* = 6.6 Hz, 3H), 0.41 (d, *J* = 6.7 Hz, 3H), 1.85 (m, 1H), 1.93 (s, 3H), 2.97 (dt, *J* = 14.7 and 5.4 Hz, 1H), 3.14 (s, 3H), 3.19 (m, 1H), 3.23 (s, 3H), 3.24 (s, 3H), 6.65 (m, 2H), 6.73 (m, 4H), 6.88 (m, 2H), 7.43 (dd, *J* = 1.4 and 8.7 Hz, 2H), 7.79 (dd, *J* = 10.6 and 8.7 Hz, 2H), 7.98 (dd, *J* = 12.1 and 8.5 Hz, 4H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 19.2 (CH_3), 20.3 (CH_3), 20.7 (CH_3), 28.0 (CH), 54.4 (CH_3), 54.48 (CH_3), 54.51 (CH_3), 55.8 (d, $^3J_{CP}$ = 5 Hz, CH_2), 113.9 (d, $^3J_{CP}$ = 9 Hz, CH), 114.0 (d, $^3J_{CP}$ = 9 Hz, CH), 114.4 (C), 126.2 (CH), 127.2 (C), 128.7 (C), 129.1 (C), 129.1 (CH), 131.0 (d, $^3J_{CP}$ = 4 Hz, CH), 131.5 (CH), 133.1 (d, $^2J_{CP}$ = 15 Hz, CH), 135.5 (d, $^2J_{CP}$ = 17 Hz, CH), 142.1 (C), 146.0 (d, $^1J_{CP}$ = 8 Hz, C), 159.6 (C), 161.2 (d, $^4J_{CP}$ = 2 Hz, C), 162.0 (d, $^4J_{CP}$ = 1 Hz, C) ppm.

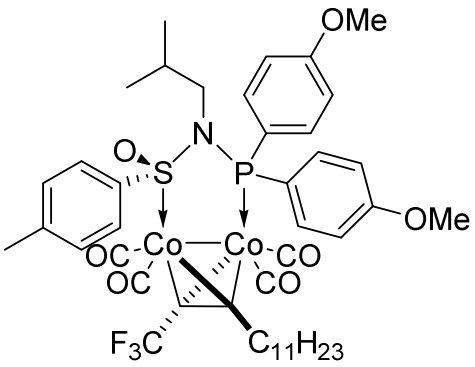
^{19}F-NMR (376 MHz, C_6D_6) δ = -47.49 (s, 3F) ppm.

^{31}P-NMR (121 MHz, C_6D_6) δ = 104.5 (s, 1P) ppm.

HRMS (ESI) calculated for $C_{39}H_{38}Co_2F_3NO_8PS$ 886.0666, found 886.0676 $[M+H]^+$.

$[\alpha]_D$ = +39^a (c 0.4, $CHCl_3$).

76A



The general procedure was followed starting from **51j** (96 mg, 0.18 mmol), **64-BH$_3$** (84 mg, 0.19 mmol) and DABCO (31 mg, 0.28 mmol, 1.6 eq.). The reaction was allowed to progress for 1.5h at 65 °C. We obtained a mixture of diastereomers (1:1 mixture, 72 mg, 45% global yield) of which the major one could be separated (red oil).

IR (film) $\nu_{max.}$ = 2927, 2854, 2050, 2019, 1995, 1595, 1254, 1098 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ = -0.03 (d, *J* = 6.6 Hz, 3H), 0.13 (d, *J* = 6.5 Hz, 3H), 0.70 (m, 1H), 0.91 (m, 3H), 1.23-1.35 (m, 20H), 1.85 (s, 3H), 2.72 (m, 1H), 3.16 (s, 3H), 3.23 (s, 3H), 3.67 (ddd, *J* = 15.1, 5.6 and 2.5 Hz, 1H), 6.75 (m, 2H), 6.80 (dd, *J* = 8.9 and 1.9 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 7.79 (dd, *J* = 10.4 and 8.7 Hz, 2H), 7.87 (dd, *J* = 10.4 and 8.7 Hz, 2H), 8.11 (m, 2H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 14.0 (CH_3), 18.2 (CH_3), 17.8 (CH_3), 20.7 (CH_3), 22.7 (CH_2), 26.5 (CH), 29.4 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 31.7 (CH_2), 31.8 (CH_2), 31.9 (CH_2), 52.8 (d, $^2J_{CP}$ = 6 Hz, CH_2), 54.4 (CH_3), 54.5 (CH_3), 114.0 (d, $^4J_{CP}$ = 11 Hz, CH), 114.9 (d, $^4J_{CP}$ = 11 Hz, CH), 125.8 (CH), 126.2 (C), 126.6 (C), 128.8 (C), 129.3 (CH), 132.6 (d, $^3J_{CP}$ = 14 Hz, CH), 135.9 (d, $^3J_{CP}$ = 17 Hz, CH), 142.3 (C), 147.0 (d, $^3J_{CP}$ = 13 Hz, C), 160.9 (C), 162.4 (C) ppm.

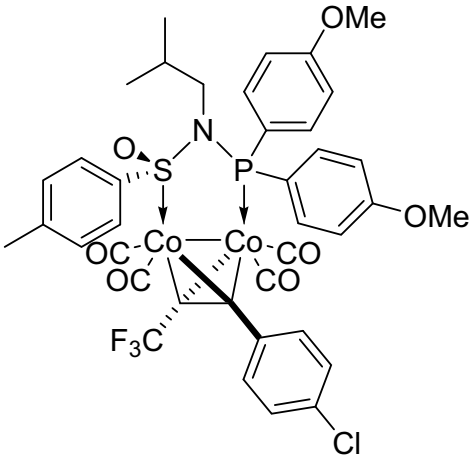
^{19}F-NMR (376 MHz, C_6D_6) δ = -48.32 (s, 3F) ppm.

^{31}P-NMR (121 MHz, C_6D_6) δ = 114.4 (s, 1P) ppm.

HRMS (ESI) calculated for $C_{43}H_{54}Co_2F_3NO_7PS$ 934.1969, found 934.2011 $[M+H]^+$.

$[\alpha]_D$ = +14^a (c 0.6, $CHCl_3$).

77A



The general procedure was followed starting from **51m** (124 mg, 0.25 mmol), **64-BH$_3$** (120 mg 0.26 mmol) and DABCO (47 mg, 0.42 mmol, 1.6 eq.). The reaction was allowed to progress for 2.5h at 65 °C. We obtained a mixture of diastereomers (1.4:1 mixture, 116 mg, 50% global yield) of which the major one could be separated (red oil).

IR (film) $\nu_{max.}$ = 2963, 2923, 2053, 2025, 1999, 1594, 1097 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ = -0.01 (d, *J* = 6.7 Hz, 3H), 0.11 (d, *J* = 6.6 Hz, 3H), 0.77 (br s, 1H), 1.85 (s, 3H), 2.77 (ddd, *J* = 16.0, 9.5 and 7.0 Hz, 1H), 3.15 (s, 3H), 3.19 (s, 3H), 3.63 (m, 1H), 6.71 (ddd, *J* = 9.0, 5.8 and 1.8 Hz, 4H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.97 (m, 2H), 7.62 (t, *J* = 9.4 Hz, 2H), 7.79 (m, 4H), 8.09 (d, *J* = 8.2 Hz, 2H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 18.3 (CH_3), 19.6 (CH_3), 20.7 (CH_3), 26.7 (CH), 52.8 (CH_2), 54.4 (CH_3), 54.5 (CH_3), 114.0 (d, $^3J_{CP}$ = 12 Hz, CH), 114.3 (d, $^3J_{CP}$ = 11 Hz, CH), 125.8 (CH), 128.9 (CH), 129.3 (CH), 130.7 (CH), 132.7 (d, $^2J_{CP}$ = 14 Hz, CH), 132.9 (C), 135.8 (d, $^2J_{CP}$ = 17 Hz, CH), 138.4 (C), 142.6 (C), 146.6 (d, $^1J_{CP}$ = 12 Hz, C), 161.1 (C), 162.4 (C) ppm.

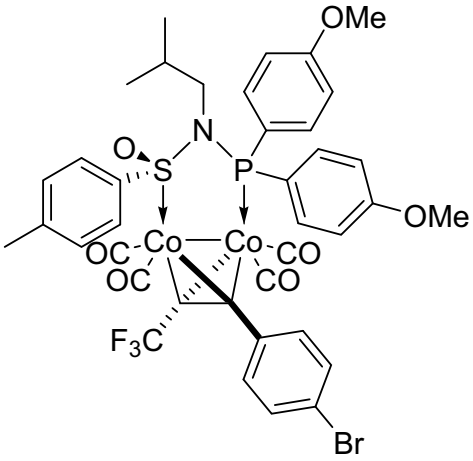
^{19}F-NMR (376 MHz, C_6D_6) δ = -48.06 (s, 3F) ppm.

^{31}P-NMR (121 MHz, C_6D_6) δ = 113.4 (s, 1P) ppm.

HRMS (ESI) calculated for $C_{38}H_{35}ClCo_2F_3NO_7PS$ 890.0171, found 890.0205 $[M+H]^+$.

$[\alpha]_D$ = -114^a (c 0.5, $CHCl_3$).

78A



The general procedure was followed starting from **51n** (144 mg, 0.30 mmol), **64-BH$_3$** (141 mg 0.30 mmol) and DABCO (202 mg, 1.80 mmol, 6 eq.). The reaction was allowed to progress for 2.5h at 65 °C. We obtained a mixture of diastereomers (1:1 mixture, 210 mg, 75% global yield) of which the major one could be separated (red oil).

IR (film) $\nu_{max.}$ = 2075, 2024, 2003, 1595, 1501, 1257 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ = 0.12 (d, *J* = 6.6 Hz, 3H), 0.21 (d, *J* = 6.5 Hz, 3H), 0.88 (m, 1H), 1.97 (s, 3H), 2.86 (ddd, *J* = 15.8, 8.7, 5.7 Hz, 1H), 3.27 (s, 3H), 3.32 (s, 3H), 3.70 (m, 1H), 6.72 (m, 4H), 6.88 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.62 (t, *J* = 9.4 Hz, 2H), 7.77 (m, 4H), 8.09 (d, *J* = 8.1 Hz, 2H) ppm.

^{13}C-NMR (100 MHz, C_6D_6) δ = 18.2 (CH_3), 19.7 (CH_3), 20.6 (CH_3), 26.6 (CH), 52.9 (CH_2), 54.5 (CH_3), 54.6 (CH_3), 114.0 (d, $^3J_{CP}$ = 11 Hz, CH), 114.3 (d, $^3J_{CP}$ = 11 Hz, CH), 121.2 (C), 129.3 (CH), 131.0 (CH), 131.9 (CH), 132.7 (d, $^2J_{CP}$ = 15 Hz, CH), 135.8 (d, $^2J_{CP}$ = 16 Hz, CH), 138.9 (C), 142.7 (C), 146.5 (d, $^1J_{CP}$ = 12 Hz, C), 161.1 (C), 162.4 (C), 198.6 (C), 199.4 (C), 201.6 (C), 201.9 (C) ppm.

^{19}F-NMR (376 MHz, C_6D_6) δ = -48.10 (s, 3F) ppm.

^{31}P-NMR (121 MHz, C_6D_6) δ = 113.2 (s, 1P) ppm.

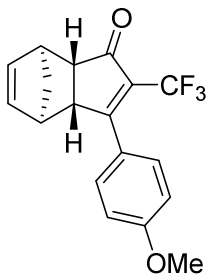
HRMS (ESI) calculated for $C_{38}H_{35}BrCo_2F_3NO_7PS$ 933.9666, found 933.9670 $[M+H]^+$.

$[\alpha]_D$ = +3.30° (c 2.7, $CHCl_3$).

General procedure for the asymmetric PKR of internal dissymmetric fluorinated alkynes.

The desired μ(PNSO)-alkyne-tetracarbonyldicobalt complex (1 eq.) was dissolved in anhydrous dichloromethane (10 mL/0.10 mmol). Norbornadiene (10 eq.) was added to the complex, followed by NMO (6 eq., added as a solid). The solution was stirred at room temperature until no more starting material could be detected by TLC. The solvent was then removed under vacuum and the crude was purified by silica gel chromatography with mixtures of hexanes/AcOEt of increasing polarities.

***(3aR,4R,7S,7aS)*-3-(4-methoxyphenyl)-2-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one ((+)-52b)**

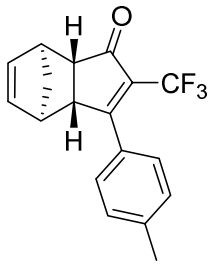


The general procedure was followed starting from the major diastereomer of cobalt complex **75A** (12 mg, 0.01 mmol). The desired product was isolated as a white solid (2.7 mg, 90% yield, 91% ee determined by HPLC*).

$[\alpha]_D$ = +76[a] (c 0.12, $CHCl_3$).

HPLC*: Chiralpack IA, heptane/EtOH (90:10), 0.5mL/min, λ=254nm, t_R(+) = 6.6 min, t_R(-) = 13.2 min.

***(3aR,4R,7S,7aS)*-3-(p-tolyl)-2-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one ((+)-52d)**

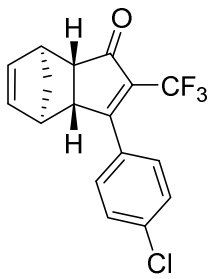


The general procedure was followed starting from the major diastereomer of cobalt complex **70A** (23 mg, 0.03 mmol). The desired product was isolated as a white solid (7.2 mg, 80% yield, 92% ee determined by HPLC*).

