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BIS-ALKOXYCARBONYLATION AND DIFUNCTIONALIZATION OF ALKENES EMPLOYING PALLADIUM(II) OR NICKEL(II) COMPLEXES AS CATALYSTS

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Table of Contents

Abstract

This thesis is constituted of two sections.

Section 1 is focused on the bis-alkoxycarbonylation reaction of olefins, catalyzed by aryl α-diimine/Pd(II) complexes, for the synthesis of succinic acid ester derivatives, important compounds in many industrial fields.
The opening chapter (*Chapter 1*) of this thesis presents an overview of the basic chemistry of organopalladium compounds and carbonylation reactions, focusing on oxidative bis-alkoxycarbonylation processes.
In *Chapter 2* the results obtained in the bis-alkoxycarbonylation of 1,2-disubstituted olefins are reported. The reaction proceeds under very mild reaction conditions, using an aryl α-diimine/Pd(II) catalyst and *p*-benzoquinone as oxidant, in the presence of a suitable alcohol. This process proved to be very efficient, selective and diastereospecific and various 2,3-disubstituted succinic esters have been obtained in high yields.
In *Chapter 3* the first bis-alkoxycarbonylation reaction of acrylic esters and acrylic amides, leading to the synthesis of 2-alkoxycarbonyl and 2-carbamoyl succinates respectively, is reported. Remarkably, the utilized aryl α-diimine/Pd(II) catalyst is able to promote the carbonylation of both the β- and the generally non-reactive α- positions of these alkenes. The proposed catalytic cycle is supported by DFT calculations.

Section 2 is mainly focused on the Ni-catalyzed difunctionalization of unactivated alkenes tethered to unstabilized ketones. This reaction allows for a wide range of pharmaceutically useful cyclic architectures to be obtained.
Chapter 4 consists of an introduction to the difunctionalization reactions of unactivated olefins. In particular, intramolecular reactions will be discussed in detail.
In *Chapter 5* the results obtained from the Ni-catalyzed difunctionalization of unactivated alkenes tethered to unstabilized ketones are reported. The reaction proceeds through the formation of a zinc-enolate compound, followed by a cyclization/cross-coupling reaction, which takes place in the presence of a phosphine/Ni(II) complex and an (hetero)aryl electrophile, leading to different cyclic and bicyilc architectures.
In *Chapter 6,* preliminary results concerning the anionic cyclization of zinc enolates tethered to unactivated alkenes are presented.

All the references are summarized in the final *Chapter 7* of the thesis.

List of Abbreviations

δ	Chemical shift
$\Delta G^{\ddagger}$	Free Gibbs energy of activation
Ar	Aryl
BINOL	1,1'-Bi-2-naphthol
BMIMOTf	1-Butyl-3-methylimidazolium trifluoromethanesulfonate
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bpy	2,2′-Bipyridine
BQ	*p*-Benzoquinone
Bz	Benzoyl
cod	1,5-Cyclooctadiene
dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DFT	Density Functional Theory
DME/dme	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPE-Phos	Bis[(2-diphenylphosphino)phenyl] ether
dppBz	1,2-Bis(diphenylphosphino)benzene
dppe	1,2-Bis(diphenylphosphino)ethane
dppp	1,3-Bis(diphenylphosphino)propane
dtbpy	4,4'-Di-*tert*-butyl-2,2'-bipyridine
ee	Enantiomeric excess
Et	Ethyl
EWG	Electron-withdrawing group
h	Hour
H_2Q	1,4-Hydroquinone
HetAr	Heteroaryl
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	Hexamethylphosphoramide

HTFA	Trifluoroacetic acid
i-Pr	*iso*-Propyl
LDA	Lithium diisopropylamide
m	*meta*
Me	Methyl
MTBE	Methyl *tert*-butyl ether
NBS	*N*-Bromosuccinimide
n-Bu	*normal*-Butyl
NHC	*N*-Heterocyclic Carbene
NMP	1-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
NPMoV	Molybdovanadophosphate
Nu	Nucleophile
o	*ortho*
OAc	Acetate
OTf	Trifluoromethanesulfonate
OX	Oxidant
p	*para*
PCy_3	Tricyclohexylphosphine
Ph	Phenyl
Piv	Pivaloyl
PMB	*p*-Methoxybenzyl
p-TSA	*p*-Toluenesulfonic acid
$TBABF_4$	Tetrabutylammonium tetrafluoroborate
$TBABPh_4$	Tetrabutylammonium tetraphenylborate
TBABr	Tetrabutylammonium bromide
TBACl	Tetrabutylammonium chloride
$TBAClO_4$	Tetrabutylammonium perchlorate
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
$TBAIO_4$	Tetrabutylammonium periodate
TBANCO	Tetrabutylammonium cyanate
$TBAN_3$	Tetrabutylammonium azide

$TBANO_3$	Tetrabutylammonium nitrate
TBAOTf	Tetrabutylammonium trifluoromethanesulfonate
TBAOTs	Tetrabutylammonium *p*-toluenesulfonate
$TBAPF_6$	Tetrabutylammonium hexafluorophosphate
TBASCN	Tetrabutylammonium thiocyanate
$TBASO_3(CF_2)_3CF_3$	Tetrabutylammonium nonafluorobutanesulfonate
TBS	*t*-Butyldimethylsilyl
t-Bu	*tert*-Butyl
TDAE	Tetrakis(dimethylamino)ethylene
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
terpy	2,2′:6′,2″-Terpyridine
TFA	Trifluoroacetate
THF	Tetrahydrofuran
TMP	2,2,6,6-Tetramethylpiperidine
TMSCl	Trimethylsilyl chloride
TMSCN	Trimethylsilyl cyanide
TsO^-	Tosylate
XRD	X-Ray powder Diffraction

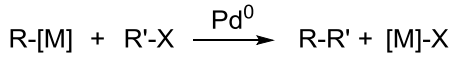
Section 1

Bis-Alkoxycarbonylation of Olefins Catalyzed by Aryl α-Diimine/Palladium (II) Complexes

1. General Introduction

1.1 Formation of New C-C Bonds through Palladium Catalysis

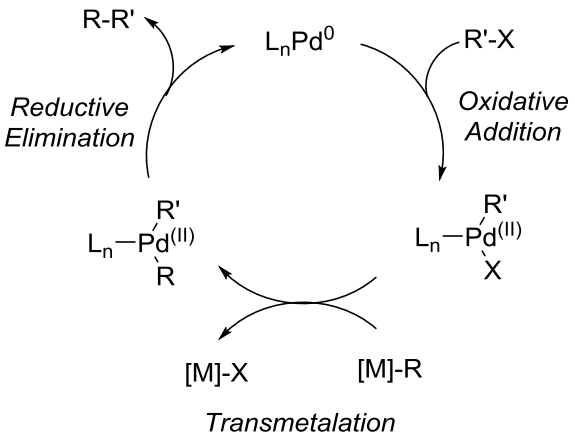
The use of organometallic complexes as catalysts in the modern fine- and bulk-chemicals industry is universally recognized as a powerful tool. As a matter of fact, in the last two decades, several Nobel prizes in chemistry have been awarded for achievements in this area. In 2001 professors W. Knowles, R. Noyori and B. Sharpless shared the prize for their contribution to asymmetric hydrogenation and oxidation catalysis.[1] Four years later, professors Y. Chauvin, R. Grubbs and R. Schrock won the prize too for their researches on the metathesis method in organic synthesis.[2] Then in 2010, professors R. F. Heck, E. Negishi and A. Suzuki were awarded for their studies on "*Palladium-catalyzed cross coupling in organic synthesis*".[3] This last prize clearly justified how palladium catalysis has gained widespread use in industrial and academic synthetic chemistry laboratories as a powerful methodology for the formation of C-C and C-heteroatom bonds. In particular, the formation of new C-C bonds by a coupling reaction of an organometallic compound with an organic halide, usually catalyzed by Pd^0, is synthetically highly valuable, and it has consequently been highly investigated, also because many metals, including main-group ones, are involved in this process (Scheme 1).[4] Grignard's reagents (RMgX), lithium reagents LiR, along with the organometallic compounds of B, Al, Si, Sn, Zn and Cu, are generally used as nucleophiles patterns.



Scheme 1 – Generic scheme of a palladium catalyzed cross-coupling reaction

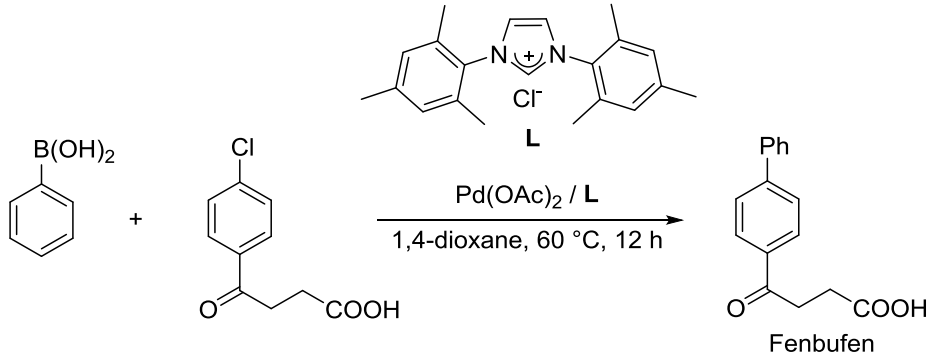
The mechanism involves the following principal steps (Scheme 2):

1. *Oxidative addition* of R'X on Pd^0 to form an alkyl/aryl-Pd^{II} halide;
2. *Transmetalation*: transfer of the carbon ligand R from the metal [M] onto Pd^{II} by means of the substitution of X;
3. *Reductive elimination* of the formal ligands R and R' from Pd^{II} to yield the desired coupled product R-R' and regeneration of Pd^0.



Scheme 2 – Principal steps in Pd-catalyzed cross-coupling reactions

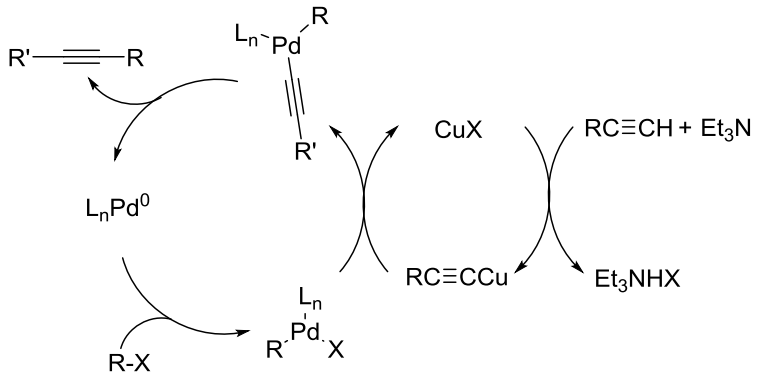
The catalytic species can be formed *in situ* by using a palladium source, such as $Pd_2(dba)_3$ or $Pd(OAc)_2$ together with the necessary ligand (L_n, Scheme 2). Alternatively, it can be introduced as a preformed catalyst such as the commercially available $Pd(PPh_3)_4$. The use of strong σ-donating ligands increases electron density around the metal, accelerating the oxidative addition of the substrate to the catalyst.[5] On the other hand, the elimination step is accelerated by the use of bulky ligands, such as phosphine ligands which exhibit a large cone angle (also known as the Tolman angle).[6] A careful choice of the ligand is essential in order to facilitate the rate determining step of the catalytic cycle. Probably the most famous and synthetically useful reactions involving the catalytic cycle reported in Scheme 2, are the so-called Negishi,[7] Stille[8] and Suzuki[9] coupling reactions. In Negishi cross-coupling, organozinc reagents, such as ZnR_2 or RZnX, are used and these are probably the best coupling agents, since their applications in synthesis are quite general, and a variety of functional groups is well tolerated.[10] In Stille and Suzuki cross-coupling, tin and boron organocompounds have been used, respectively. In particular, the Suzuki coupling has gained a lot of interest in the last few years, especially in the synthesis of natural products or drugs (Scheme 3)[11], since organoboron reagents are commercially available or easily synthesized.[12]



Scheme 3 – Synthesis of anti-inflamatory Fenbufen by Suzuki cross-coupling

Other cross-coupling reactions, such as the Corriu-Kumada[13] and the Hiyama[14] reactions, in which Grignard reagents or trimethoxysilanes compounds are used respectively, follow the same catalytic process which is described in Scheme 2. In all the reactions mentioned above, the electrophile is usually a vinyl or an aryl halide and the reactivity follows the general order I > Br > Cl. Triflates could be also employed.

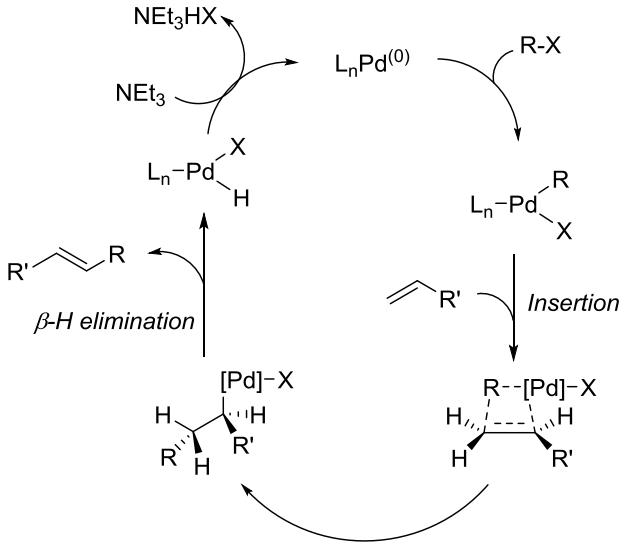
Another synthetically powerful reaction is the Sonogashira cross-coupling,[15] which occurs between terminal alkynes and vinyl/aryl halides, using organocuprates as nucleophiles. In this case, the copper (or sometimes the Pd itself),[16] plays a catalytic role and therefore there is no need to isolate any organometallic reagents. The catalytic cycle, which again involves the previously described steps, requires the presence of a base, in order to deprotonate the terminal alkyne (Scheme 4).