$[\alpha]_D$ = +333[a] (c 3.00, $CHCl_3$).

HPLC*: Chiralcel OD-H, heptane/IPA (98:2), 0.5mL/min, λ= 254nm, t_R(+) = 12.2 min, t_R(-) = 13.8 min.

***(3aR,4R,7S,7aS)*-3-(4-chlorophenyl)-2-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one ((+)-52m)**

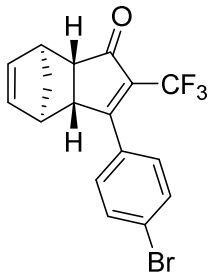


The general procedure was followed starting from the major diastereomer of cobalt complex **77A** (20 mg, 0.02 mmol). The desired product was isolated as a white solid (1.7 mg, 30% yield, 92% ee determined by HPLC*).

$[\alpha]_D$ = +299[a] (c 0.50, $CHCl_3$).

HPLC*: Chriralpack IA, heptane/EtOH (50:50), 0.5mL/min, λ=220nm, t_R(+) = 8.4 min, t_R(-) = 12.2 min.

***(3aR,4R,7S,7aS)*-3-(4-bromophenyl)-2-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one ((+)-52n)**



The general procedure was followed starting from the major diastereomer of cobalt complex **78A** (54 mg, 0.06 mmol). The desired product was isolated as a colorless oil (12 mg, 57% yield, 90% ee determined by HPLC*).

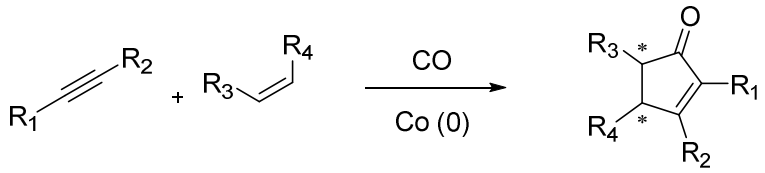
$[\alpha]_D$ = +250[a] (c 0.60, $CHCl_3$).

HPLC*: Chriralpack AD-H, heptane/EtOH/IPA (50:35:15), 0.5mL/min, λ=210nm, t_R(+) = 8.0 min, t_R(-) = 11.9 min.

Appendix I. Summary in Catalan

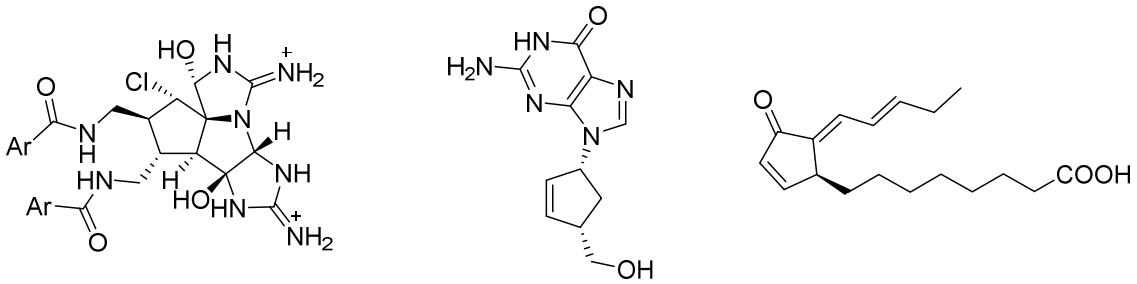
1. Introducció i objectius

La reacció de Pauson-Khand (PKR) és, formalment, una cicloaddició [2+2+1] típicament mediada o catalitzada per un complex de cobalt (0) on un alquè, un alquí i una molècula de monòxid de carboni formen una ciclopentenona. En aquesta reacció es formen tres nous enllaços carboni-carboni i fins a dos nous centres estereogènics, en funció de la substitució de l'alquè (Esquema 1).



Esquema 1: Reacció de Pauson-Khand.

Des del seu descobriment l'any 1971[1] per P. L. Pauson i I. U. Khand, la PKR ha estat un dels mètodes més emprats per la construcció de compostos amb anells de cinc baules a la seva estructura com, per exemple, productes naturals[2] o d'interès farmacèutic[3] (Figura 1).



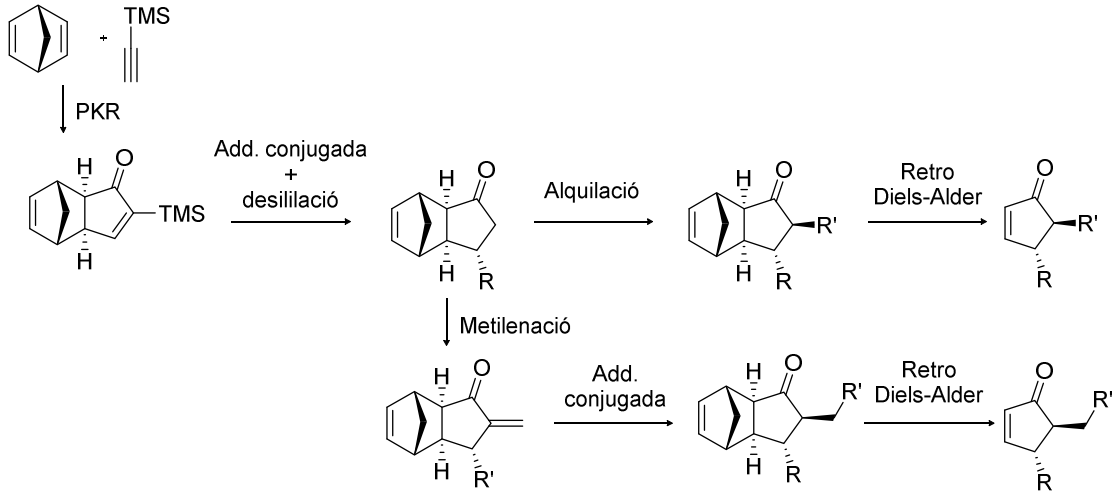
Axinellamine A (-)-Carbovir dPPJ$_1$-I

Figura 1: Alguns compostos d'interès sintetitzats mitjançant la PKR intermolecular.

La PKR pot ser intramolecular o intermolecular. El fet que la PKR intramolecular doni lloc a estructures policícliques complexes en pocs passos sintètics i que tingui poques restriccions quant a la reactivitat dels sistemes emprats fa que aquesta hagi estat la versió més emprada de la PKR. Per una altra banda, i tot i el seu potencial sintètic, la PKR intermolecular ha estat menys estudiada i explotada. Un dels motius per això és que rang d'aplicabilitat d'alquens en la PKR intermolecular és baix. Només alquens cíclics i tensionats reaccionen d'una manera acceptable, essent l'etilè una excepció a aquesta regla. Un altre aspecte a tenir en compte és la regioselectivitat de la reacció quan es treballa amb alquins interns. Tot i que la regioselectivitat de la PKR en favor de l'adducte amb el substituent en α es total quan l'alquí és terminal, els alquins interns

poden donar lloc a mescles de regioisòmers en proporcions variables[4]. Per últim, tot i que el desenvolupament de versions asimètriques de la PKR intermolecular en els últims anys ha afegit valor a la reacció la possibilitat de dur a terme la PKR asimètrica de manera catalítica és encara un repte no assolit[5].

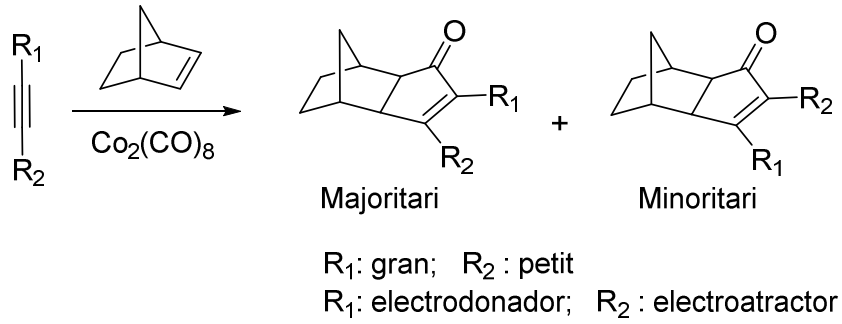
Probablement dues de les famílies més importants de compostos ciclopentànics són les prostaglandines i els fitoprostans. Les prostaglandines es generen per acció de la ciclooxigenasa (COX) sobre els àcids grassos de la membrana lipídica, essent el substrat més comú per aquest procés en el cos humà l'àcid araquidònic[6]. En plantes es dóna un procés similar amb l'àcid linolènic com a substrat i els fitoprostans com a productes[7]. Les interessants propietats d'aquests productes, entre les quals destaca la activitat antitumoral[8], juntament amb la dificultat d'aïllar-los de fonts naturals han fet que hagi crescut l'interès en trobar mètodes senzills i eficients per accedir-hi. El fet que aquests productes comparteixin un anell de ciclopentenona (o un derivat) com a element estructural fa que siguin uns substrats ideals per ser preparats mitjançant una PKR. En el nostre grup s'ha sintetitzat amb èxit i de manera òpticament activa ciclopentenones amb substituents a la posició 4 i 5-alquilidenciclopent-2-enones a partir de l'adducte de PK del norbornadiè i el trimetilsililacetilè[3,9], tot i que la introducció d'una cadena alifàtica en α al carbonil sempre ha estat problemàtica. La primera aproximació a la introducció de substituents saturats en aquesta posició la va fer Agustí Lledó durant la seva tesi doctoral. La seva estratègia consistia en alquilar o metilenar el carboni en α a la cetona resultant de la desililació del producte derivat de realitzar una addició conjugada sobre l'adducte de PK del norbornadiè i el trimetilsililacetilè. Tot i que la addició conjugada i la desililació funciona bé[10] la alquilació i la metilació donaven crus complexes i rendiments baixos (Esquema 2).



Esquema 2: Aproximació d'Agustí Lledó a la síntesi de ciclopentenones α, β-disubstituides.

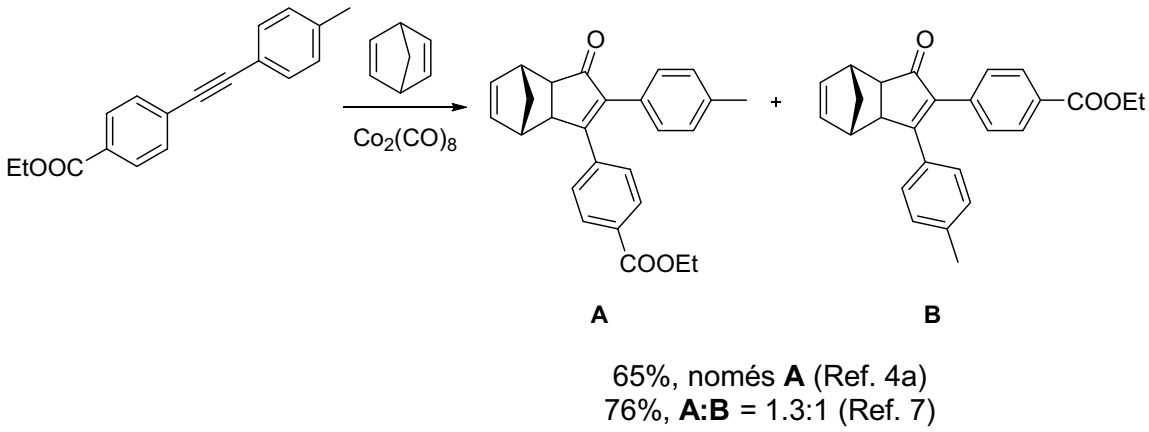
En aquest context, es feia patent que calia **desenvolupar una nova metodologia per accedir ciclopentenones α, β-disubstituides a partir d'adductes de PK** que solucionés el problema de la introducció d'un substituent α al carbonil. Aquest seria un altre objectiu de la present tesi doctoral. Tanmateix, un cop posada a punt aquesta metodologia, ens plantejaríem aplicar-la a la síntesi d'un fitoprostà natural: l'àcid 13-*epi*-12-oxo fitodienòic.

S'ha dedicat molts esforços a la racionalització de la regioselectivitat de la PKR intermolecular d'alquins interns dissimètrics. La primera hipòtesi va ser formulada per Greene y col·laboradors l'any 2001[4a]. Els autors van proposar que, en el cas d'alquins interns dissimètrics, hi ha dos factors que influencien en la regioquímica dels productes finals: la mida dels substituents i les seves propietats electròniques. Així, el substituent més voluminós tendirà a ocupar la posició α al carbonil final, mentre que el substituent més petit preferirà la posició β. Si tots dos substituents tinguessis mides similars, el grup més electrodonador aniria α a la cetona i el més electroatraient, β. Aquests efectes electrònics podrien ser anul·lats degut a efectes estèrics (Esquema 3).



Esquema 3: Regioselectivitat en la PKR intermolecular.

Tot i que aquesta teoria ha estat amplament acceptada durant la última dècada, estudis més recents han demostrat que no és general i que no pot explicar molts dels resultats observats. A més, estudis recents[11] han demostrat que, de fet, l'exemple que Greene i col·laboradors van fer servir per il·lustrar la seva hipòtesi va ser conseqüència d'una anàlisi incorrecta dels resultats experimentals i que, per tant, les conclusions que van extreure i la teoria que van elaborar no era correcta (Esquema 4).



Esquema 4: Resultats de Greene[4a] i Helaja[7].

Helaja i col·laboradors[11] han proposat recentment una aproximació diferent per explicar la regioselectivitat de la PKR intermolecular amb alquins amb substituents de mida semblant, però de propietats electròniques diferents. Es el seu estudi, van explorar les densitats de càrrega dels àtoms de carboni en α al carboni de l'alquí en lloc de considerar els substituents com una unitat. La raó d'això és que aquests carbonis estan directament relacionats amb orbitals de tipus p, que tenen una enorme influència en la PKR. Helaja i col·laboradors van confirmar la tendència general proposada per Greene, però amb matisos i una millor correlació entre predicció i resultats.

La PKR intermolecular ha demostrat ser un procediment molt tolerant quant a alquins es refereix. Probablement, aquesta característica ha fet que no trobem molts estudis quant al rang d'aplicabilitat d'alquins. Molts substituents romanen inexplorats, entre ells els alquins fluorats. Al començament d'aquest treball només hi havia descrits uns pocs exemples de PKR amb substrats fluorats, tots ells intramoleculars[12]. Per aquesta raó, un dels objectius fixats per aquesta tesi doctoral va ser **l'estudi de la PKR intermolecular amb alquins interns dissimètric fluorats i de com la presència de substituents fluorats i substituents amb diferents propietats estereoelectròniques afecten la regioselectivitat de la PKR.**

Una de les línies de recerca més importants del nostre grup de recerca en els últims anys ha estat la inducció de quiralitat en la PKR. Aquests estudis es van iniciar amb l'ús d'auxiliars quirals enllaçats bé a l'alquí o a l'alquè[13], però es va evolucionar cap a l'ús de lligands quirals units al clúster metàl·lic. Entre aquests lligands destaquen els lligands bidentats hemilàbils de tipus *N*-fosfino sulfinamida (PNSO)[5b, c] (Figura 2).

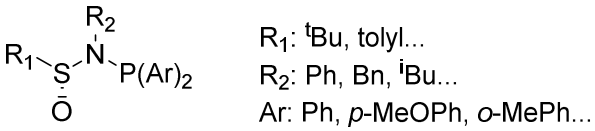


Figura 2: Estructura general d'un lligand PNSO.

Aquesta família de lligands s'ha emprat amb èxit en la PKR asimètrica intermolecular d'alquins interns simètrics[5d], però mai s'ha dut a terme la reacció amb alquins interns dissimètrics. Per aquest motiu, vam decidir **desenvolupar la PKR intermolecular asimètrica pels nostres alquins interns fluorats**.

Així, en resum, els objectius principals d`aquesta tesi es van definir com:

I. Desenvolupar una nova metodologia per accedir ciclopentenones α, β-disubstituides a partir d'adductes de PK.

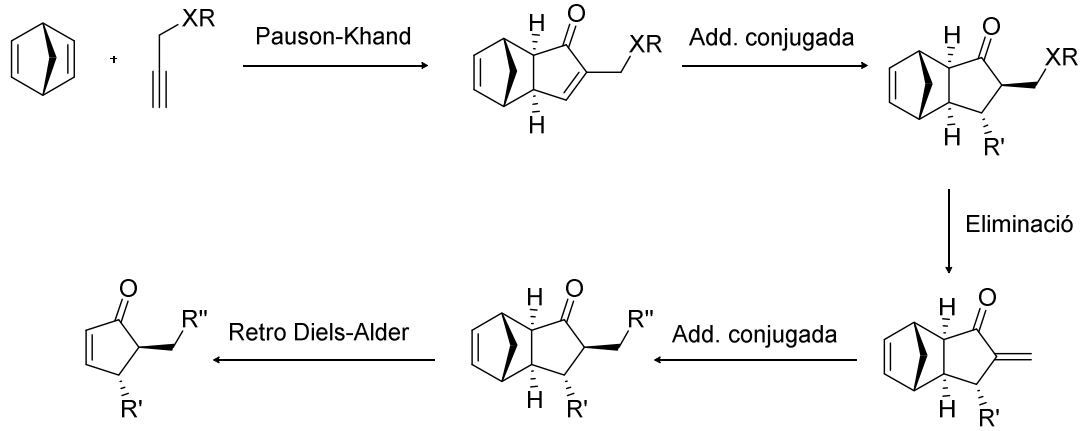
II. Aplicar aquesta metodologia a la síntesi d'un producte natural.

III. Estudiar la PKR intermolecular d'alquins fluorats i avaluar com la presència de fluor afecta a la regioquímica de la reacció.

IV. Desenvolupar una versió asimètrica per la PKR d'alquins interns dissimètrics fluorats.

2. Desenvolupament d'una nova metodologia per a la síntesi de ciclopentenones 4,5-disubstituides.

Amb l'objectiu de resoldre els problemes que el nostre grup havia trobat al intentar instal·lar un substituent saturat en la posició α al carbonil de la cetona β substituïda resultant de realitzar una addició conjugada i una desililació sobre l'adducte de PK del norbornadiè i el trimetilsililacetilè, es va dissenyar una nova aproximació sintètica que es pot veure en l'esquema 5.



Esquema 2: Nova aproximació sintètica.

La clau de la nostra estratègia rau en l'ús d'alquins amb grups sortints potencials (XR) en la posició propargílica com a substrats per la PRK. Això ens permetria realitzar les transformacions desitjades en la posició β i, després, eliminar el grup sortint a voluntat. Després d'aquest procés, obtindríem una enona exoxíclica sobre la qual podríem introduir el substituent desitjat sense haver de realitzar els problemàtics processos de metilenació o alquilació. Un cop duta a terme la reacció de retro Diels-Alder, arribaríem a la ciclopentenona 4,5-disubstituida desitjada.

Amb aquesta estratègia en ment, el primer pas a fer era seleccionar una sèrie d'alquins amb grups sortints potencials. Vam triar el fenilpropargiltioèter, tres derivats de l'alcohol propargílic i, per últim, tres derivats de la propargilamina (Figura 3).

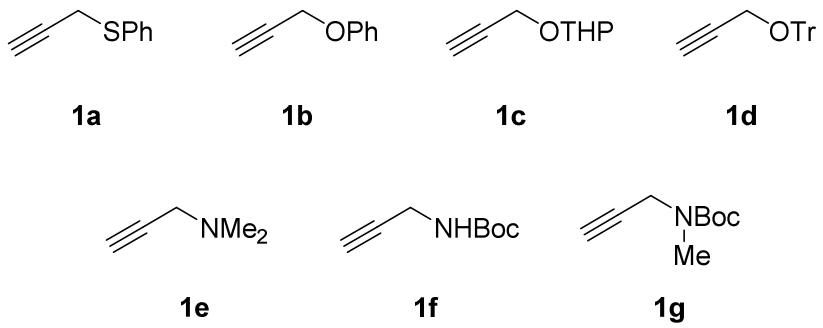
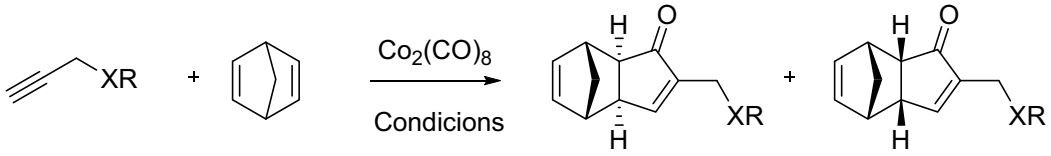


Figura 3: Alquins assajats.

Es va dur a terme la PKR amb tots els substrats triats, obtenint-se en tots els casos l'adducte de PK desitjat amb rendiments de moderats a excel·lents (Taula 1).

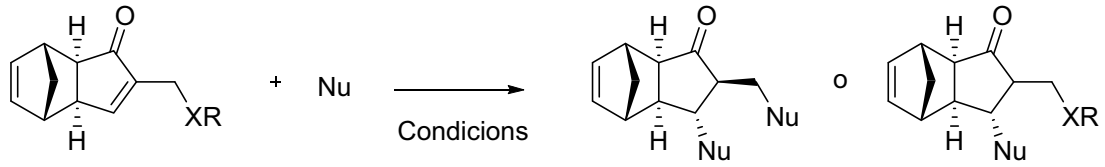


Entrada	Alquí	Condicions	*exo:endo*	Prod.	Rendiment
1	**1a**	Toluè, 60°C	>99:1	**2a**	35-40%
2	**1a**	$Co_2(CO)_8$ (5 mol%), toluè, 2 bars CO, 75°C	39:1	**2a**	69%
3	**1a**	$Co_2(CO)_7(PPh)_3$ (5 mol%), toluè, 2 bars CO, 75°C	49:1	**2a**	43%
4	**1b**	Toluè, 70°C	25:1	**2b**	71%
5	**1c**	Toluè, 70°C	15:1	**2c**	86%
6	**1d**	Toluè, 70°C	>99:1	**2d**	85%
7	**1e**	Hexà, 60°C	>99:1	**2e**	87%
8	**1f**	Hexà, 60°C	11:1	**2f**	61%
9	**1f**	$Co_2(CO)_8$ (5 mol%), toluè, 2 bars CO, 60°C	5:1	**2f**	60%
10	**1f**	$Co_2(CO)_7(PPh)_3$ (5 mol%), toluè, 2 bars CO, 65°C	>99:1	**2f**	86%
11	**1g**	Toluè, 65°C	40:1	**2g**	85%

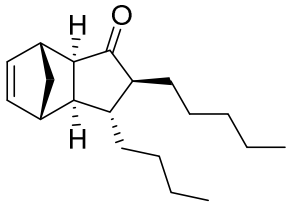
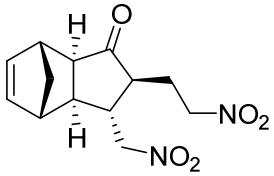
Taula 1: PKRs amb els alquins **1a-f**.

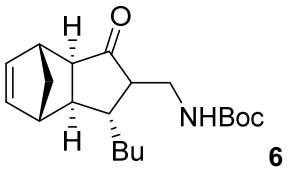
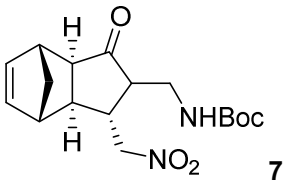
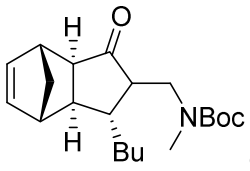
Un cop amb els adductes en mà, es va procedir a avaluar la seva reactivitat. Es van triar dues reaccions model: l'addició conjugada de dibutil cuprat de liti i la de nitrometà catalitzada per base.

Quan el producte de partida per aquestes reaccions era un dels adductes **3a-e**, s'observava que, en lloc d'obtenir el producte desitjat, la reacció donava un producte corresponent a la doble addició del nucleòfil corresponent, mentre que si la reacció es duia a terme amb els adductes **3f** o **3g** sí s'obtenia el producte d'addició simple desitjat (Taula 2).



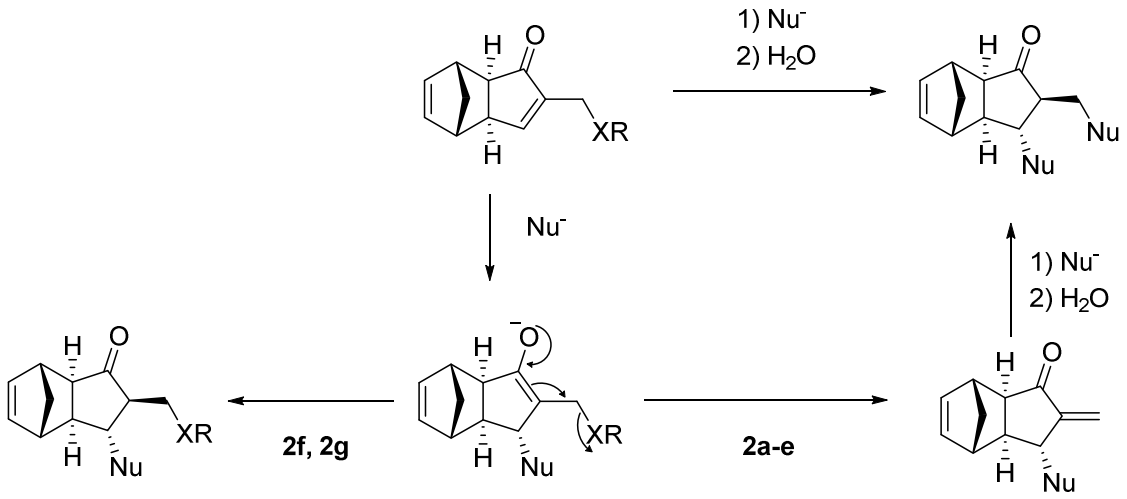
3a-g

Entrada	Pp[a]	Condicions	Producte	Rendiment
1	**2a**	Bu_2CuLi, Et_2O, -78°C	 **4**	49%
2	**2a**	CH_3NO_2, TBAF·$3H_2O$, t. amb.	 **5**	86%
3	**2b**	Bu_2CuLi, Et_2O, -78°C	**4**	56%
4	**2b**	CH_3NO_2, TBAF·$3H_2O$, t. amb.	**5**	99%
5	**2c**	Bu_2CuLi, Et_2O, -78°C	**4**	55%
6	**2d**	Bu_2CuLi, Et_2O, -78°C	**Pp**	-
7	**2e**	Bu_2CuLi, Et_2O, -78°C	**4**	40%
8	**2e**	CH_3NO_2, 80°C	**4**	46%

9	**2f**	Bu_2CuLi, Et_2O, -78°C	 **6**	71%
10	**2f**	CH_3NO_2, TBAF·$3H_2O$, t. amb.	 **7**	99%
11	**2g**	Bu_2CuLi, Et_2O, -78°C	 **8**	89%

Taula 2: Reactivitat dels adductes **2a-g** front a reaccions d'addició conjugada. a: producte de partida.