Scheme 4 – General mechanism for the Sonogashira cross-coupling using Cu as co-catalyst

Just like the Sonogashira reaction, the Heck reaction[17] does not requires the isolation of an organometallic derivative, which is clearly an enormous advantage. This reaction allows for the coupling of vinyl, aryl or benzyl halides with olefins, under palladium

catalysis. The Heck reaction is quite different with respect to the previously mentioned methods, because it involves the ***insertion*** of an olefin after the oxidative addition step. Moreover it ends up with a ***β-hydride elimination*** instead of the reductive elimination (Scheme 5). A base prevents the formation of the acid after the elimination step, regenerating the $Pd^{(0)}$ species.

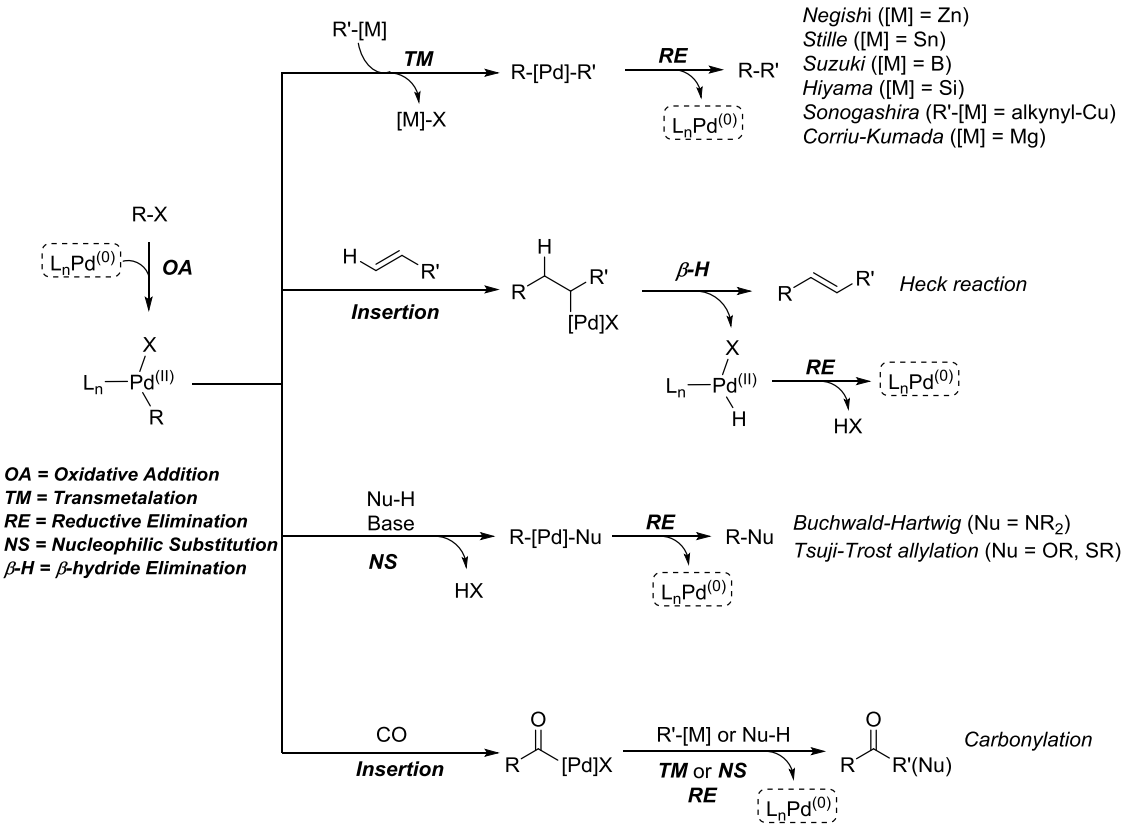


Scheme 5 – Heck reaction, general scheme. R' = EWG.

The R group should not contain any flexible β C-H bond, so the Pd-alkyl intermediate resulting from the oxidative addition is prevented from undergoing β-hydride elimination before the insertion step. Moreover, the nature of the group R' can influence the regioselectivity on the olefin. Electron-withdrawing groups lead to the regioselectivity reported in Scheme 5, while electron-donating groups reverse the regioselectivity, which could also be influenced by the nature of the halogen (X) or the ligands.[18]

The Buchwald-Hartwig reaction[19] and the Tsuji-Trost allylation,[20] are both employed for the construction of new C-N and C-O bonds respectively. Here, a *nucleophilic substitution* of the halide on the R-[M]-X species allows for the formation of a R-[M]-Nu intermediate, which then undergoes reductive elimination, achieving the desired R-Nu product.

A brief synthesis of the palladium catalyzed reactions described above is reported in Scheme 6 together with the carbonylation reaction for the formation of new C-CO bonds.



Scheme 6 – Synthesis of the main palladium catalyzed reactions

Among all the methods reported in Scheme 6, the carbonylation reaction is probably the most important for industrial chemistry[21] and will be discussed in detail in the following chapters.

1.2 Carbonylation Reactions

Carbonylation is a general term for a large number of reactions that incorporate carbon monoxide in an organic molecule. Carbon monoxide is a colorless and odourless gas (bp = -191.5 °C). It is a poisonous gas, which enters the organism through the respiratory system. At elevated concentrations, it is highly toxic to organisms because it has about 245 times greater affinity for hemoglobin and myoglobin than oxygen. Moreover, the increase in CO tissue concentration leads to disruption of the mitochondrial function, inhibiting cellular respiration.[22] Prolonged exposure to lower concentrations causes shortness of breath and headache followed, when exposure is severe, by confusion, dizziness and impaired hearing and vision. Hence, when it is required to work with carbon monoxide, an efficient fume cupboard is necessary to keep emissions to an absolute minimum. The limits of flammability in air for CO at 1 atm and 25°C are 12.5 vol% (lower) and 74.2 vol% (upper).[23]

The conventional valence bond description of carbon monoxide involves two resonance forms: the first one is a "carbine-like" structure, in which divalent carbon is linked to oxygen by a double bond, while the second form is a "dinitrogen-like" structure and a triple bond links both atoms, which carry a lone pair. The latter is the most frequently used in organometallic chemistry, and shows a small negative charge on carbon and a small positive charge on oxygen (Figure 1A).

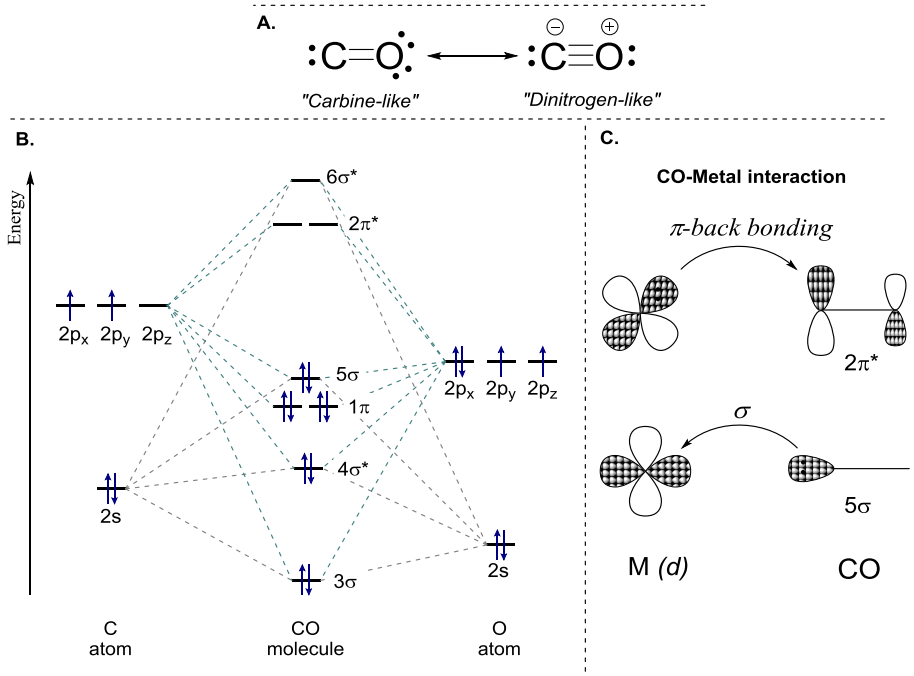


Figure 1 – Carbon monoxide resonance forms (**A**); Molecular orbital diagram for carbon monoxide (**B**); Bonding of CO with transition metals (**C**).

This representation is coherent with the physical properties of CO, such as the short bond length (1.128 Å) or the very high C–O bond dissociation energy (1076 kJ/mol), as reported in Table 1.

Table 1 – Physical properties of carbon monoxide

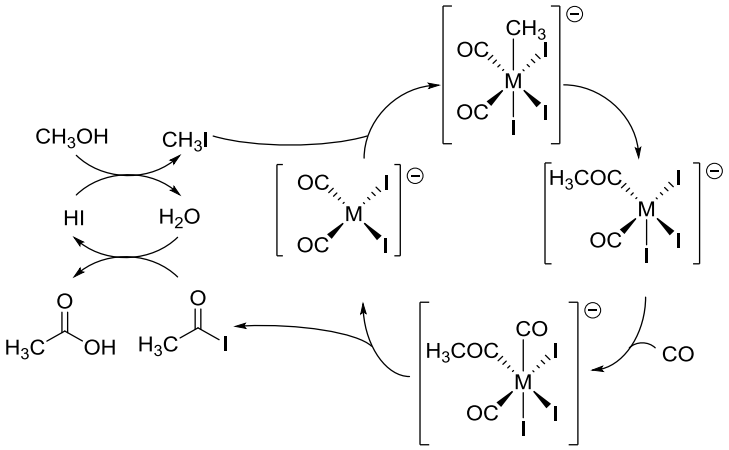
Melting point	68.13 K
Boiling point	81.6 K
Density (gas, 1 bar at 273 K)	1.25 $g \cdot L^{-1}$
Bond length	1.128 Å
Bond energy	1076 $kJ \cdot mol^{-1}$
Dipole moment	1.2 10^{-2}
Ionization potential	1.35 $MJ \cdot mol^{-1}$
Heat capacity	29.1 $J \cdot mol^{-1} \cdot K^{-1}$
Standard Molar Entropy (S^0_{298})	197.7 $J \cdot mol^{-1} \cdot K^{-1}$
Standard Formation Enthalpy (ΔH^0_{298})	-110.5 $kJ \cdot mol^{-1}$

These triple bond characteristic can also be deduced from the molecular orbital (MO) diagram of CO (Figure 1B). Four of the resulting molecular orbitals are occupied, but only one is an anti-bonding MOs, resulting in an exceptionally strong bond. However, the presence of relatively low-lying empty MOs of π* character is important for the reactivity and binding of CO to metals.

A σ-donor interaction can occur by overlapping the highest filled orbital of CO with an empty *d* orbital of the metal center (Figure 1C, bottom). However, back-bonding is among the characteristic features of the different types of metal carbonyl complexes and the stability of this type of compounds. Indeed, a π-acceptor interaction could occur from an occupied metal *d* orbital and the empty LUMO of CO (Figure 1C, top).[24] Therefore, since metal centers with filled *d* orbitals facilitate the back-bonding, carbonyl complexes are preferentially formed with transition metals in low oxidation states. Clearly, electron-donating or electron-withdrawing ligands on the metal center can influence the strength of the [M]-CO bond, modulating the facility of the CO release from the metal coordination sphere.

The first metal carbonyl compound, $Ni(CO)_4$, was synthesized by L. Mond in 1890 by the direct reaction of nickel metal with CO.[25] The decomposition of the pale-yellow

liquid $Ni(CO)_4$ is the basis of the well-known ‘‘Mond process’’ for the purification of metallic nickel. In 1897, L. Gattermann and J. A. Koch developed a process for the formylation of toluene with CO under Friedel-Crafts acylation conditions, using HCl as an acylating agent.[26] In the early 1920s, Fischer and Tropsch discovered that the reaction of CO with hydrogen on Fe/ZnO and Co/Cr_2O_3 gave a mixture of liquid hydrocarbons.[27] Since then the Fischer-Tropsch process has been industrially applied in coal liquefaction and gas-to-liquids technology. The first transition-metal-catalyzed carbonylation reaction was discovered in 1938 by Otto Roelen while he was working on the Fischer-Tropsch reaction.[28] When ethylene was added to a Fischer-Tropsch reactor, propanal was obtained. Roelen suggested that this new process was catalyzed by the homogeneous catalyst $HCo(CO)_4$.[29] This reaction is now well known as hydroformylation (or oxo-synthesis).[30] This process, which introduces a formyl group (-CHO) and a hydrogen atom to the C=C double bond, has been widely applied in industry for the production of aldehydes from alkenes. Another of the most important examples of the industrially applied carbonylations is the synthesis of acetic acid starting from methanol. Initially, a strong acid, such as boron trichloride and phosphoric acid, was used as catalysts, but these reactions suffer from harsh conditions, serious corrosion process and low selectivity. In 1941, Reppe and co-workers found that the carbonylation of methanol could be carried out at 250°C-270°C under 500-700 bar, employing carbonyl complexes of iron, cobalt, and nickel.[31] The cobalt-catalyzed carbonylation of methanol was first commercialized at BASF in 1960. In 1967, Monsanto developed a more efficient Rh-catalyzed process that operated under milder conditions (30-40 bar of CO, at 180°C-220°C) with almost complete selectivity. In the Catavia process (Scheme 7), which was introduced at the end of the 20^{th} century, Ir complexes are employed as catalyst,[32] which, otherwise to be less expensive, also reduces the amount of water in the reaction mixture, decreasing the formation of by-products.