A la vista d'aquests resultats, es va proposar una explicació mecanística per tal de raonar-los. Proposem que, un cop es dóna la primera addició conjugada, l'enolat format evoluciona ràpidament en la mescla de reacció (en els casos dels productes **2a-e**) per fornir l'enona exocíclica *in situ*. Aquesta enona podria llavors reaccionar amb l'excés de nucleòfil present en el medi per generar els productes de doble addició detectats. Aquest procés no ocorreria en el cas dels adductes **2f** i **2g** on, presumiblement, hi ha una estabilització de l'enolat intermedi que evita que evolucioni cap a l'enona exocíclica (Esquema 6).



Esquema 3: Mecanisme proposat per a la doble addició conjugada.

Es va realitzar un estudi teòric a nivell computacional sobre l'estabilitat relativa dels intermedis presents en aquest mecanisme proposat, tot i que els resultats no concorden amb les observacions experimentals.

Ja que els únics adductes que satisfeien les condicions de reactivitat que necessitàvem per dur a terme el nostre esquema sintètic, i ja que la PKR asimètrica de **1f** amb lligands PNSO (amb tetrametilnorbornadiè com alquè) ja havia estat estudiada[14], vam decidir continuar estudiant, únicament, l'adducte **2f**. Es va procedir a realitzar una sèrie d'addicions conjugades de diferents nucleòfils (organometàl·lics, no organometàl·lics i addició fotoquímica de metanol) que en tots casos van procedir satisfactòriament. Seguidament, es va desprotegir i eliminar la amina bocada per obtenir la enona exocíclica, sobre la qual es van realitzar un nou conjunt d'addicions conjugades també amb èxit. La reacció de retro Diels-Alder un dels productes disubstituïts obtingut va generar una ciclopentenona α,β-disubstituïda, tal com havíem dissenyat.

En resum, hem pogut desenvolupar una nova metodologia per accedir ciclopentenones α, β-disubstituides a partir d'adductes de PK.

3. Aplicació de la metodologia: síntesi de l'ester metílic de l'àcid 13-*epi*-12-oxo fitodienòic.

Un cop amb la metodologia per accedir ciclopentenones α, β-disubstituides a partir de l'adducte de PK entre el norbornadiè i la *N*-Boc-propargilamina posada a punt, vam decidir aplicar-la a la síntesi d'un derivat de producte natural: l'ester metílic de l'àcid 13-*epi*-12-oxo fitodienòic (Figura 4).

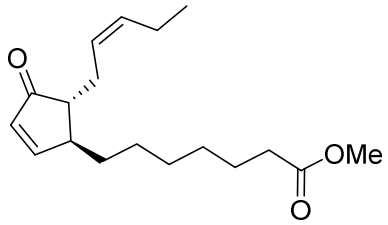
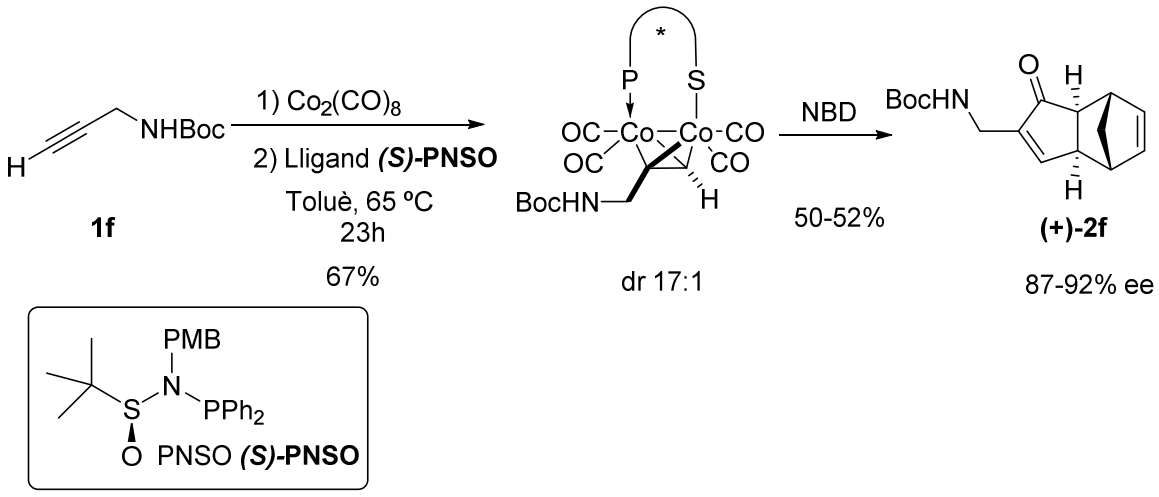


Figura 4: Ester metílic de l'àcid 13-*epi*-12-oxo fitodienòic.

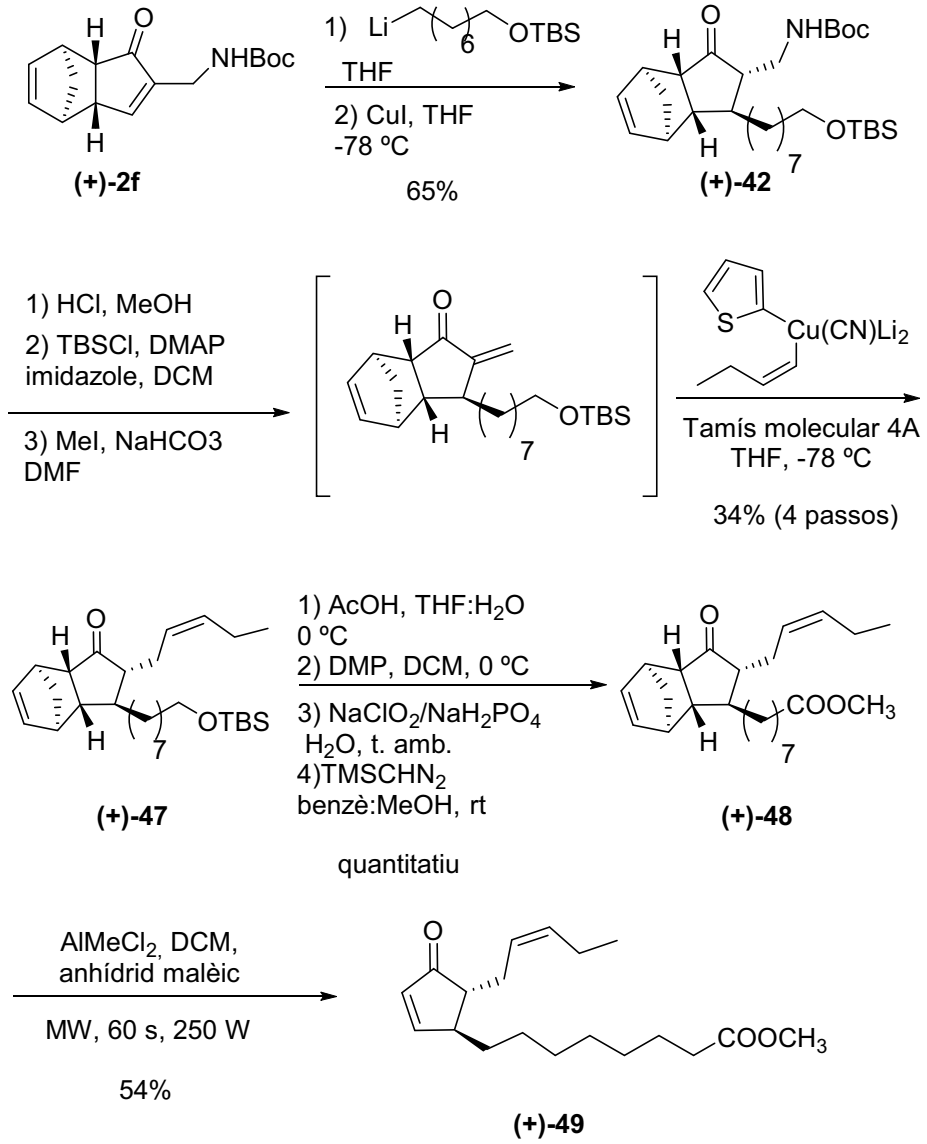
La nostra síntesi va començar a partit de l'adducte òpticament actiu **(+)-2f**, que es va obtenir a partir de la PKR asimètrica de la *N*-Boc-propargilamina i el norbornadiè emprant un lligand PNSO desenvolupat al grup unit al clúster metàl·lic (Esquema 7).



Esquema 4: obtenció de **(+)-2f**.

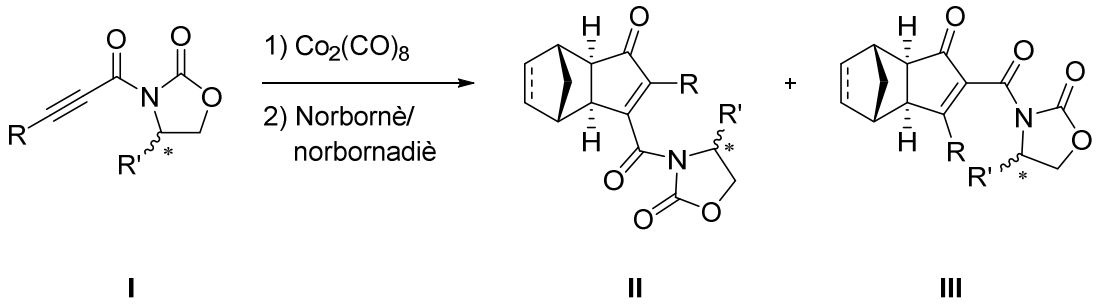
Aquest adducte va ser tractat amb el cuprat derivat del 8-yodo-1-*terc*-butildimetilsiloxioctà per donar el producte d'addició conjugada **(+)-42**. Aquest va ser tractat amb HCl/MeOH per tal de desprotegir la amina. Simultàniament, però, l'alcohol també es va desprotegir. Tot i que es van explorar diferents condicions per intentar desprotegir la amina selectivament, no es va aconseguir, de manera que vam procedir a re-protegir tant la amina com l'alcohol amb un grup TBS. El producte resultant es va tractar amb MeI i $NaHCO_3$ per generar la enona exocíclica. El cru d'aquesta reacció es va fer reaccionar amb el cuprat d'ordre superior derivat del 2-tienil cianocuprat de liti i el (*Z*)-but-1-en-1-il liti, reacció que va fornir l'adducte α, β-disubstituït **(+)-47**.

Seguidament, es va transformar l'alcohol en el metil ester **(+)-48** i aquest es va sotmetre a la reacció final de retro Diels-Alder amb microones[15], la qual va donar lloc al producte desitjat **(+)-49** en un total de 10 passos sintètics i amb un 12% de rendiment global (Esquema 8).



Esquema 5: Síntesi de l'ester metílic de l'àcid 13-*epi*–12-oxo fitodienòic.

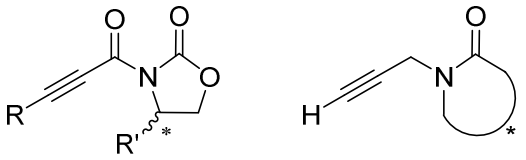
Durant molts anys, l'ús d'auxiliars quirals enllaçats a l'alquí o l'alquè ha estat un dels mètodes més emprats per accedir adductes de PK òpticament actius. De fet, el nostre grup hi va treballat àmpliament durant la dècada dels 90 del segle passat[16]. Un dels auxiliars que van resultar més exitosos va ser la família de derivats *N*-(2-alquinoil) de 2-oxazolidinones. Les PKRs transcorrien en condicions suaus i amb bons rendiments i diastereoselectivitats, que podien arribar a 18:1 en funció de la substitució de l'auxiliar quiral (Esquema 9).



I **II** **III**

Esquema 6: PKR entre derivats *N*-(2-alquinoil) de 2-oxazolidinones i norbornadiè.

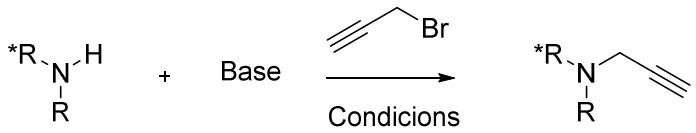
Amb aquests antecedents en ment, i tenint en compte que els carbamats no patien el procés d'addició conjugada/eliminació *in situ* descrit en la secció 2, vam decidir assajar alquins d'estructura general **IV** (Figura 5).

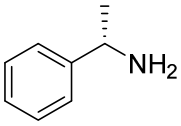
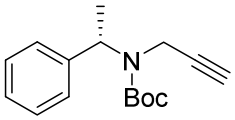
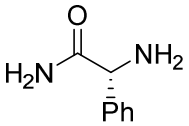
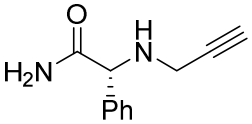


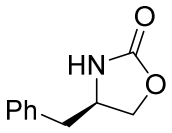
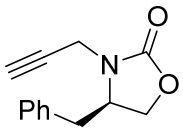
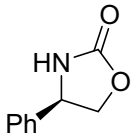
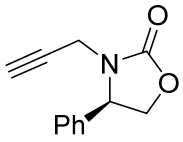
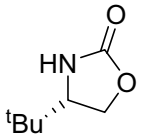
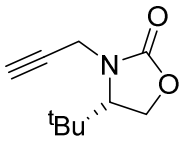
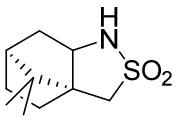
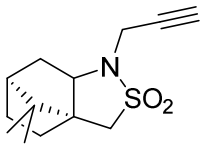
I **IV**

Figura 5: Estructura general dels derivats d'amines quirals proposats.

Vam triar set auxiliars quirals per provar la viabilitat de la nostra estratègia, i en vam preparar els alquins corresponents amb èxit (Taula 3).

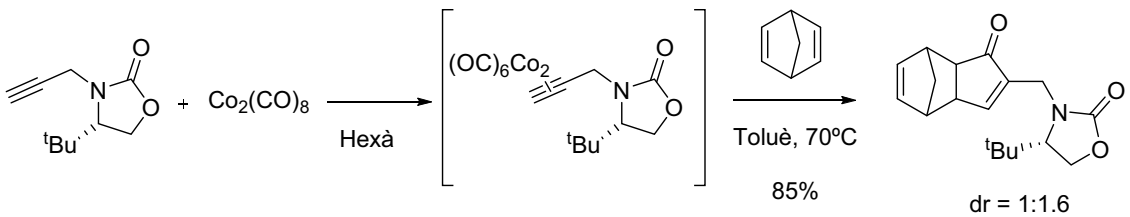


Entrada	Auxiliar	Condicions	Producte	Rdt.
1		1) K_2CO_3, ACN 2) Boc_2O, DMAP, DCM	 **25**	37%
2		K_2CO_3, ACN	 **26**	42%

4		NaH, THF	 **27**	57%
5		BuLi, THF	 **28**	80%
6		BuLi, THF	 **29**	94%
7		BuLi, THF	 **30**	82%

Taula 3: Alquilació dels derivats d'amines quirals seleccionats.

Un cop preparats els alquins, vam procedir a estudiar les PKRs corresponents. Malauradament, les diastereoselectivitats eren pràcticament inexistents en tots el casos i, a més, els diastereòmers no es podien separar per cromatografia o cristal·lització excepte en el cas en el qual l'auxiliar quiral era la *(R)*-4-(*terc*-butyl)oxazolidin-2-ona, on els diastereòmers sí podien separar-se per cromatografia en columna (Esquema 10).

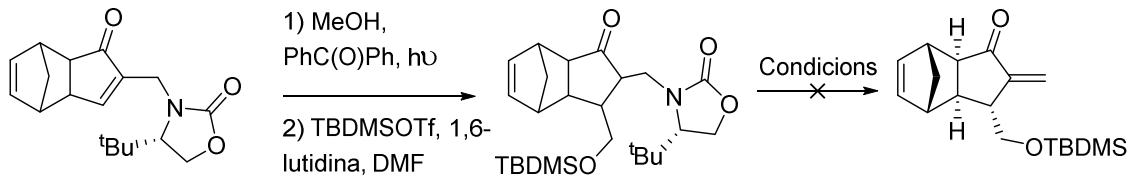


29 **34**

Esquema 7: PKR de **29** amb norbornadiè.

Un cop amb aquest adducte en mà, vam procedir a estudiar la seva reactivitat. L'addició conjugada de dialquil cuprats de liti no va funcionar, ja que només es

recuperava producte de partida després de la reacció. L'addició fotoquímica de metanol, però, sí que resultava fructífera i, ja que el producte oferia grans possibilitats a nivell d'aplicacions sintètiques, vam decidir protegir l'alcohol instal·lat per després intentar eliminar l'auxiliar quiral per tal d'obtenir una enona exocílica. Desgraciadament, no vam aconseguir arribar a aquest producte en cap dels casos, i totes les condicions assajades donaven lloc a la descomposició del producte de partida o a traces del producte final en crus molt complexos (Esquema 11).



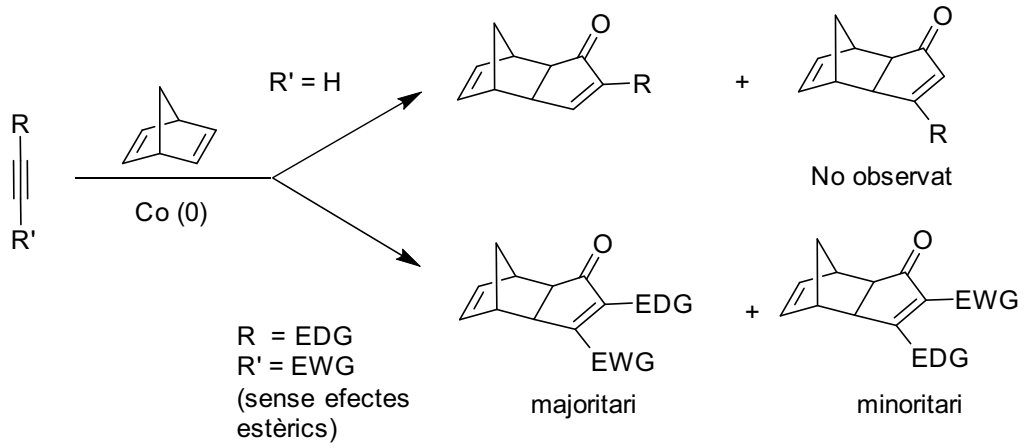
34 46%

Esquema 8: Reactivitat de **34** front a les reaccions d'addició conjugada i eliminació.

A la vista d'aquests descoratjadors resultats, vam decidir no continuar invertint esforços en aquesta aproximació.

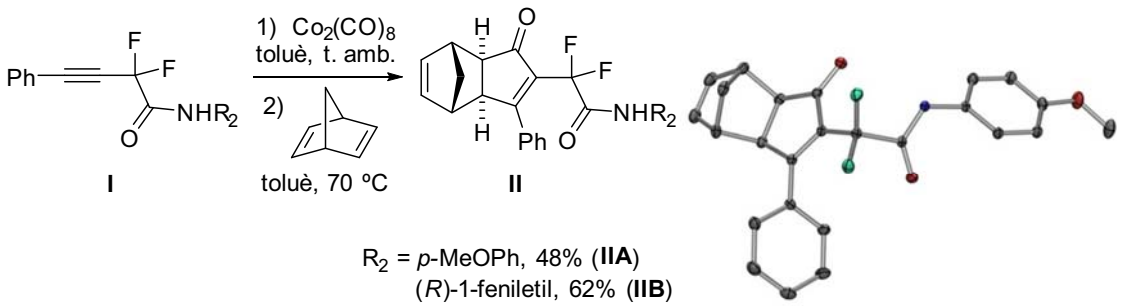
4. PKR intermolecular d'alquins dissimètrics fluorats.

Com ja hem discutit anteriorment, la regioquímica de la PKR intermolecular no és un factor trivial. De fet, pot ser problemàtica quan treballem amb alquins interns dissimètrics, ja que generalment es formen mescles de regioisòmers. La tendència general en aquests casos és que el grup més voluminós preferirà la posició α al carbonil i, en absència d'efectes estèrics, aquesta posició serà preferida pel substituent més electrodonador. En el cas d'alquins terminals, sempre s'obté l'adducte de PK α-substituït (Esquema 12).



Esquema 9: Regioselectivitat de la PKR.

El nostre grup va començar l'estudi de la PKR amb alquins fluorats l'any 2009, i els estudis preliminars van mostrar que, en tots els casos, s'obtenia un únic producte com a resultat de la PKR. Aquests productes es van estudiar curosament per RMN, i es va arribar a la conclusió que es tractava, en tots els casos, del producte amb els substituents fluorats en α al carbonil. Aquest resultat contra intuïtiu va ser confirmat per anàlisi de rajos X d'un dels adductes sintetitzats (Esquema 13).



Esquema 10: Primera PKR intermolecular amb un alquí dissimètric fluorat.

Un cop corroborada la regioquímica dels adductes de PK d'alquins fluorats, vam procedir a estudiar la generalitat d'aquest fet. Es va seleccionar un ampli rang d'alquins

trifluorometilats amb una gran varietat de substituents amb diferents propietats electròniques com anells aromàtics amb grups electrodonadors i electroatractors, un doble enllaç, dues cadenes alifàtiques i un ester[17] (Figura 6).

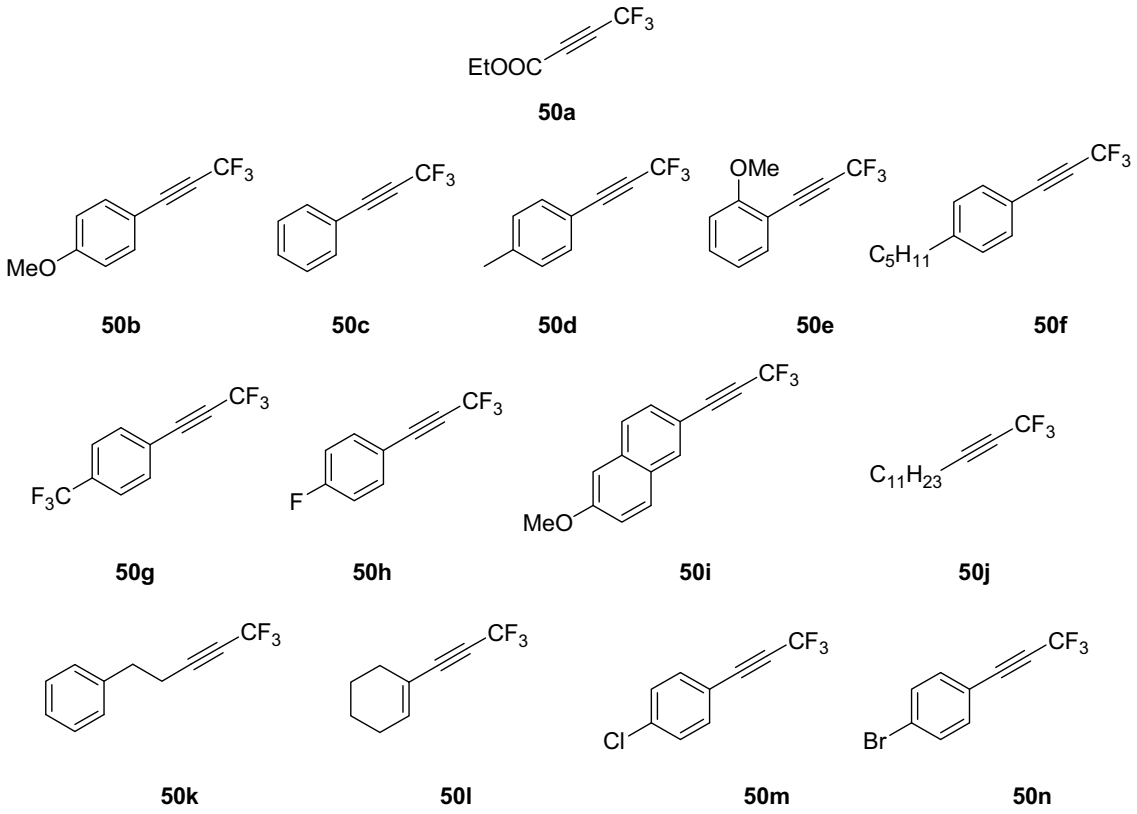
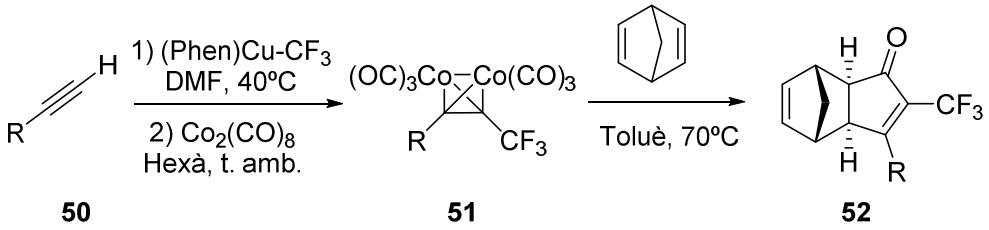
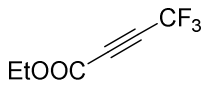
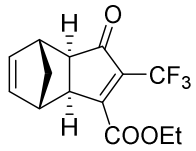
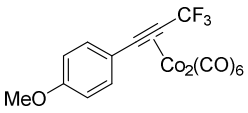
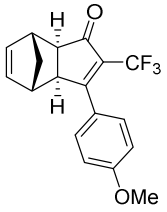
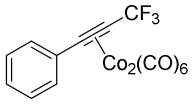
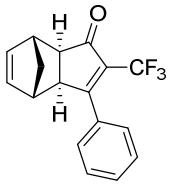
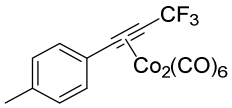
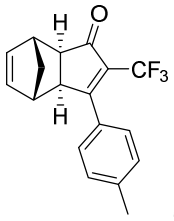
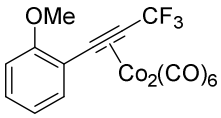
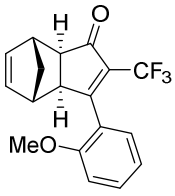
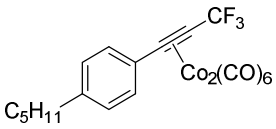
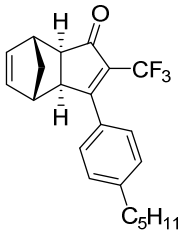
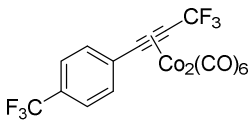
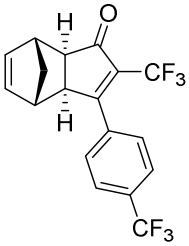
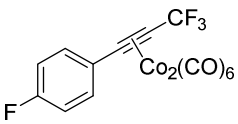
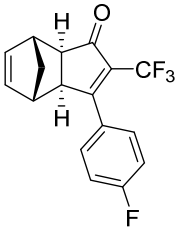
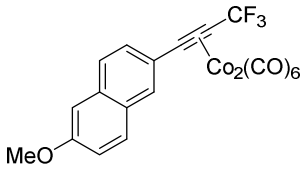
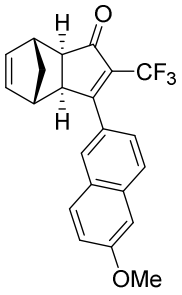
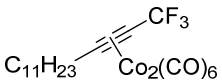
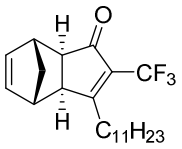
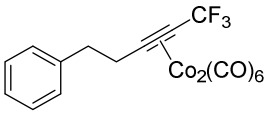
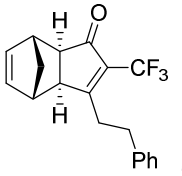
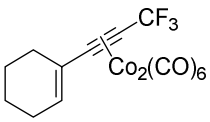
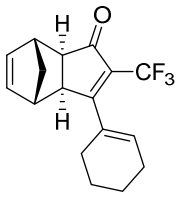
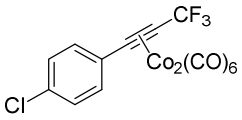
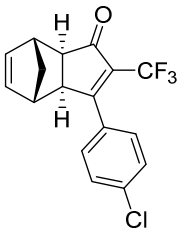
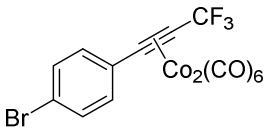
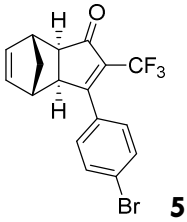


Figura 6: Alquins seleccionats.