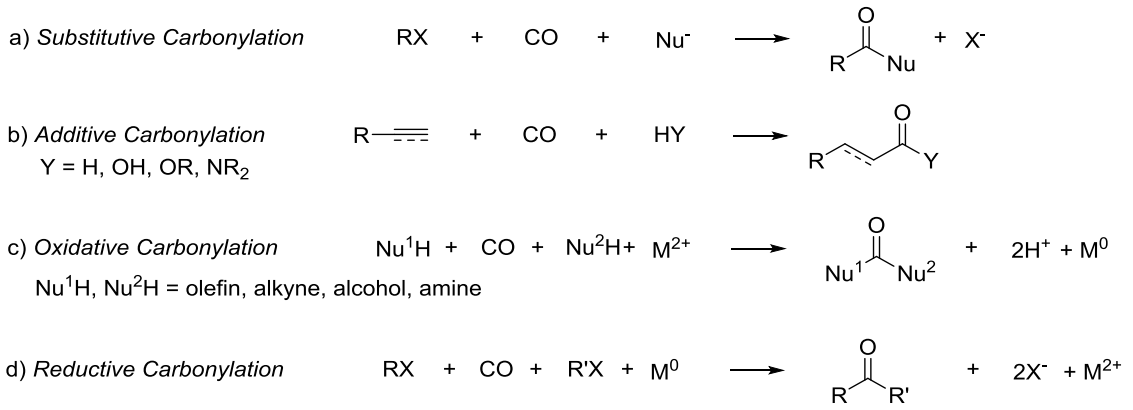


Scheme 7 – General scheme for the Monsanto (M = Rh) and Catavia (M = Ir) processes for the production of acetic acid from methanol.

With the work of Wilkinson, Heck and Tsuji, the carbonylation chemistry dramatically changed.[33] The discovery of stable but extremely active catalysts based on organophosphine complexes of Rh and Pd, in addition to the application of new techniques, such as phase transfer, allowed for many carbonylation reactions to be carried out at low temperature (below 100°C) and at nearly atmospheric pressure. In addition, only very small quantities (less than 1 mol%) of non-volatile and air-stable catalyst precursors, such as $Pd(PPh_3)_2Cl_2$ or $RhCl(CO)(PPh_3)_2$, were necessary for these processes.[33a]

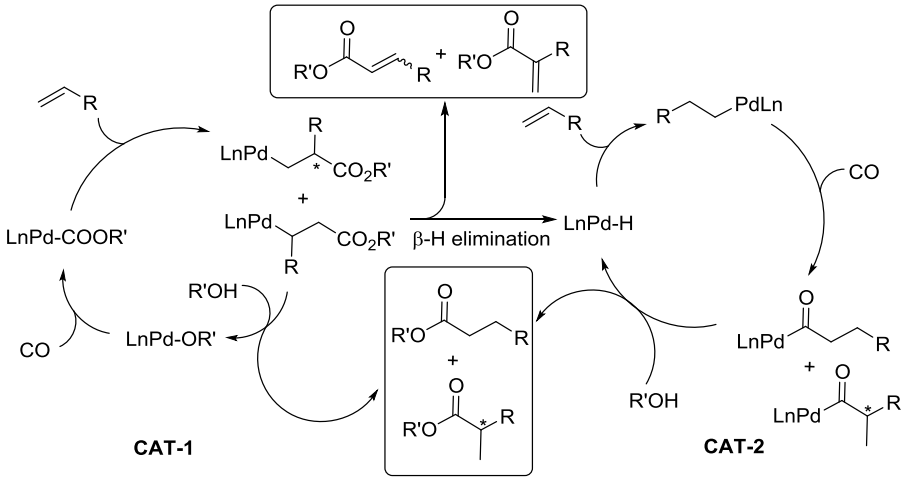
Recently, besides noble metals, such as Pd, Rh and Ir, which remain the most frequently used type of catalyst,[34] first-row transition metals have been proved to have an high catalytic activity in carbonylations.[35] Moreover, it is possible to tune the reactivity and the selectivity of the process by employing an opportune phosphine or nitrogen ligand.[36] Furthermore, carbonylation reactions have gained a new interest since a series of CO-gas-free processes have been developed, employing metal carbonyls, formic acid derivatives or even CO_2 as carbon monoxide surrogates, which avoid all the toxicity problems related to the use of gaseous CO.[37] More recently, some attention has been given to carbonylations reactions which are not catalyzed by transition-metals, such as cationic, anionic or free-radical-mediated carbonylations.[38]

Different kinds of carbonylation reactions can be defined, according to the particular type of process under consideration, as depicted in Scheme 8.[23]



Scheme 8 – Classification of some types of carbonylation reaction.

The most common of these is named *substitutive carbonylation*, in which an halide ion is replaced by a nucleophile, allowing the synthesis of many carboxylic acid derivatives directly from organic halides (Scheme 8a). *Additive carbonylation* occurs, for example, when an hydrogen atom is added to one of the C=C double bond and a formyl group to the other (Scheme 8b). In this synthesis, by replacing H_2 with water, the reaction yields carboxylic acid (hydrocarboxylation). On the other hand, using an alcohol as nucleophile esters can be obtained (mono-alkoxycarbonylation or hydroesterification). The latter reactions have been widely studied[39] and different ester derivatives could be obtained according to the generally accepted mechanism that is reported in Scheme 9.



Scheme 9 - Generally accepted catalytic cycles for the hydroesterification of olefins.

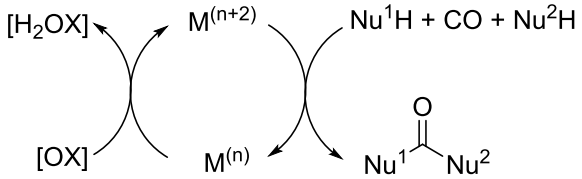
Here, the catalytic cycle can either start from an alkoxycarbonyl-palladium species(CAT-1, Scheme 9) or from a Pd-H complex (CAT-2, Scheme 9).

Carbonylations, in which the transition metal undergoes a reduction during the process are known as *oxidative carbonylations* (Scheme 8c). In this case, in order to achieve a catalytic reaction, it is necessary to use an oxidant to re-oxidize the metal back to the active species. On the other hand, in *reductive carbonylations*, it is necessary to use a reductant in order to regenerate the oxidized catalyst (Scheme 8d).

Since my PhD studies have focused mainly on oxidative carbonylation reactions, these will be next described in detail.

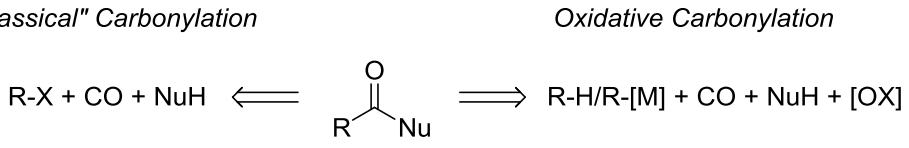
1.3 Oxidative Carbonylation Catalyzed by Palladium

Metal-catalyzed oxidative carbonylation reactions lead to carbonylated derivates *via* the coupling of two nucleophiles with the assistance of a suitable oxidant, that allows the oxidation of the metal $M^{(n)}$ to $M^{(n+2)}$, in order to promote a catalytic cycle (Scheme 10).[40]



Scheme 10 – Oxidative carbonylation reaction. [OX] = oxidant; [H_2OX] = reduced form of the oxidant.

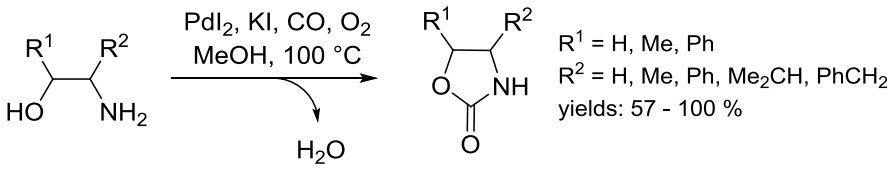
In the last decades, this reaction has acquired great importance with respect to substitutive carbonylation ("classical" carbonylation), due to the possibility of using milder reactions conditions (Scheme 11). Indeed, high temperature and high pressure of CO are generally required when organohalides are used, because the oxidative addition of the electrophile to $Pd^{(0)}$ species does not easily occur, due to the π-acceptor character of carbon monoxide.[41] In oxidative carbonylation reactions, the carbon monoxide is inserted into two nucleophiles, such as alkenes or alkynes and alcohols, generally catalyzed by Pd(II) complexes. Moreover, the oxidative carbonylation of alkenes, alkynes or arenes (R-H compounds in Scheme 11) would greatly reduce the cost of the carbonylation process, as it does not require an additional synthetic step to prepare R-X compounds.



Scheme 11 – "Classical" carbonylation (left) compared with oxidative carbonylation (right). R-H = alkenes, alkynes, arenes. R-[M] = organometallic compound.

The most common oxidants are usually organic compounds, such as benzoquinone derivatives, inorganic salts, such as copper or silver salts, or directly oxygen. Sometimes, the resulting reduced form could be re-oxidized *in situ* by an additional sacrificial

oxidant of low value. Oxidative carbonylations have been widely used for the synthesis of CO-hetoratoms bonds, such as O-C(O)-O and N-C(O)-N bonds. The first oxidative carbonylation of amines to ureas using palladium catalysis were reported at the end of the 1960s by Tsuji and Iwamoto.[42] Since urea derivatives are probably the most important products for agriculture, being applied in the preparation of fine chemicals, dyes and other materials, different papers were reported concerning the synthesis of this kind of molecules, using oxidative carbonylation.[43] Regarding O-C(O)-O new bonds, it is well known that the palladium-catalyzed oxidative carbonylation of alcohols finds applications in the synthesis of industrially useful carbonates.[44] For example, in Scheme 12 is depicted the catalytic carbonylation of amino alcohols to 2-oxazolidinones, reported by Gabriele and co-workers in 2000, that proceeded in the presence of PdI_2, in conjunction with 200 equiv of KI, under 60 atm of a 1/6/5 mixture of CO/O_2/air.[45]



Scheme 12 - Oxidative carbonylation of 2-amino-alcohols catalyzed by PdI_2.

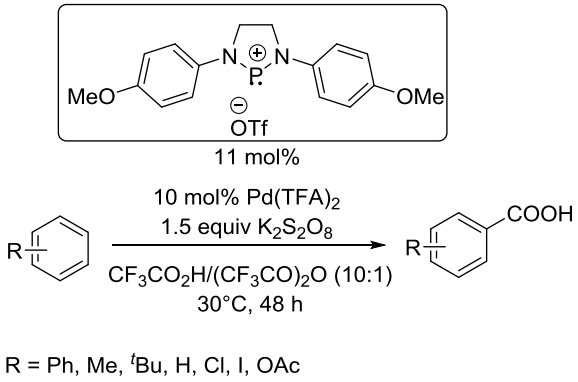
However, the most challenging and probably the most synthetically useful application of this kind of carbonylation is in the formation of new C-CO bonds, as described in the following chapters, based on the nature of the R-H/R-[M] bond of the nucleophile (Scheme 11). Moreover, since palladium has a privileged role in this area of chemistry, only Pd-catalyzed oxidative carbonylations will be discussed.