Excepte **50a**, cap dels altres alquins triats és comercial, de manera que es van sintetitzar a partir dels corresponents alquins terminals seguint un procediment descrit per Qing i col·laboradors[18]. Els alquins trifluorometilats eren, en general, difícils de purificar degut a la seva volatilitat i gran caràcter lipofílic, raó per la qual es va decidir preparar els seus complexes de cobalt i purificar aquests derivats. En tots casos, es van aïllar els productes desitjats amb rendiments bons o excel·lents. Els complexes de cobalt es van fer reaccionar amb norbornadiè en condicions tèrmiques per fornir, en tots els casos, un sol regioisòmer que va ser identificat en tots els casos com l'addcute de PK α-trifluorometilat (Taula).



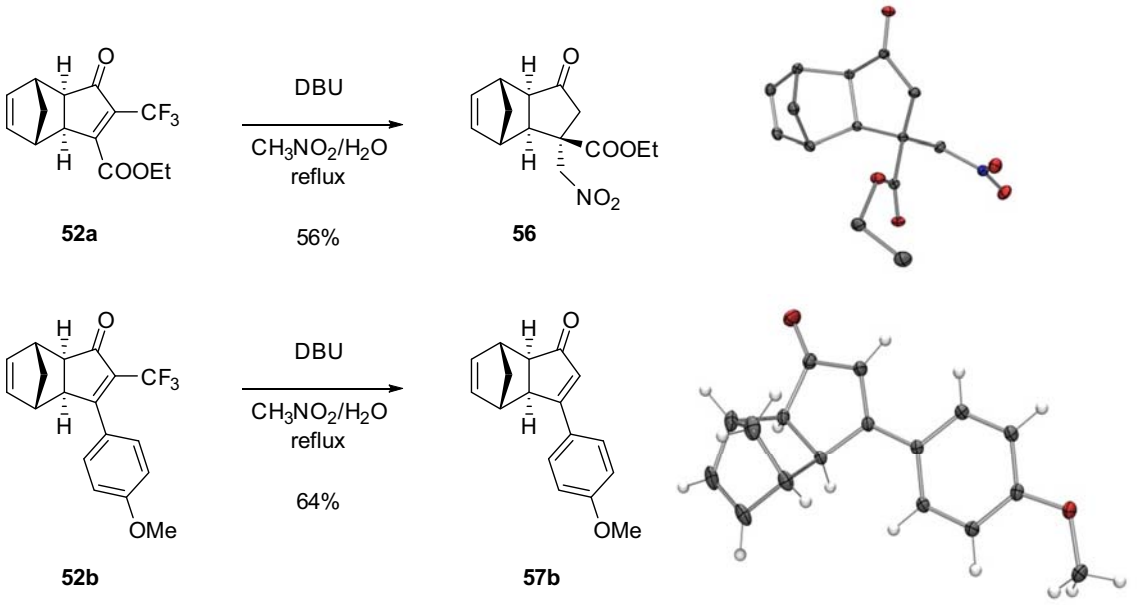
Entrada	Alquí	Rdt. 51	Adducte PK	Rdt. 52
1	 **50a**	-	 **52a**	92%
1	 **50b**	43%	 **52b**	81%
2	 **50c**	55%	 **52c**	77%
3	 **50d**	91%	 **52d**	95%
4	 **50e**	70%	 **52e**	74%
5	 **50f**	69%	 **52f**	99%
6	 **50g**	44%	 **52g**	70%
7	 **50h**	62%	 **52h**	81%

8	 **50i**	70%	 **52i**	80%
9	 **50j**	87%	 **52j**	79%
10	 **50k**	60%	 **52k**	77%
11	 **50l**	70%	 **52l**	70%
12	 **50m**	nd	 **52m**	51%
13	 **50n**	45%	 **52n**	67%

Taula 4: Síntesi i PKRs dels complexes de cobalt **51**.

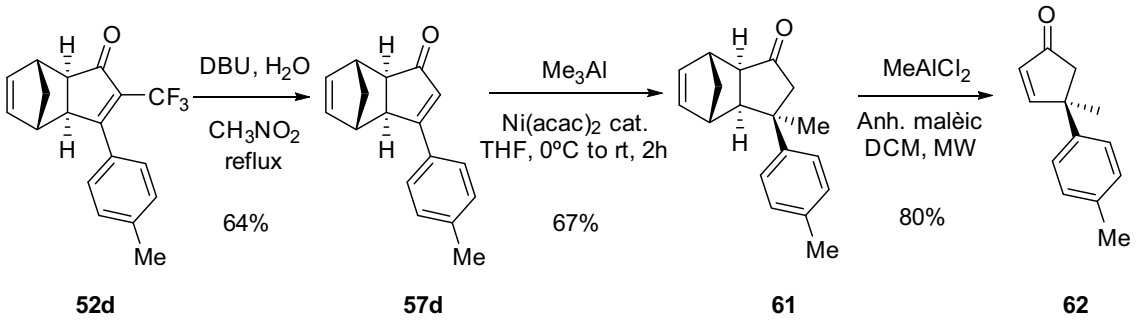
El fet que alquins amb substituents amb propietats estèriques i electròniques tan diferents dugués invariablement als adductes α–trifluorometilats suggereix que, o bé l'efecte electroatraient d'aquest grup és molt menys important de l'esperat o que es sobrepassat per la seva mida.

Seguidament, es va examinar la reactivitat d'aquests adductes front a reaccions d'addició conjugada, observant-se dos comportaments diferents quan es tractaven amb nitrometà en medi bàsic (Esquema 14).



Esquema 11: Estructura de difracció de rajos X dels productes **56** i **57b.**

La reactivitat observada per **52b** va resultar ser la general per la resta d'adductes a excepció de **52a,** representant doncs aquesta transformació una manera ràpida i eficient d'accedir els prèviament desconeguts adductes β-substituïts de la PKR d'alquins terminals amb norbornadiè. La regioselectivitat de la PKR així com de la reacció de des-trifluorometilació va resultar ser general pels adductes amb etilè i norbornè. Com aplicació sintètica de la reactivitat dels adductes de PK amb alquins trifluorometilats i norbornadiè es va realitzar una síntesi formal de la α-cuparenona en la seva forma racèmica (Esquema 15).

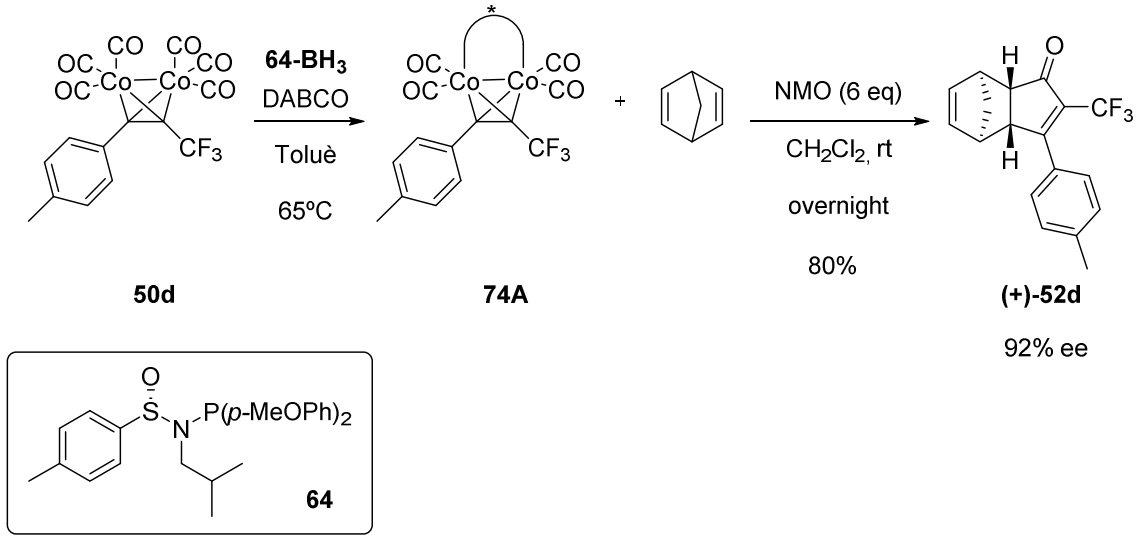


Esquema 12: Síntesi formal de la α-cuparenona a partir de **52d.**

5. PKR intermolecular asimètrica d'alquins interns dissimètrics fluorats amb norbornadiè.

Els lligands hemi-làbils *N*-fosfino sulfinamida (PNSO) van ser desenvolupats en el nostre grup de recerca i han estat àmpliament emprats en els últims anys. Els lligands de tipus *N*-fosfino-*p*-tolil-sulfinamida van ser aplicats molt recentment en la PKR asimètrica d'alquins interns simètrics[19]. Però, la PKR asimètrica d'alquins interns dissimètrics encara no havia estat explorada i, donades les interessants propietats i reactivitat dels nostres alquins fluorats, vam considerar que explorar aquesta reacció era de molt alt interès.

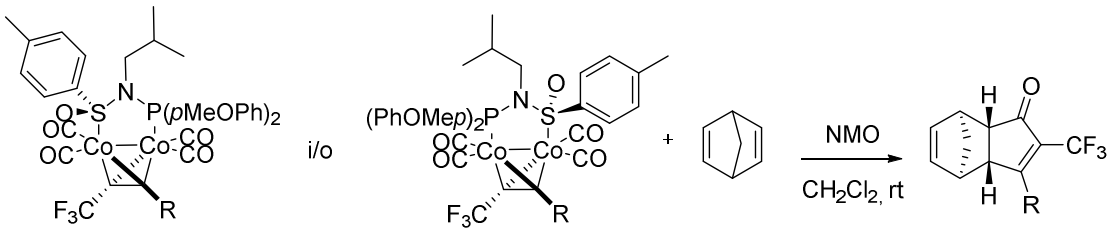
Es va seleccionar l'alquí **1c** com a model, i es va procedir a avaluar una sèrie de lligands PNSO i un lligand PNP sintetitzats al grup. Es va dur a terme la complexació de **51d** amb els diferents lligands i es va realitzar la PKR asimètrica. Tot i que la diasteroselectivitat en el procés de complexació era pràcticament nul·la per tots els lligands, els excessos enantiomèrics obtinguts van ser excel·lents per dos dels lligands assajats. Per continuar amb el nostre estudi es va triar el lligand que va donar lloc a l'adducte **(+)-52d** amb millor excés enantiomèric (Esquema 16). La configuració absoluta del producte va ser establerta per correlació química amb l'intermedi de la síntesi formal de la α-cuparenona **(-)-62.**



Esquema 13: PKR asimètrica de per obtenir **(+)-52d**.

Tanmateix, es va observar que els dos possibles diastereòmers del complex alquí-cobalt amb el lligand PNSO conduïen al mateix enantiòmer, fet que no s'havia descrit prèviament. Per tant, no calia separar els dos complexos, tot i que la reacció amb la mescla influïa en detriment de l'excés enantiomèric. Aquest fet era aplicable als altres alquins provats **50d, 50m** i **50n,** amb els quals també s'obtingueren bons

rendiments i excessos enantiomèrics excel·lents (Taula 5), constituint aquests els primers exemples de reacció de PK asimètrica amb alquins interns dissimètrics. L'estructura dels complexes de cobalt que donaven el millor excés enantiomèric van poder ser estudiades per difracció de rajos X, i l'estructura dels diastereòmers es va analitzar per IR i estudis de reactivitat amb CO, experiments que van demostrar que es tractava de complexes tetracarbonílics.



Entrada	Complex	R	Prod.	Rdt 52	ee 52
1	**74A**	tolil	**(+)-52d**	80%	92%
2	**74A'+74B' (1:1)[a]**	tolil	**(+)-52d**	59%	70%
3	**77A**	4-clorofenil	**(+)-52m**	30%	92%
4	**77A+77B (6.8:1)**	4-clorofenil	**(+)-52m**	63%	85%
5	**77A+77B (1:1)**	4-clorofenil	**(+)-52m**	60%	73%
6	**75A**	4-metoxifenil	**(+)-52b**	90%	91%
7	**75B**	4-metoxifenil	**(+)-52b**	83%	56%
8	**75A+75B (1:1)**	4-metoxifenil	**(+)-52b**	61%	73%
10	**78A**	4-bromofenil	57%	90%	+
11	**78B**	4-bromofenil	42%	28%	+
12	**78A+78B (1.3:1)**	4-bromofenil	71%	73%	+

Taula 5: Reaccions de PKR asimètriques de complexes de cobalt purs i de mescles de diastereòmers. a: lligand PNSO amb la sulfinamida *R*.