1.3.1 Oxidative Carbonylation of Arenes

In 1980, Fujiwara and co-workers reported the first palladium-catalyzed oxidative carbonylation of arenes to give benzoic acids.[46] Benzene, toluene, anisole, chlorobenzene, furan and thiophene were all carbonylated under 15 atm of CO pressure using $Pd(OAc)_2$, achieving the corresponding benzoic acids in modest yields (up to 43 %). Later, this reaction was performed using catalytic amounts of palladium salts and $K_2S_2O_8$ as oxidant, achieving nearly quantitative yields and operating under mild reaction conditions.[47] Between the 1980s and 1990s, the Pd-catalyzed carbonylation has been

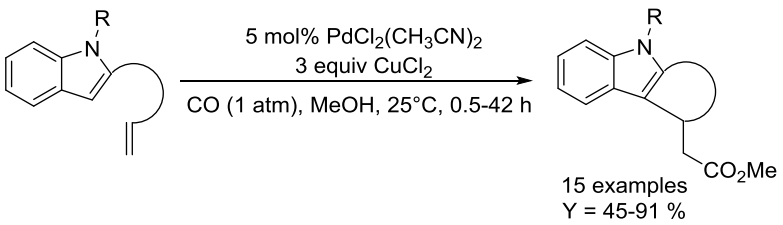
applied to differently substituted arenes and heteroarenes, obtaining a wide range of products.[48,49,50,51]

In 2004, the Nozaki group, employing formic acid as a carbonyl source to avoid the use of CO gas,[52] carried out the palladium-catalyzed oxidative hydroxycarbonylation of arenes and biphenyls in the presence of CF_3COOH as solvent and $K_2S_2O_8$ as oxidant, achieving moderate yields of the respective carboxylic acids.[52a] One year later, this reaction was improved by utilizing strong electron-withdrawing phosphenium salts as ligands[53] (Scheme 13).[52b]



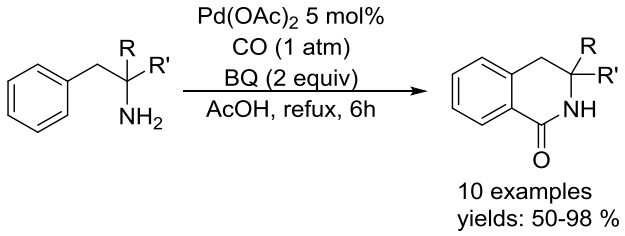
Scheme 13 - Carboxylation of aromatic C–H bond, using phosphenium salts as ligands

Widenhoefer and Liu developed a mild and effective Pd(II)-catalyzed protocol for the cyclization/carboalkoxylation of alkenylindoles, which succeeded in the synthesis of the corresponding tetrahydrocarbazoles,[54] useful heterocycles for both pharmaceuticals and agrochemicals, with high regioselectivity and good yields (Scheme 14). The reaction proceeded by using $CuCl_2$ as an oxidant under 1 bar of CO at room temperature. These transformations represent the first examples of the catalytic addition of a carbon nucleophile and a carbonyl group across the C=C bond of an olefin.



Scheme 14 - Palladium-catalyzed Cyclization/Carboalkoxylation of alkenyl indoles

Interestingly, a procedure for the carbonylation *N*-unprotected arylethylamines has been proposed by Granell's and Garcia's group (Scheme 15).[55] The NH_2-group directed the carbonylation with high selectivity, affording benzolactams. Benzoquinone was used as oxidant.



Scheme 15 - Pd(II)-catalyzed carbonylation of *N*-unprotected arylethylamines

In the last 10 years, other important contributions on the oxidative carbonylations of arenes have also been reported by Orito,[56] Ishii,[57] Yu,[58] Lei,[59] Bell,[60] Shi,[61] Jiang[62] and Wu.[63]

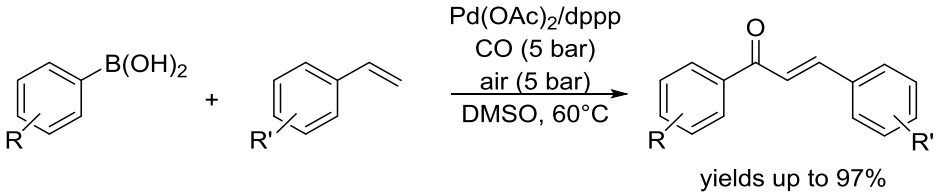
1.3.2 Oxidative Carbonylation of Organometallics

In 1974, Stille and Wong published the first oxidative alkoxycarbonylation of organomercury cyclic compounds.[64] This stereoreoselctive carbonylation occurred at room temperature, but only low yields of the desired carbonylated products were achieved and stoichiometric amounts of $PdCl_2$ were necessary. Subsequently, Larock realized a catalytic version of this process starting from vinylmercurials,[65] utilizing a large excess of $CuCl_2$.

Starting from organosilanes, vinyl esters have been formed in good to excellent yields, employing a stoichiometric amount of $PdCl_2$, under 1 bar of CO at room temperature, as reported by Kumada in 1979.[66]

However the use of organoboron reagents has probably made the Suzuki oxidative carbonylation the most investigated. In 1981, Suzuki et al. reported the first oxidative carbonylation of alkenylboranes. Catalytic amounts of $PdCl_2$ were used in the presence of NaOAc and BQ in methanol, obtaining unsaturated esters in good yields.[67] Later, a stereoselective version of this reaction was also realized.[68] Yamamoto et al. described the oxidative carbonylation of arylboronates in alcohols.[69] In 2010 Lei and co-workers reported the first example of simply applying air as oxidant in the carbonylation of arylboronates.[70] This reaction proceeded at room temperature, using a balloon pressure

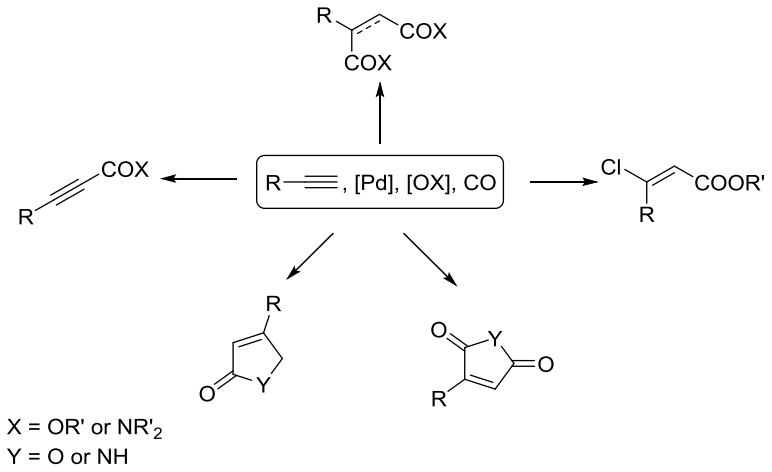
of a CO/air mixture, obtaining esters in good yields. More recently, the Beller group reported an efficient protocol for a palladium-catalyzed oxidative carbonylation of boronic acids and styrenes, using air as oxidant (Scheme 16).[71]



Scheme 16 - Oxidative carbonylative coupling reactions of arylboronic acids

1.3.3 Oxidative Carbonylation of Alkynes

The oxidative carbonylation of alkynes is a tunable reaction that allows for a wide range of products to be obtained (Scheme 17).[34b,39,40,72]

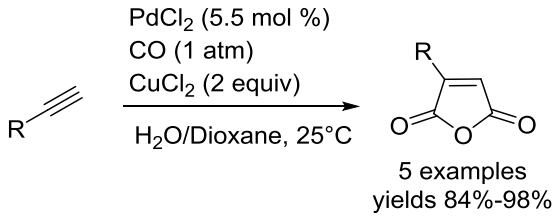


Scheme 17 – Pd-catalyzed oxidative carbonylation of alkynes.

This method does not require pre-functionalization of the substrate, as is necessary when either arenes or organometallics are used.

In 1964 Tsuji and co-workers reported the first Pd-mediated oxidative carbonylation of alkynes, transforming acetylene into a mixture of unsaturated acyl chlorides in the presence of stoichiometric amount of $PdCl_2$.[73] Later, they further developed oxidative carbonylations of terminal alkynes,[74] achieving propiolates in excellent yields, at room temperature and 1 bar of CO, using $CuCl_2$ as oxidant.[75] In 1983, Alper et al. reported the synthesis of *cis*-diesters from terminal alkynes, while using internal alkynes *cis*-monoesters were achieved, under particularly mild conditions.[76] Also in this case, the

catalytic system was constituted by $PdCl_2$ and $CuCl_2$, utilizing O_2 as final oxidant. Ishii and co-workers developed a system for the oxidative carbonylation of terminal alkynes, employing $Pd(OAc)_2$ and chlorohydroquinone, together with NPMoV, in which propiolates or maleic acid esters were synthesized depending on the solvent.[77] A similar process has been described by Jiang using the most common catalytic system that involves $PdCl_2$ and $CuCl_2$, leading to the synthesis of maleic anhydrides (Scheme 18)[78]

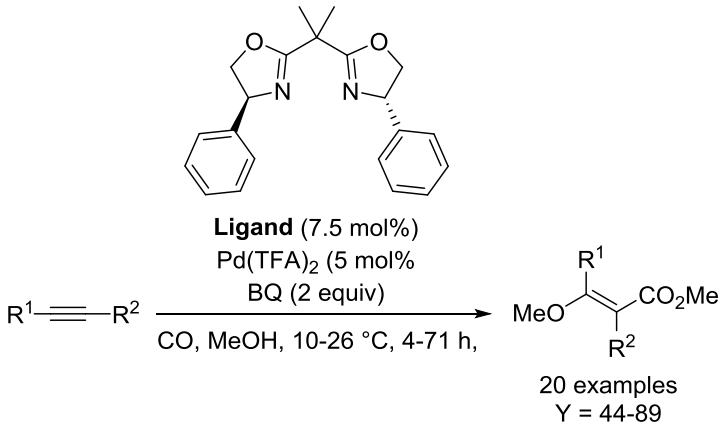


Scheme 18 - Synthesis of maleic anhydrides by palladium-catalyzed dicarbonylation of terminal acetylenes in H_2O/dioxane.

Notably, Yamamoto et al. obtained propiolates from alkynes using directly molecular oxygen as oxidant without additives and employing a palladium/phosphine catalyst.[79]

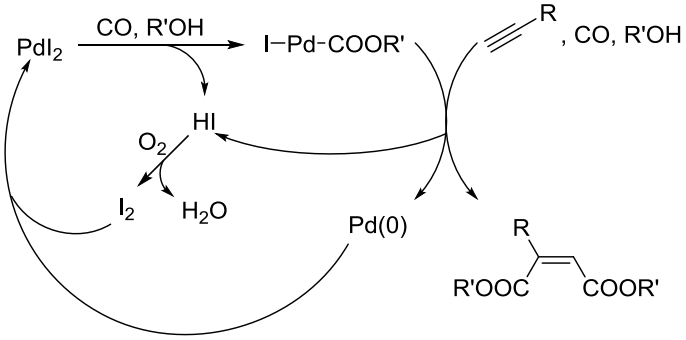
Among alkynes, starting from hydroxyalkynes, many processes for the synthesis of β-lactones[80] and cyclic-β-alkoxyacrylates[81] have been reported. Tamaru at the beginning of the 1990s,[82] carbonylated 3-butyn-1-ols at room temperature achieving γ-butyrolactones, while Yanik reported the synthesis of ketopyranosides.[83]

Interestingly, in 2009, Kato and co-workers applied bis(oxazoline) ligands in the intermolecular Pd-catalyzed methoxycarbonylation of terminal alkynes, obtaining β-methoxyacrylates in good yields. Remarkably, this methodology tolerates a wide range of functional groups (Scheme 19).[84]



Scheme 19 – Synthesis of β-methoxyacrylates

A large contribution to the field of oxidative carbonylations of unsaturated compounds has been made by Gabriele and co-workers,[85] which is mainly focused on the use of alkynes as starting materials.[72,86] In particular at the beginning of the 1990s, they developed a catalytic system utilizing PdI_2 as palladium source together with an excess of KI, which is necessary to form the soluble species PdI_4^{2-}, and with O_2 as oxidant. The Pd(0) species formed during the reaction, was eventually re-oxidized by the I_2 formed *in situ*, as reported in Scheme 20.



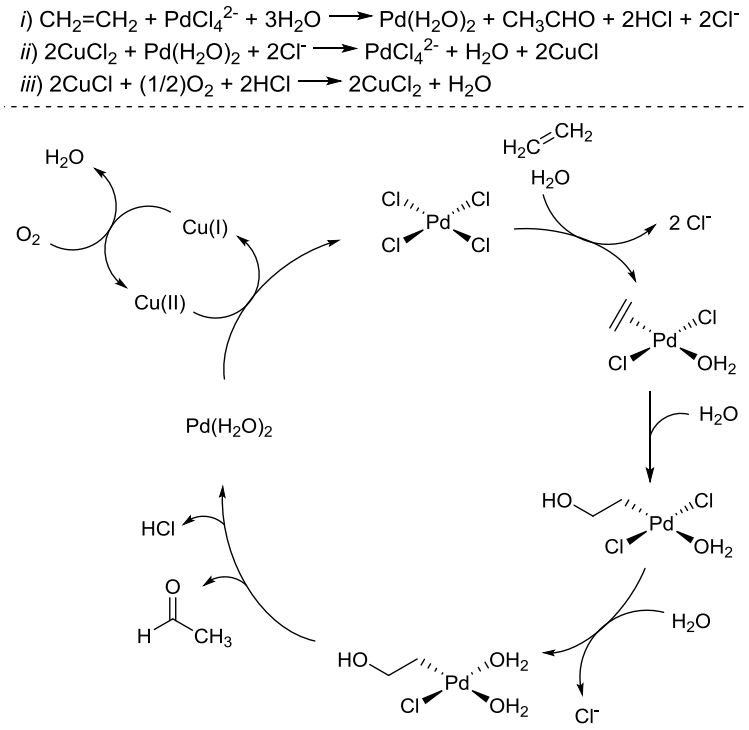
Scheme 20 – Catalytic system developed by Gabriele and co-workers

Remarkably, many applications of oxidative carbonylation of alkynes in total synthesis are also described.[84,87]

1.3.4 Oxidative Carbonylation of Alkenes

Besides all the substrates which have been previously described, alkenes are probably the most employed starting materials in the field of oxidative carbonylation. The Wacker process (Scheme 21), which is the most important synthetic route for the formation of

acetaldehyde from ethylene, was discovered in the late 1950s and it has been considered the prototype for the Pd-catalyzed oxidative carbonylation of olefins, even if carbon monoxide was not used, due to the necessity of utilizing an oxidant to regenerate the catalyst.[88]

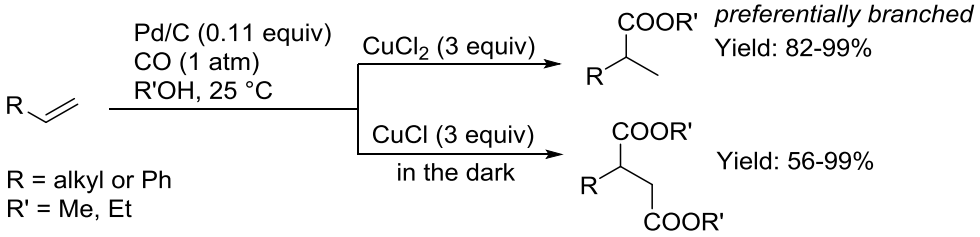


Scheme 21 - Redox reactions involved in the Wacker process (top) and the simplified catalytic cycle (bottom)

Tsuji and co-workers, in 1963, reported the synthesis of β-chloroacyl chlorides starting from olefin-palladium chloride complexes and CO,[89] employing both internal and terminal alkenes in the presence of an alcohol. Almost 15 years later, Cometti and Chiusoli published their results on the synthesis of methyl cinnamate and dimethyl phenylsuccinate from styrene.[90] The reaction was conducted at room temperature under 1 bar of CO, using $PdCl_2$ together with $CuCl_2$ in the presence of methanol. Later, Alper and co-workers reported a methodology for the hydroxycarbonylation of alkenes, which were transformed into branched propionic acids in the presence of H_2O, O_2 and HCl, using $PdCl_2$ as catalyst.[91] The same process was subsequently extended to diols.[92]

Inomata and co-workers reported the palladium-on-carbon catalyzed oxidative carbonylation of terminal olefins.[93] Here they noticed how the use of $CuCl_2$ or CuCl as

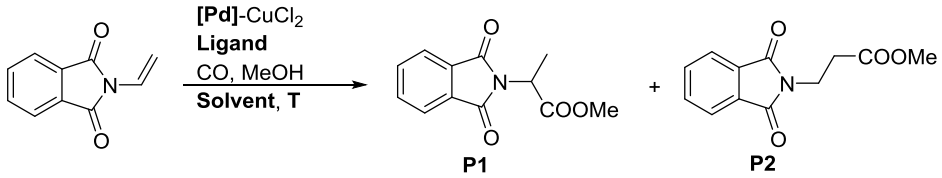
oxidant could influence the selectivity of the reaction, allowing the formation of the mono- and bis-carbonylated product respectively (Scheme 22).



Scheme 22 – Pd/C catalyzed oxidative carbonylation of terminal olefins

In 2001, Bianchini reported the synthesis of the methyl cinnamate through mono-carbonylation of the styrene followed by β-hydride elimination, catalyzed by diphosphine/Pd(II) complexes.[94]

More recently, a palladium-catalyzed alkoxycarbonylation of *N*-vinylphthalimide was realized by Jiang et al. using phosphine ligands.[95] Here, changing some parameters of the reactions, such as the solvent or the promoter, greatly influenced the regioselectivity, achieving the branched or the linear products in good yields (Scheme 23).

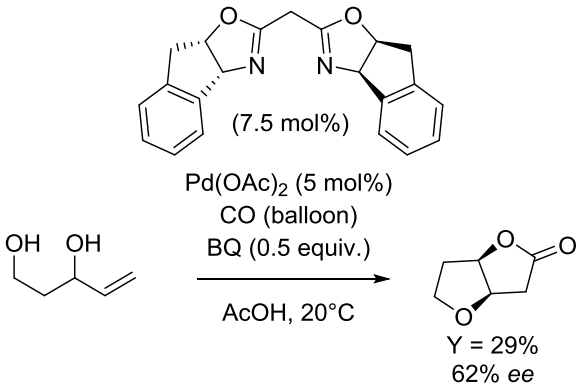


Parameters		*Ratio **P1/P2***	*Parameters*		*Ratio **P1/P2***
[Pd]	$PdBr_2$	44 : 56	Solvent	CH_3CN	100 : 0
	$Pd(dba)_2$	87 :13		DCE	42 : 58
Ligand	PPh_3	74 : 26	Additive	Bu_4NCl	95 : 5
	dppb	38 : 62		Bu_4NI	9 : 91
T	105 °C	54 : 46	Acidic promoters	HCl	74 : 26
	45 °C	100 : 0		*p*-TSA	47 : 53

Scheme 23 – Examples of modulation of the regioselectivity in the alkoxycarbonylation of *N*-vinylphthalimide changing the reaction parameters.

Methyl formate can be used as a "green" CO source. For example, in 1996, Castanet reported the synthesis of unsaturated esters in one step using methyl formate as a source of both CO and MeOH.[96]

Besides simple olefins, alkene bearing alcohol functionality would react in an intramolecular way giving cyclic esters as the main product. As a matter of fact, oxidative carbonylation reaction has been applied to several different hydroxyl-substituted alkenes, in order to obtain synthetically useful substituted furans and pyrans.[97] Moreover, these hydroxyl-substituted alkenes were also used for the synthesis of lactones[98] and heterocyclic compounds more generically.[99] For example, in 2008, the stereocontrolled oxidative carbonylation of diols in acetic acid at room temperature was reported by applying $Pd(OAc)_2$ together with a chiral bis-(oxazoline) ligand and BQ as oxidant, leading to the synthesis of lactones in good yields (Scheme 24).[100]



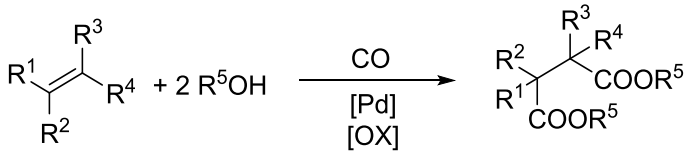
Scheme 24 - Asymmetric Pd(II)-catalyzed oxidative carbonylation of diol (±)-pent-4-ene-1,3-diol

Due to the wide range of products that could be obtained by these means, a large number of oxidative carbonylations of alkenes have been utilized in total syntheses.[101]

In the next chapter the oxidative bis-alkoxycarbonylation of olefins will be described in more detail.

1.4 Palladium-Catalyzed Bis-Alkoxycarbonylation of Olefins

In the bis-alkoxycarbonylation reaction of olefins, a double addition of the carboxylate group occurs to form succinates (Scheme 25), which are very important building blocks in both organic and medicinal chemistry.



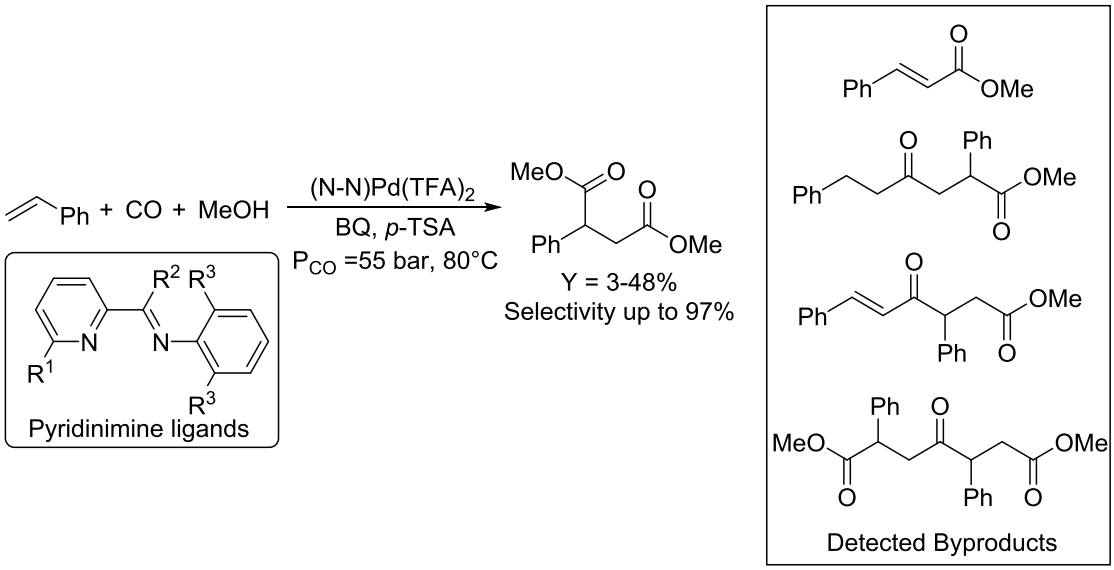
Scheme 25 – General scheme for the oxidative palladium-catalyzed bis-alkoxycarbonylation of olefin.

Succinic acid moiety is ubiquitous in molecules that act as inhibitors of renin[102] and matrix metalloproteinases.[103] Moreover succinic acid derivatives are employed in various industrial fields, such as in cosmetics,[104] agricultural chemistry, and material science, where they are largely used as non-phthalate plasticizers[105] and as monomers for polymers and dendrimers.[106] Recently, Beller reported that succinates can also be synthesized starting from alkynes,[107] although olefins remain the most common substrate.

After the pioneering works of Yukawa[108] and Heck[109], in which stoichiometric amount of palladium was used, the first Pd-catalyzed oxidative carbonylation of olefins leading to succinates was reported in 1972 by Fenton.[110] In this process, high yields of products were achieved applying $PdCl_2$ as catalyst and oxygen, together with a mixture of $FeCl_3$ and $CuCl_2$, as oxidant.[111] Stille later investigated this kind of reaction in order to elucidate the mechanism.[112]

Later, Chauvin reported the use of butyl nitrile as oxidant in the oxidative carbonylation of alkenes, leading to dibutyl succinates with moderate selectivities under 45 bar of CO.[113]

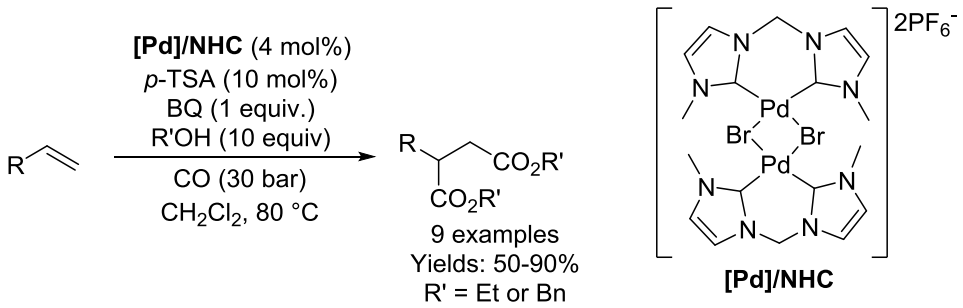
In 2002, Bianchini and co-workers selectively obtained dimethyl phenylsuccinate by an appropriate choice of the pyridinimine ligand.[114] In particular, they carried out a study on the influence of the various parameters (palladium initiator, concentrations of organic oxidant, amount of the protic acid and CO pressure) on the selectivity of the reaction (Scheme 26).



Scheme 26 - Oxidative carbonylation catalyzed by pyridinimine palladium complexes.

Ishii studied the oxidative carbomethoxylation of cyclopentene under CO and air by utilizing a catalytic amount of $Pd(OAc)_2$ and molybdovanadophosphate (NPMoV), and achieving dimethyl *cis*-1,2-cyclopentanedicarboxylate and dimethyl *cis*-1,3-cyclopentanedicarboxylate in good yields.[115]

Recently, the use of *N*-Heterocyclic Carbene (NHC) ligands was investigated by Jang and co-workers for the formation of succinates from olefins through oxidative carbonylation.[116] The reaction proceeded using BQ as an oxidant, under 30 bar of CO at 80 °C (Scheme 27).

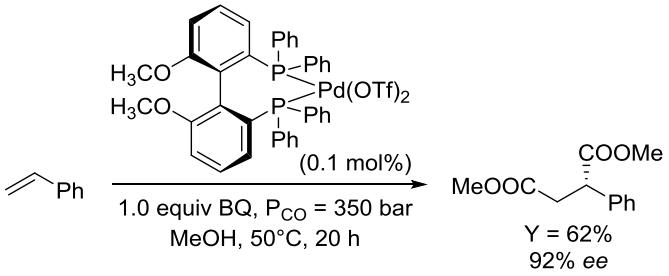


Scheme 27 – NHC ligands employed in the synthesis of succinates from olefins.

Asymmetric versions of Pd-catalyzed bis-alkoxycarbonylation of olefins have also been widely described over the years. In 1998, Saigo and co-workers[117] obtained low enantioselection in the oxidative carbonylation of styrene when chiral biphosphine

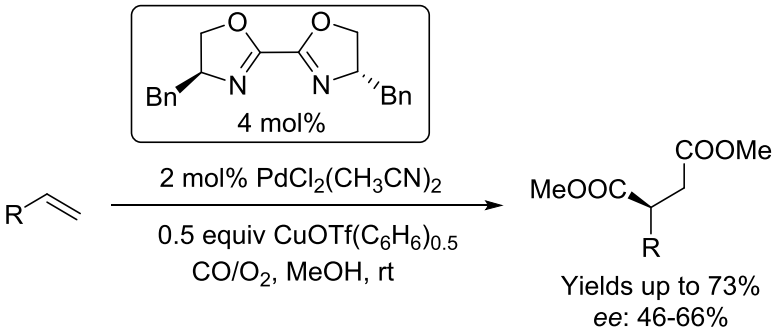
sulfide ligands were tested. Interestingly, no conversion was observed in the presence of phosphine ligands.