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[17] NOTA: els productes **50e, 50g, 50h, 50i, 50l** i els seus derivats van ser preparats pel grup del Profesor Santos Fustero a València. S'han inclòs en la memòria per la seva importància en la discussió dels resultats.

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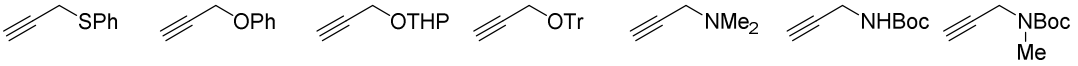
Appendix II. Index of Structures



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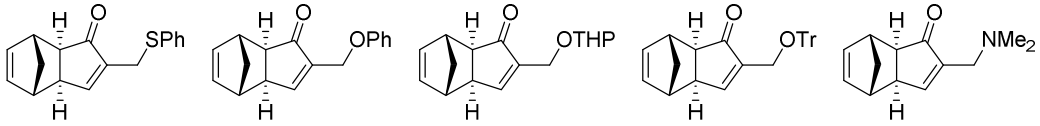

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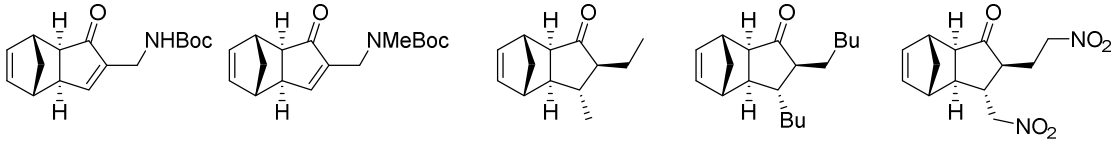

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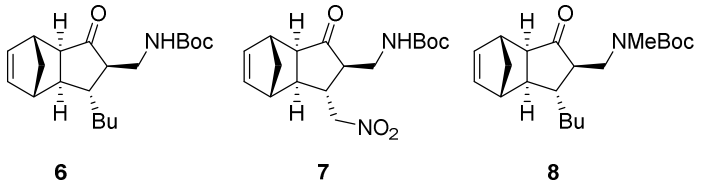

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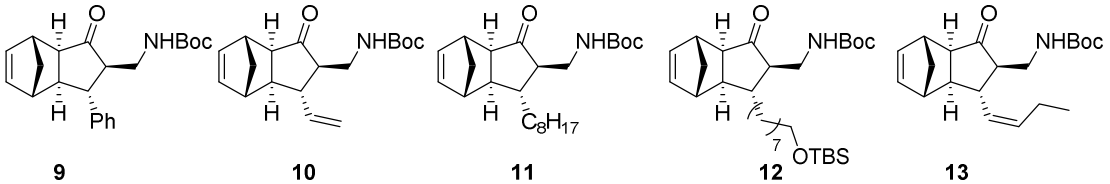

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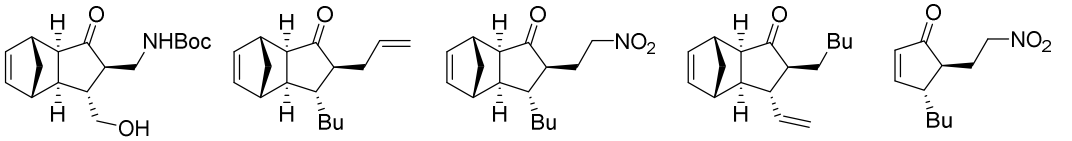

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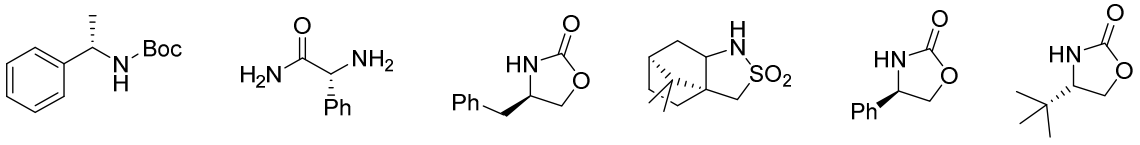

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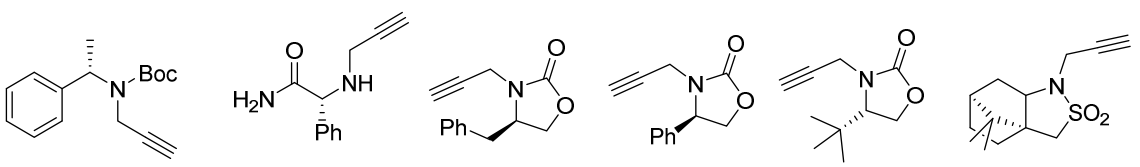

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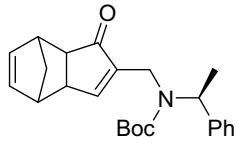

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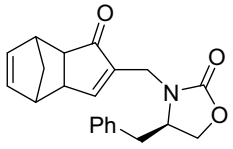

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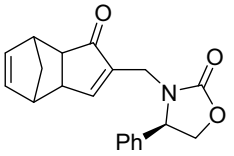

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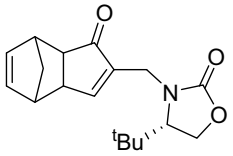

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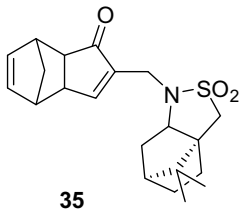

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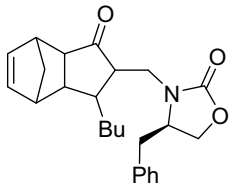

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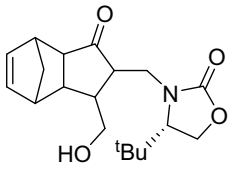

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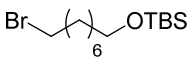

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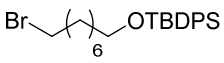

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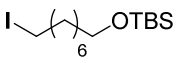

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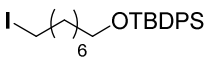

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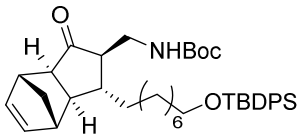

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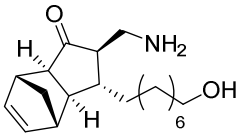

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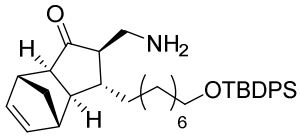

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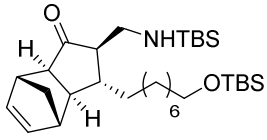

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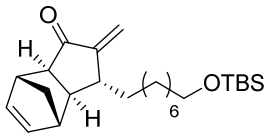

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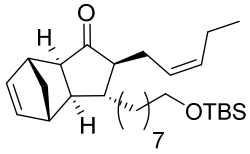

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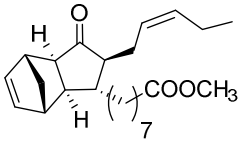

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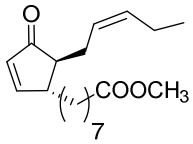

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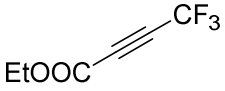

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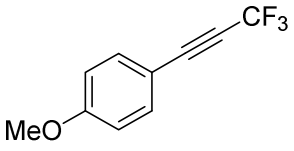

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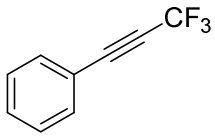

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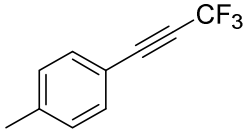

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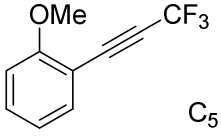

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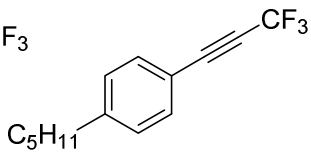

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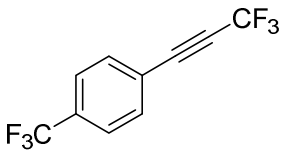

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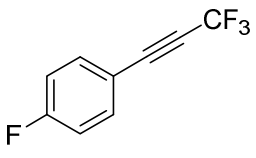

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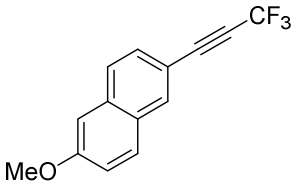

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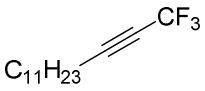

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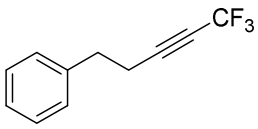

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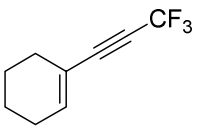

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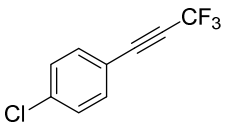

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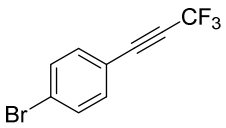

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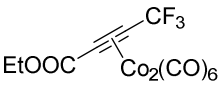

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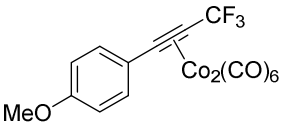

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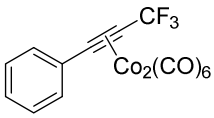

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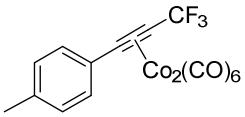

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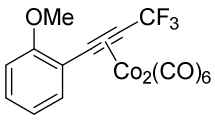

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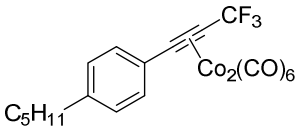

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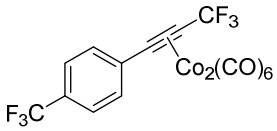

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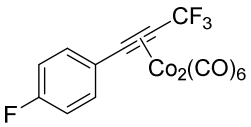

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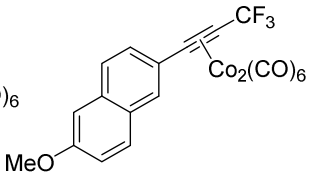

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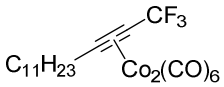

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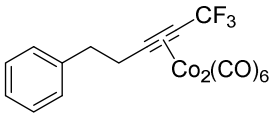

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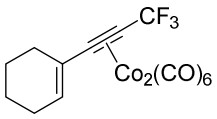

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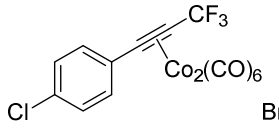

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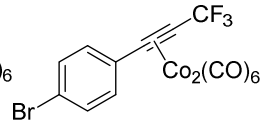

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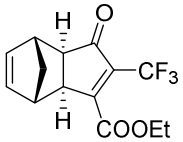

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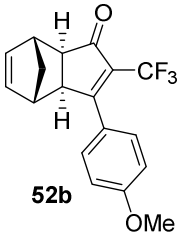

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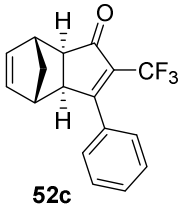

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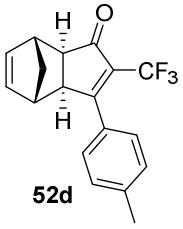

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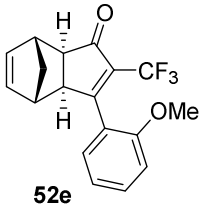

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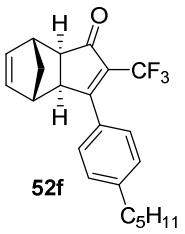

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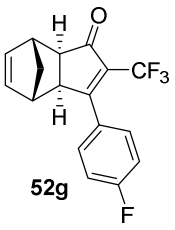

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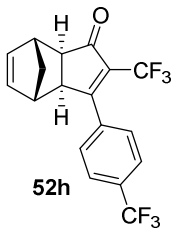

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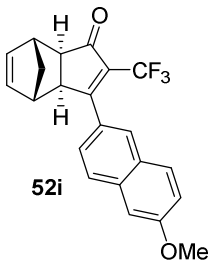

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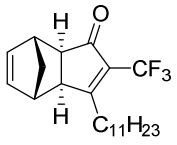

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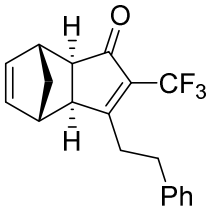

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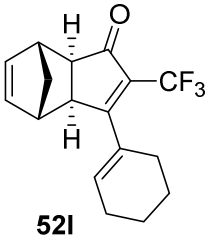

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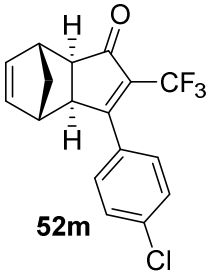

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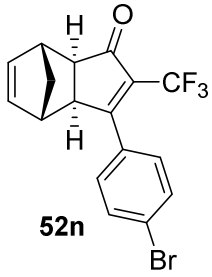

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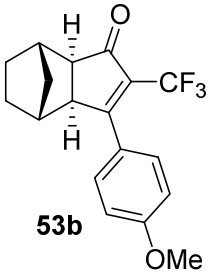

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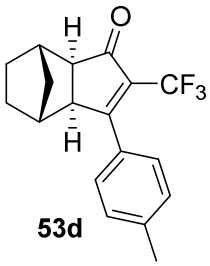

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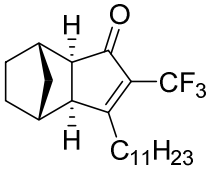

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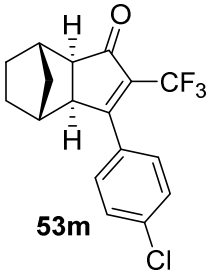

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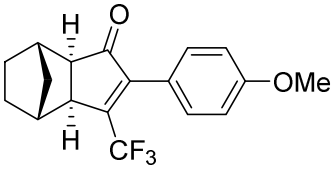

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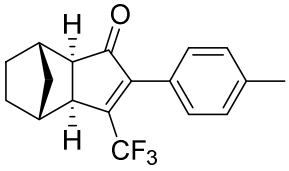

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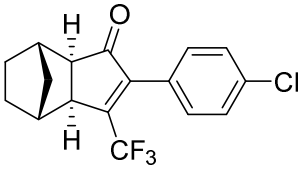

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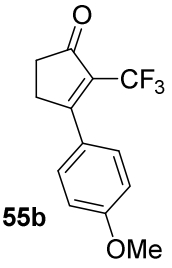

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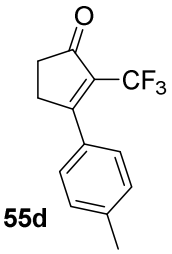

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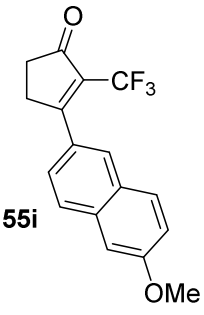

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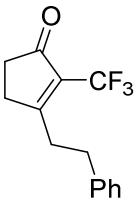

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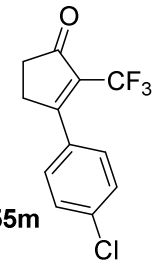

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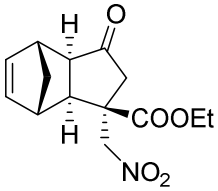

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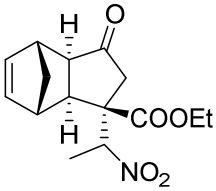

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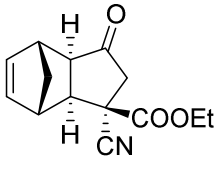

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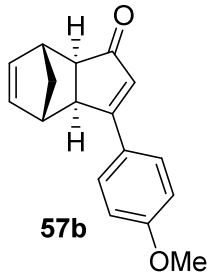

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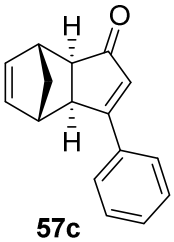

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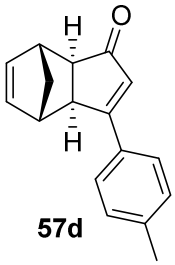

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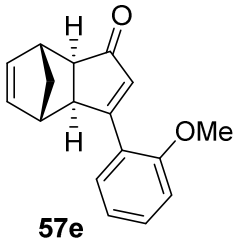

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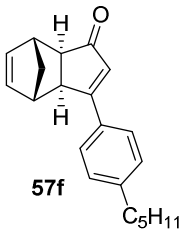

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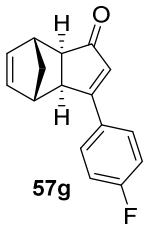

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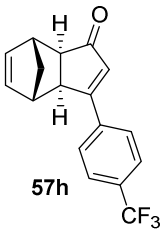

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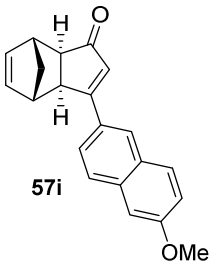

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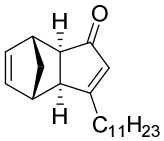

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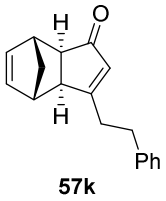

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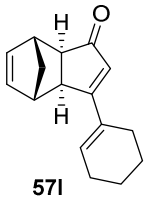

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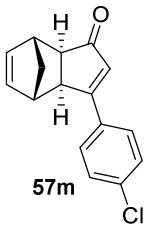

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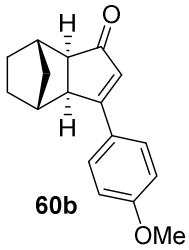

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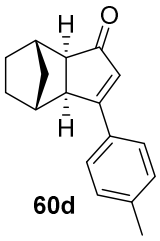

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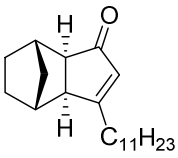

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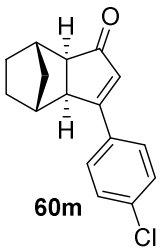

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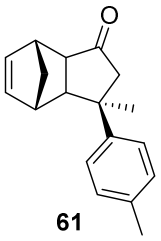

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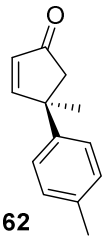

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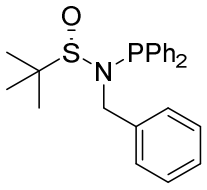

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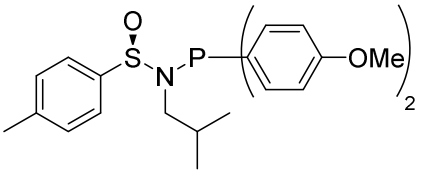

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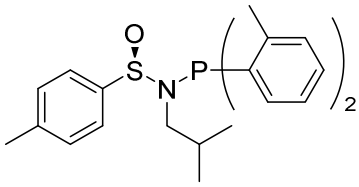

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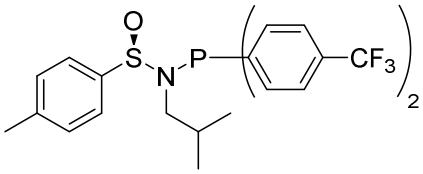

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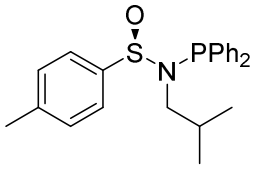

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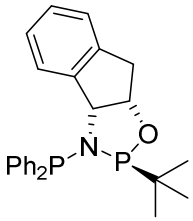

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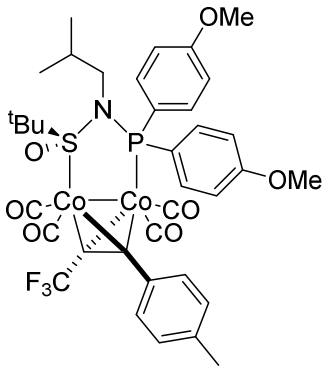

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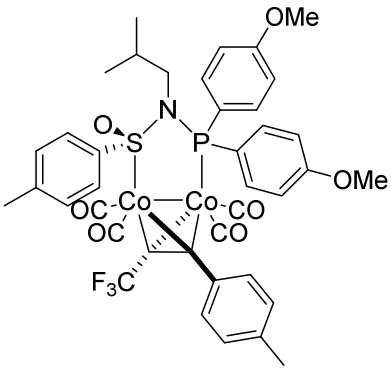

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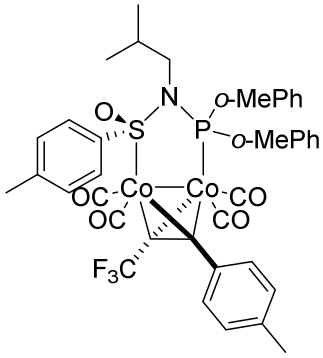

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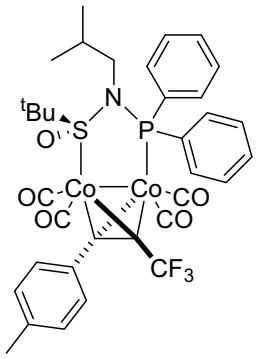

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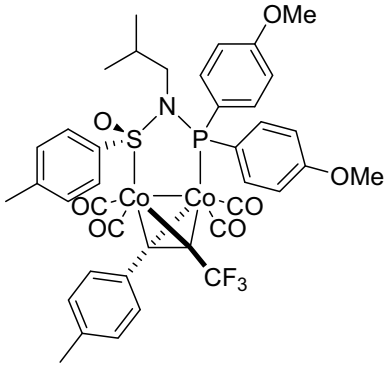

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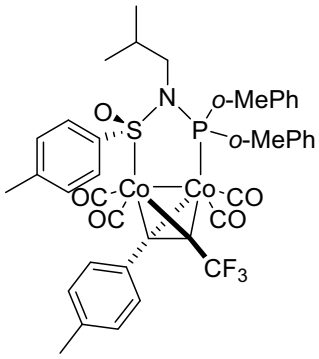

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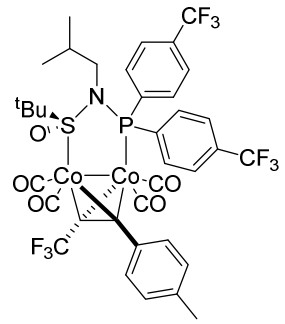

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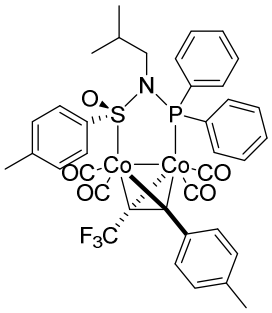

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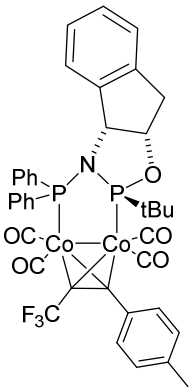

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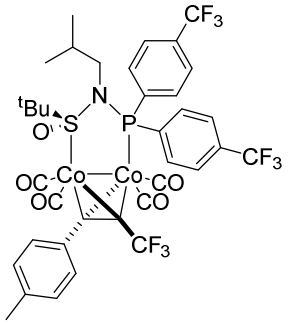

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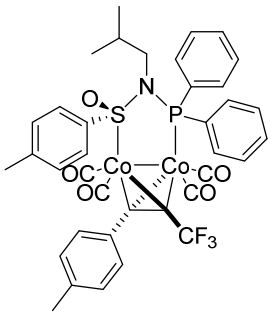

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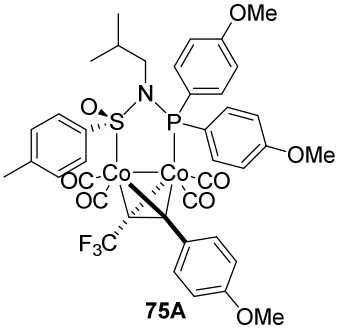

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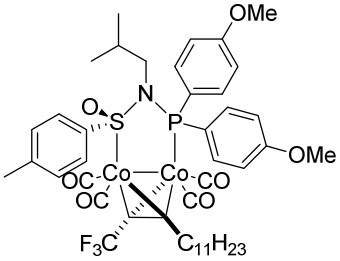

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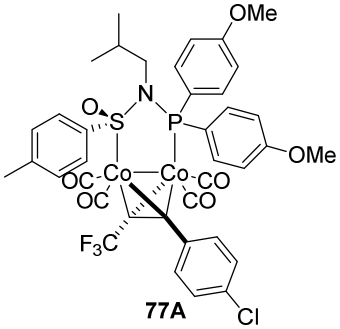

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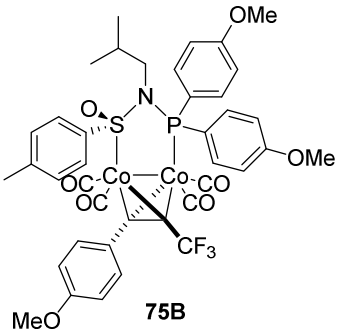

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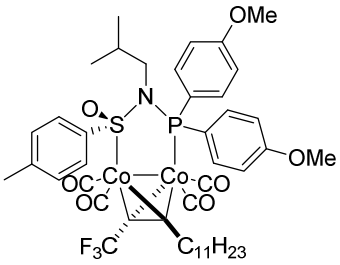

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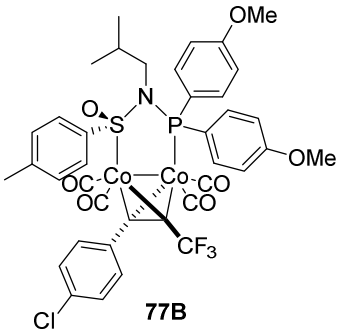

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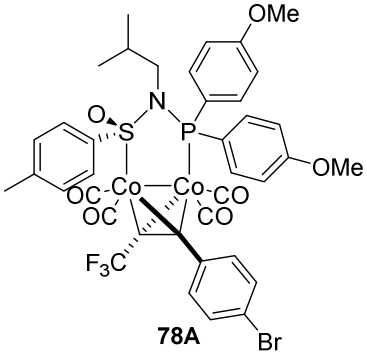

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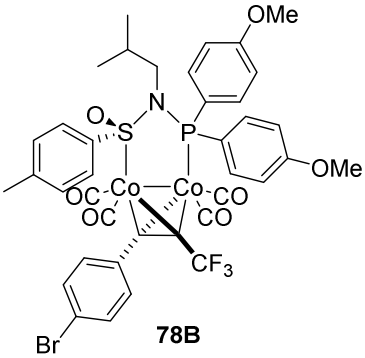

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