Consiglio and co-workers reported the bis-alkoxycarbonylation of alkenes by using chiral diphosphine ligands and BQ to re-oxidize Pd(0) to Pd(II).[118] In particular, when the (*S*)-(6,6'-dimethoxy-[1,1'-biphenyl]-2,2'-diyl)bis(diphenylphosphane) ligand was tested, the styrene was bis-carbonylated in good yield and high selectivity (Scheme 28), while for aliphatic olefins only modest chemo- and enantioselectivity were observed.



Scheme 28 - Enantioselective bis-alkoxycarbonylation of styrene employing diposphine ligands

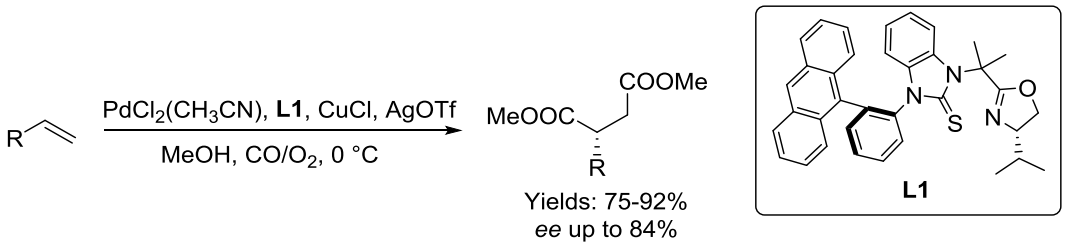
In 2001, using a chiral bisoxazoline ligand, Inomata obtained enantiomerically enriched succinic acid esters derivatives in good yields with a modest *ee*, up to 66% (Scheme 29). [119]



Scheme 29 – Bisoxazoline ligands in the bis-methoxycarbonylation of olefins

Chan and co-workers succeeded in obtaining dimethyl phenylsuccinate in *ee* up to 88% and good chemoselectivity with chiral dipyridylphosphine cationic Pd-complexes.[120]

In 2003, thiourea-based ligands were used by Yang for the synthesis of various phenylsuccinates.[121] Afterwards, he developed an enantioselective version of this reaction, using chiral thiourea-oxazoline ligands, as depicted in Scheme 30.[122] Unfortunately, the synthesis of this class of ligands requires at least nine synthetic steps.



Scheme 30 - Enantioselective bis-alkoxycarbonylation using thiourea-oxazolines as ligand.

Despite all these important contributions, a very general and efficient methodology to synthesize succinic acid esters with both high yields and complete selectivity, under mild reaction conditions, was still lacking.

1.5 Aryl α-Diimine Ligands

The rational design and synthesis of ligands have been a long-standing goal in organometallic chemistry, since the properties of metal coordination complexes are determined as much by the ligands as by the nature of the metal itself. As a consequence, the ligand has a central role in determining the efficiency and selectivity of a catalytic system. In carbonylation reactions phosphine and nitrogen ligands have been widely used and some of them are reported in Figure 2. Generally, the use of phosphine ligands requires higher CO pressure respect to nitrogen ones.

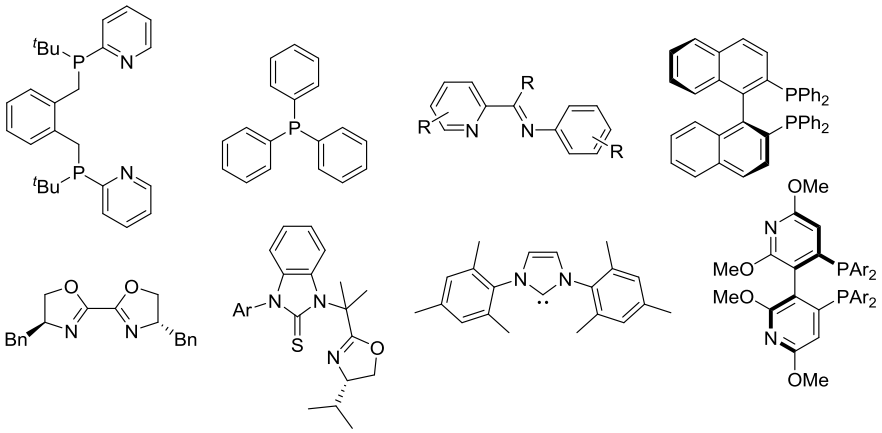
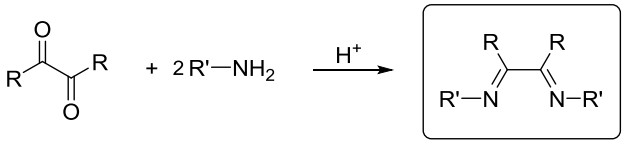


Figure 2 - Examples of ligands utilized in Pd-catalyzed carbonylation reactions

Among the nitrogen ligands, recently, aryl α-diimine ligands have been employed for the first time in carbonylation reactions, by the research group where I worked during my PhD.

Aryl α-diimines find important applications in catalysis,[123] such as in olefin polymerization,[124] because they are very robust and versatile ligands, possessing finely tunable steric and electronic properties.[125] These ligands can be easily synthesized through the condensation of a diketone with two equivalents of an arylamine, generally catalyzed by a Lewis or Brønsted acid (Scheme 31).

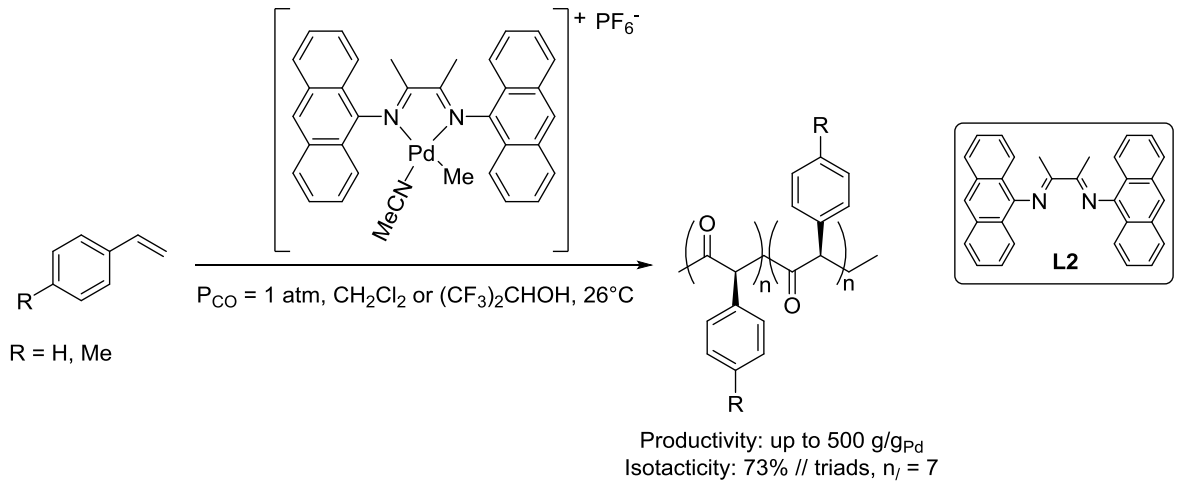


Scheme 31 – General scheme for the synthesis of α-diimine ligands.

The backbone and the aryl substituents are readily variable, allowing the preparation of arrays of ligands.

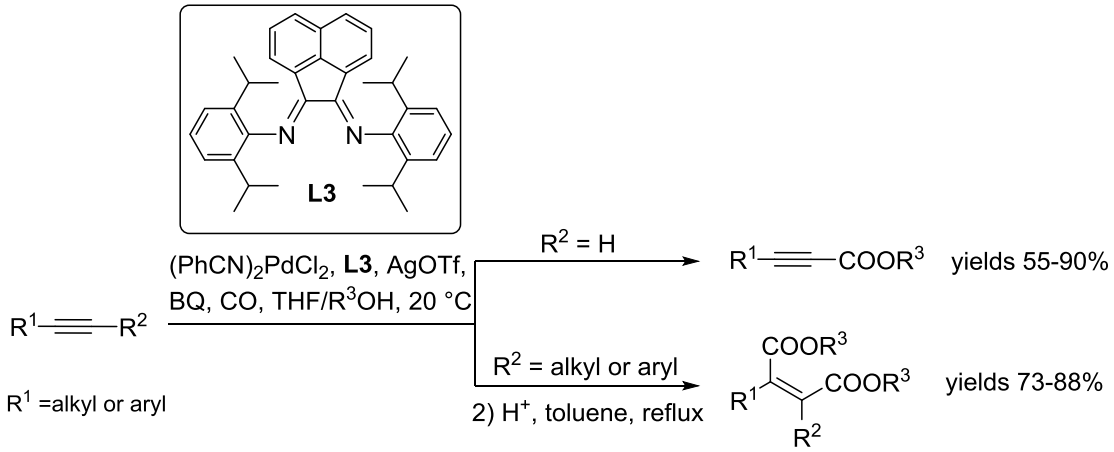
Brookhart and co-worker reported for the first time a family of new cationic Pd(II) and Ni(II) aryl α-diimine catalysts, which represented a real innovation in the development of the classes of polymerization catalysts.[126] Furthermore, catalysts developed by Brookhart, consisting of a late transition metal coupled with a bulky diimine ligand, have shown their efficiency in the polymerization of a variety of polyfunctionalized olefins.[127]

In the field of copolymerization, the research group where I worked during my PhD has conducted deep investigation into the CO/vinylarenes copolymerization promoted by palladium(II)/aryl-α-diimine catalysts, achieving polyketones with a stereoblock isotactic microstructure (Scheme 32).[128]



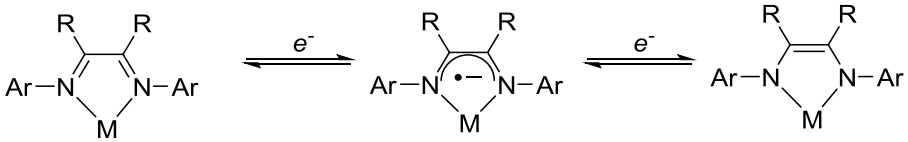
Scheme 32 - Aryl α-diimine/Pd(II) catalyzed stereocontrolled CO/vinyl arene copolymerization

Moreover, they developed an efficient process for the oxidative carbonylation of α-olefins[129] and terminal and internal alkynes[130] (Scheme 33) using bis(9-anthracenyl)butane-2,3-diimine **L2** and bis(2,6-diisopropylphenyl)acenaphthylene-1,2-diimine **L3** respectively, together with palladium(II) salts, under mild reaction conditions. These reactions were carried out in the presence of *p*-benzoquinone, avoiding the use of oxygen as oxidant, which brings up security issues especially for a bench-scale process.[131]



Scheme 33 – Oxidative mono- and bis-alkoxycarbonylation of terminal and internal alkynes

The α-diimine is a very useful ligand and the studies around its role in the organometallic chemistry is not closed but in continuous extension. For example, α-diimine ligands are described as being non-innocent ligands that can be reduced to their radical mono-anionic form as well as the doubly reduced dianion (Scheme 34).



Scheme 34 – Non-innocent properties of aryl α-diimine ligands. M = metal.

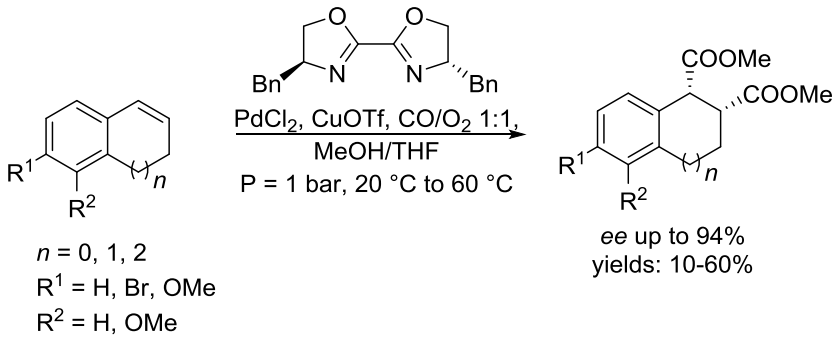
In this form they can effectively stabilize low-valent metals, such as Co(I)-complexes, leading to a rich variety of novel structures.[132] Furthermore, the use of metal complexes bearing aryl α-diimine ligands is not limited to the catalysis, indeed their applications showed promising results also in the context of medicinal chemistry.[133]

2. Bis-Alkoxycarbonylation of 1,2-Disubstituted Olefins

2.1 Introduction

Despite the big efforts recently made in the field of alkoxycarbonylation reactions of disubstituted alkenes,[134] only very few examples regarding the bis-alkoxycarbonylation of internal olefins have been reported so far. In 1975, poor yields of the bis-alkoxycarbonylated products were achieved by Stille and co-workers, using *cis*- or *trans*-butene as substrate, under $PdCl_2$ catalysis.[112a] Later, they developed the bis-alkoxycarbonylation of cyclic olefins,[112b] however only with norbornene an high yield of the 1,2-bis-carbonylated product was obtained, while with cyclopentene, cyclohexene, cycloheptene and cyclooctene, only modest yields of mixtures of *cis*-1,2- and *cis*- 1,3-diester derivatives were attained.

In1998, Saigo et al. reported the bis-alkoxycarbonylation of alkyl-vinylsilanes and of the 1,2-dihydronaphthalene, yielding modest amount of products.[117] In 2007 Inomata and co-workers described the asymmetric bis-alkoxycarbonylation of cyclic olefins (Scheme 35) and of β-methylstyrene, using as catalyst a Pd(II) complex bearing a bioxazoline ligand, together with CuOTf and O_2 as oxidant.[135] The reaction resulted to be highly enantioselective, but only modest yields were achieved.



Scheme 35 – Asymetric bis-alkoxycarbonylation of internal olefins

Later, Becker group developed an highly diastereoselective bis-alkoxycarbonylation process of chiral allylic alcohols with $PdCl_2$ as catalyst, proceeding through a chiral transfer mechanism.[136]

The difficulty in developing bis-alkoxycarbonylation reactions of internal olefins is probably due to their lower reactivity compared to α-olefins.[134] Moreover, side reactions, like the isomerization of the double bond, are often observed when dialkyl substituted olefins are used. Indeed, the alkoxycarbonylation of internal olefins generally

leads to the synthesis of terminal linear esters,[137] and even using unsaturated fatty acid methyl esters, α,ω dicarboxylic acid diesters were obtained,[138] through a Pd-catalyzed isomerizing methoxycarbonylation process.

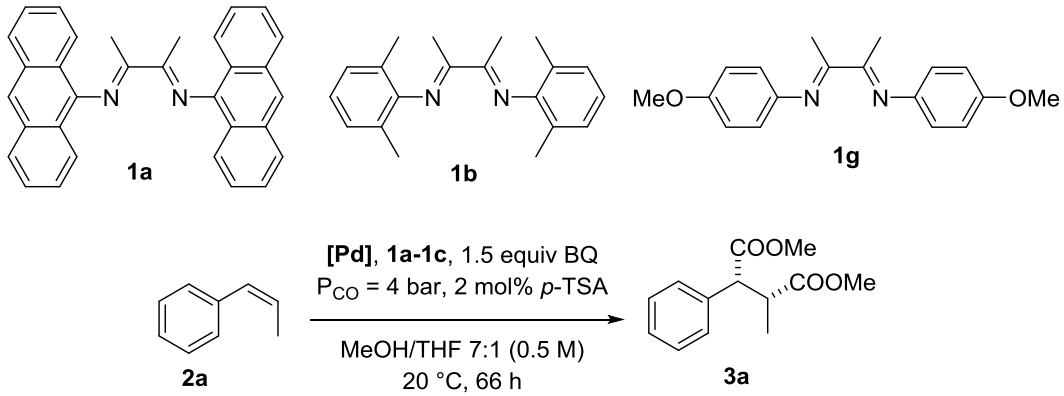
So far, no methods are reported for a selective and efficient bis-alkoxycarbonylation process using disubstituted alkenes and proceeding under mild reaction conditions. Therefore, on the base of the excellent results obtained by Carfagna group in the bis-alkoxycarbonylation of terminal olefins, using aryl α-diimine/Pd(II) catalysts,[129] we decided to investigate the feasibility of the bis-alkoxycarbonylation of 1,2-disubstited olefins.

2.2 Results and Discussion

2.2.1 Scope of the Bis-Alkoxycarbonylation of 1,2-Disubstituted Olefins

Taking into account the conditions previously employed in the bis-alkoxycarbonylation of terminal olefins,[129] a further optimization study on the ligand and palladium source was performed, utilizing *cis*-β-methylstyrene **2a** as olefin benchmark (scheme of Table 2). Employing 0.5 mol% of the *in situ* formed complex $Pd(TFA)_2$/**1a**, *p*-benzoquinone and *p*-TSA, in 7:1 MeOH/THF (0.5 M) as reaction medium, under 4 bar of CO at 20 °C, only 50% of **2a** was converted (Table 2, entry 1). The same result was obtained with ligand **1b** in the same conditions (entry 2), while a detrimental effect on the conversion was noticed when a lower catalyst loading was employed (entries 3 and 4). On the other hand, using ligand **1g** no conversion was observed, confirming the already disclosed necessity of an *ortho*-disubstitution on the diaryl α-diimine ligand in order to achieve high yields (entry 5).[129] Besides ligands, other palladium sources were tested in order to improve the efficiency of the process. However, neither $Pd(OAc)_2$ nor $(PhCN)_2PdCl_2$/2AgOTf were active enough to raise up the conversions (entries 6 and 7), highlighting that ancillary ligands of the catalyst also affect the reactivity of the process (compare entries 2, 6 and 7). Eventually, utilizing $Pd(TFA)_2$, a complete substrate conversion was achieved increasing the catalyst loading to 2 mol% with both ligands **1a** and **1b** (Table 2, entries 8 and 9). Due to the easier synthesis, the ligand **1b** was chosen for the next experiments.

Table 2 - Optimization of bis-methoxycarbonylation reaction of *cis*-β-methylstyrene **2a.**



Entry[a]	[Pd]	Ligand **1**	Conversion (%)[b]
1	$Pd(TFA)_2$ 0.5 mol%	**1a** 0.55 mol%	50
2	$Pd(TFA)_2$ 0.5 mol%	**1b** 0.55 mol%	50

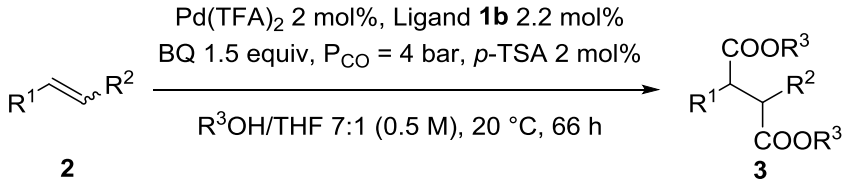
3	$Pd(TFA)_2$ 0.1 mol%	**1b** 0.11 mol%	21
4	$Pd(TFA)_2$ 0.01 mol%	**1b** 0.011 mol%	< 5
5	$Pd(TFA)_2$ 0.5 mol%	**1g** 0.55 mol%	< 5
6	$Pd(OAc)_2$ 0.5 mol%	**1b** 0.55 mol%	25
7[c]	$(PhCN)_2PdCl_2$ 0.5 mol%	**1b** 0.55 mol%	35
8	$Pd(TFA)_2$ 2 mol%	**1a** 2.2 mol%	≥ 98
9	Pd(TFA)2 2 mol%	**1b** 2.2 mol%	≥ 98
10[d]	Pd(TFA)2 2 mol%	**1b** 2.2 mol%	77

[a] Reaction performed in autoclave at P_{CO}=4 bar, with **2a** (2 mmol-scale), palladium salts [Pd] (0.01–2 mol%), ligands **1a, 1b** or **1g** (0.011–2.2 mol%), 2 mol% of *p*-TSA and 1.5 equiv. of BQ, in 7:1 MeOH/THF (0.5 M) as the reaction medium, for 66 h. [b] Determined by direct ^{1}H NMR analysis on a sample of the reaction mixture. [c] Reaction performed by using 1.2 mol% of AgOTf instead of *p*-TSA. [d] Reaction time: 48 h.

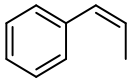
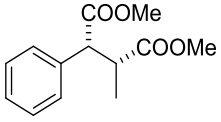
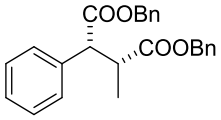
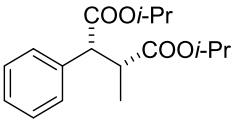
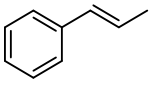
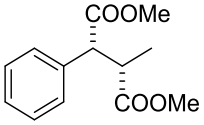
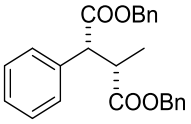
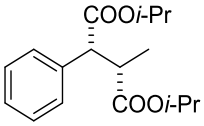
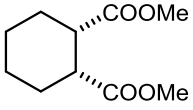
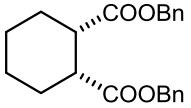
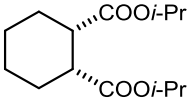
Summarizing, the combination of $Pd(TFA)_2$/**1b** (2 mol% of catalyst loading), with 1.5 equivalents of *p*-benzoquinone as the oxidizing agent and 2 mol% of *p*-TSA (2 mol%) as the acidic additive in a 7:1 MeOH/THF (0.5 M) solution allowed to obtain the selective synthesis of the *syn*-2,3-disubstituted succinic acid methyl ester **3a** with total diastereospecificity, under particularly mild reaction conditions, such as 20 °C and 4 bar of CO.

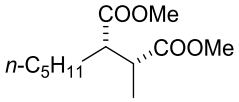
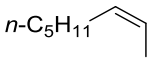
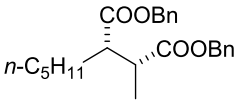
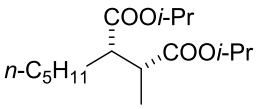
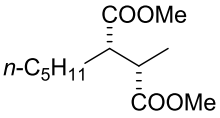
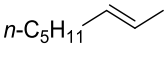
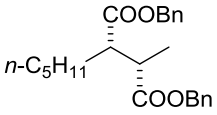
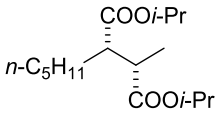
With these optimized reaction conditions in hand, we investigated the scope of the reaction. Several 1,2-disubstituted aromatic, aliphatic and cyclic olefins were successfully tested together with different alcohols (Table 3). Starting from *cis*- and *trans*-β-methylstirene (**2a** and **2b**), the respective 2,3-disubstituted methyl succinates (Table 3, entries 1 and 4) and benzyl succinates (entries 2 and 5) were obtained with excellent isolated yields and a total diastereospecificity. Interestingly, the 1,2-dialkyl substituted olefins **2d** and **2e** (entries 10, 11, 13 and 14) gave similar results to those obtained with the aromatic ones and, at the best of our knowledge, this was the first time that the bis-alkoxycarbonylation reaction was successfully applied to such alkenes. Even with the cyclic olefin **2c**, good results were achieved (Table 3, entries 7 and 8).

Table 3 – Scope of the bis-alkoxycarbonylation of aromatic and aliphatic 1,2-disubstituted olefins **2a-2e**



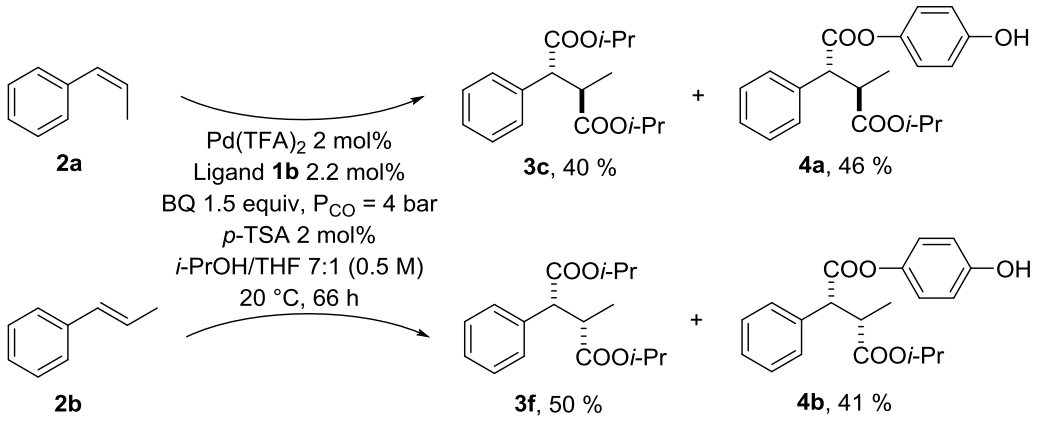
2 **3**

Entry[a]	**2**	R^3OH	**3**	Yield (%)[b]
1	 **2a**	MeOH	 **3a**	87
2		BnOH	 **3b**	92
3		*i*-PrOH	 **3c**	40
4	 **2b**	MeOH	 **3d**	93
5		BnOH	 **3e**	90
6		*i*-PrOH	 **3f**	50
7	 **2c**	MeOH	 **3g**	85
8		BnOH	 **3h**	80
9		*i*-PrOH	 **3i**	43[c] (49)[d]

10		MeOH	 **3j**	92
11	 **2d**	BnOH	 **3k**	89
12		*i*-PrOH	 **3l**	42[c] (43)[d]
13		MeOH	 **3m**	96
14	 **2e**	BnOH	 **3n**	97
15		*i*-PrOH	 **3o**	65[c] (46)[d]

[a] Reactions performed in autoclave at P_{CO} of 4 bar, with olefins **2a-2e** (2 mmol-scale), 2 mol% of $Pd(TFA)_2$, 2.2 mol% of **1b**, 2 mol% of *p*-TSA and 1.5 equiv. of BQ, in 7:1 R^3OH/THF (0.5 M) as the reaction medium, for 66 h. [b] Isolated yields after column chromatography. [c] Conversion of the 1,2-disubstituted olefins. [d] Isolated yield of product relative to the olefin conversion.

In all cases, using the less nucleophilic isopropyl alcohol, less satisfactory results were attained. Indeed, although the aromatic β-methylstyrenes **2a** and **2b** were fully converted, only 40 % and 50 % isolated yields of the corresponding succinic acid diisopropyl esters **3c** and **3f** were achieved (Table 3 entries 3 and 6). Together with **3c** and **3f**, the by-products **4a** (yield: 46%) and **4b** (yield: 41%), deriving from the ability of hydroquinone (generated by reduction of benzoquinone) to act as a nucleophile, were formed (Scheme 36).

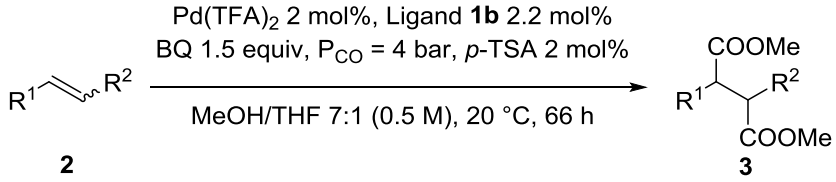


Scheme 36 – Formation of by-products **4a** and **4b**. Isolated yields are reported.

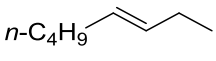
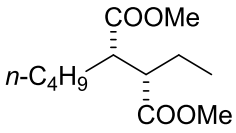
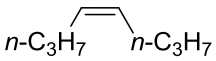
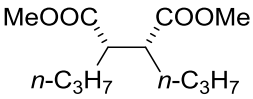
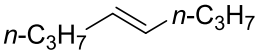
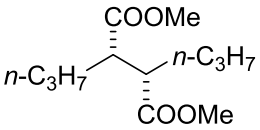
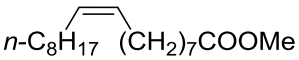
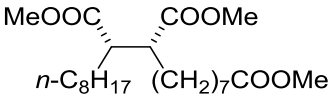
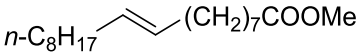
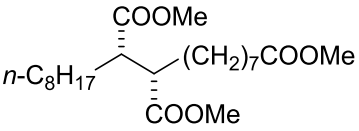
Unfortunately, although the isopropyl esters **3i**, **3l** and **3o**, deriving from aliphatic olefins, were isolated stereospecifically, conversions and yields were much less satisfactory (Table 3, entries 9, 12 and 15).

In order to evaluate the generality of the process, aliphatic alkenes with a double bond remote from the terminal methyl group, such as *trans*-3-octene **2f**, *cis*-4-octene **2g** and *trans*-4-octene **2h**, were also tested. With the *trans* olefins **2f** and **2h**, complete conversions were achieved, obtaining the corresponding carbonylated products **3p** and **3r** in high isolated yields (Table 4, entry 1 and entry 3). When the *cis* olefin **2g** was employed, even if almost all the product **3q** was recovered, only 49% of the olefin was transformed (Table 4, entry 2). The higher reactivity of *trans* olefins respect to *cis* olefins was also confirmed when alkenes containing a more internal double bond, such as unsaturated fatty acid methyl esters (FAMEs), were tested. Indeed, while the methyl *trans*-9-octadecenoate **2j** was fully converted, obtaining the bis-carbonylated product **3t** in 78% isolated yield (Table 4, entry 5), with the methyl oleate **2i** a 50% of conversion was observed (Table 4, entry 4). As expected all the products **3p-3t** were obtained with a total diastereospecificity. Moreover, this was the first time that the bis-alkoxycarbonylation of such internal olefins was reported without observing isomerization of the double bond.[137,138]

Table 4 - Bis-methoxycarbonylation of aliphatic 1,2-disubstituted olefins **2f-2j**



2 **3**

Entry[a]	**2**	**3**	Yield (%)[b]
1	 **2f**	 **3p**	92
2	 **2g**	 **3q**	49[c] (91)[d]
3	 **2h**	 **3r**	76
4[e]	 **2i**	 **3s**	50[c] (92)[d]
5	 **2j**	 **3t**	78

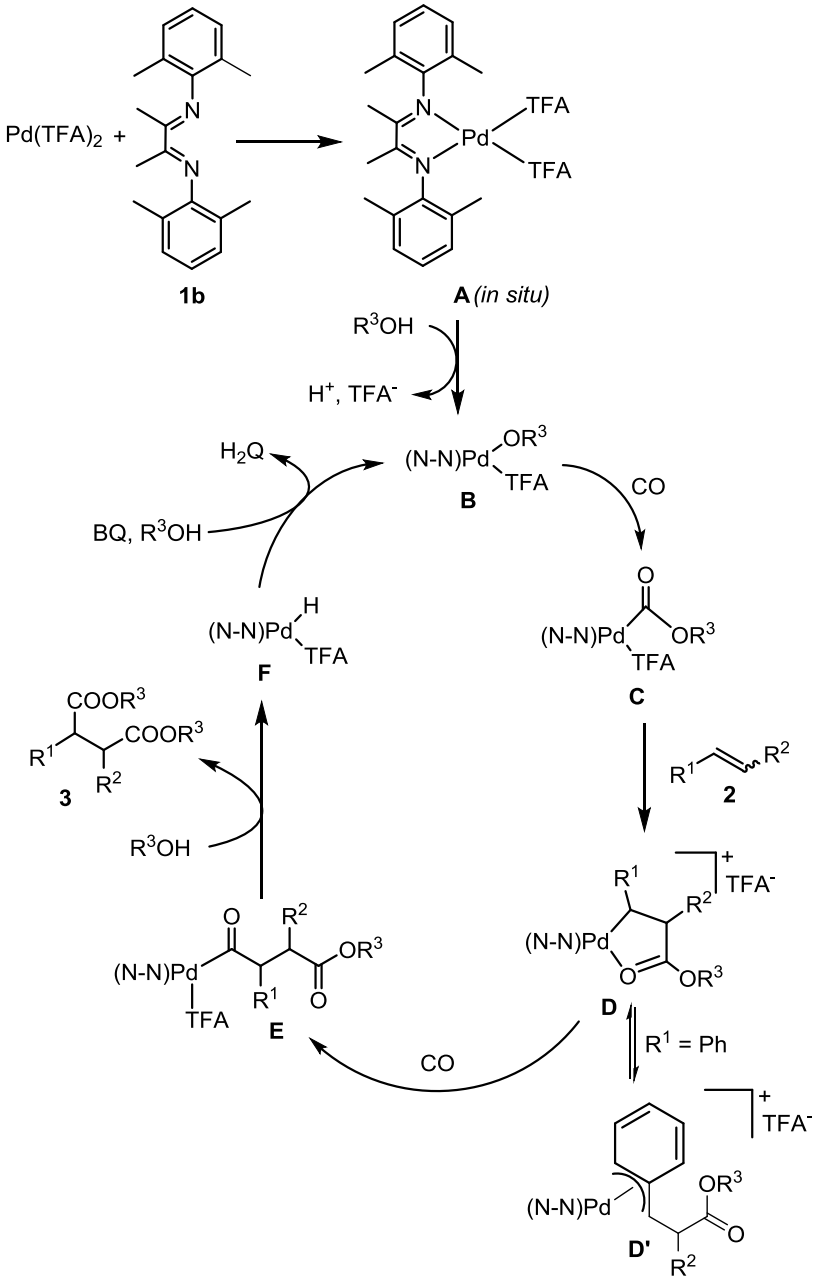
[a] Reactions performed in autoclave at P_{CO} of 4 bar, with olefins **2f-2j** (2 mmol-scale), 2 mol% of $Pd(TFA)_2$, 2.2 mol% of **1b**, 2 mol% of *p*-TSA and 1.5 equiv. of BQ, in 7:1 MeOH/THF (0.5 M) as the reaction medium, for 66 h. [b] Isolated yields after column chromatography. [c] Conversion of the 1,2-disubstituted olefins. [d] Isolated yield of product relative to the olefin conversion. [e] Reaction time 96 h.

2.2.2 Proposed Catalytic Cycle

On the base of the above reported results and literature data,[114,128-130,139,140] the catalytic cycle depicted in Scheme 37, summarizing all the steps involved in the process, is proposed.

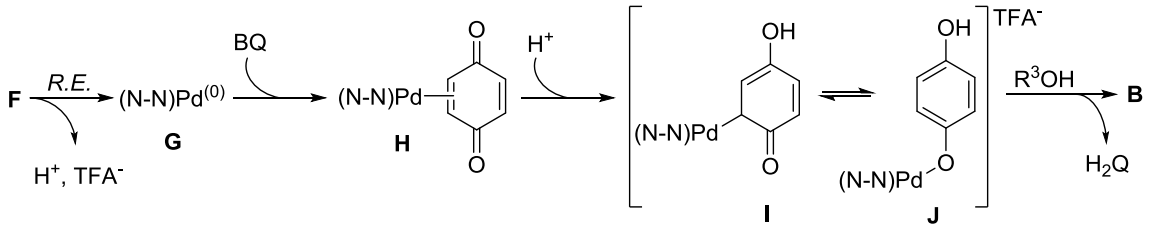
The catalyst **A**, formed *in situ* my mixing $Pd(TFA)_2$ and the ligand **1b** in THF, reacts with the alcohol allowing the formation of the active species **B**.[114,141] The successive insertion of CO leads to the alkoxycarbonyl-palladium complex **C**.[142] The coordination and insertion of the alkene in **C** affords the 5-membered palladacycle **D**. When *cis*- or

trans-β-methylstyrene **2a** or **2b** are employed as substrate, the presence of an η^3-allylic intermediate **D'** in equilibrium with **D** cannot be ruled out.[128c,143] In any case, further CO insertion gives the complex **E**. The nucleophilic attack of the alcohol on the carbonyl linked to Pd in the intermediate **E**, leads to the final product **3** and the palladium hydride complex **F**.



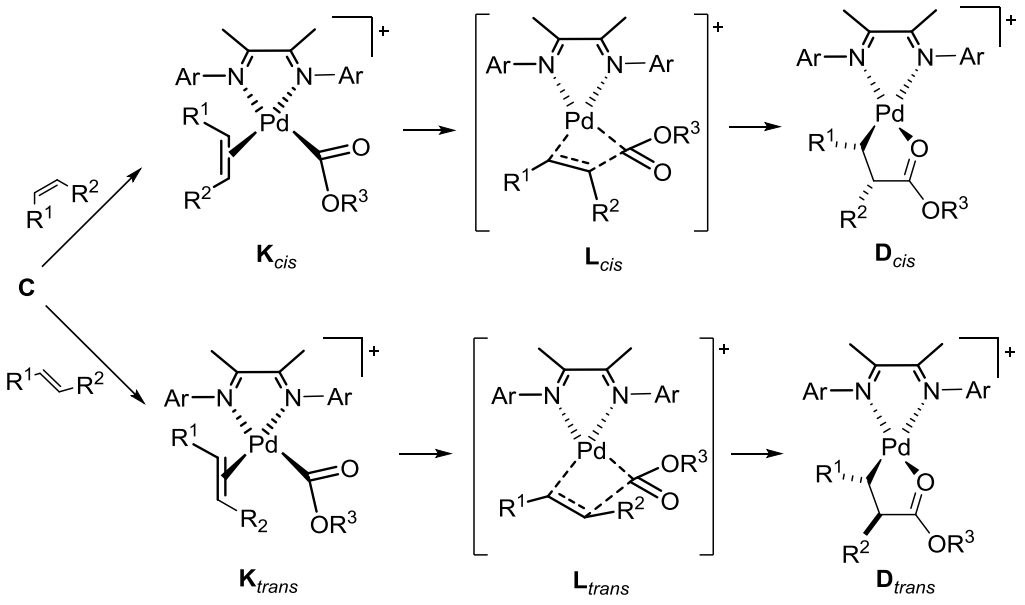
Scheme 37 – Proposed catalytic cycle for the bis-alkoxycarbonylation of 1,2-disubstitited alkenes. BQ = *p*-benzoquinone. H_2Q = 1,4-hydroquinone.

Eventually, benzoquinone regenerates the active species **B**[144] through the formation of an (N-N)Pd(0)-BQ complex,[145] probably with a mechanism similar to that reported by Bäckvall et al. (Scheme 38).[146] Intermediates analogous to **D**,[140] **D'**[139] and **E**[139b] bearing aryl α-diimine ligands have been previously reported in the literature. Since the reaction occurs in the presence of carbon monoxide, an equilibrium between intermediates **C** and **E** with the corresponding Pd-acyl-carbonyl complexes, in which the TFA is substituted by a CO molecule, cannot be excluded.[114]



Scheme 38 – Regeneration of the active specie **B**. *R.E.* = Reductive Elimination.

The conservation of the *trans* or *cis* geometry of internal alkenes, in the palladacycle intermediate **D**, can be explained through a concerted *syn* addition of the Pd-alkoxycarbonyl moiety to the olefinic double bond (Scheme 37).[140a,147] The resulting four-membered transition states $\mathbf{L}_{\boldsymbol{trans}}$ and $\mathbf{L}_{\boldsymbol{cis}}$, depicted in Scheme 39, account for the diastereospecificity of our bis-alkoxycarbonylation reaction.



Scheme 39 – *Syn* addition of the Pd-alkoxycarbonyl fragment to the *cis* and *trans* olefins

2.2.3 Isolation and Characterization of the bis(2,6-dimethylphenyl)butane-2,3-diimine palladium(II)bis(trifluoroacetate) Complex A

We were able to isolate and fully characterize the complex **A** (Figure 3). Unfortunately, **A** resulted to be insoluble in the most common solvents and, considering its degradation in deuterated DMSO, we eventually recorded the NMR spectra in $CDCl_3$, after dissolving the complex in few microliters of HFIP.

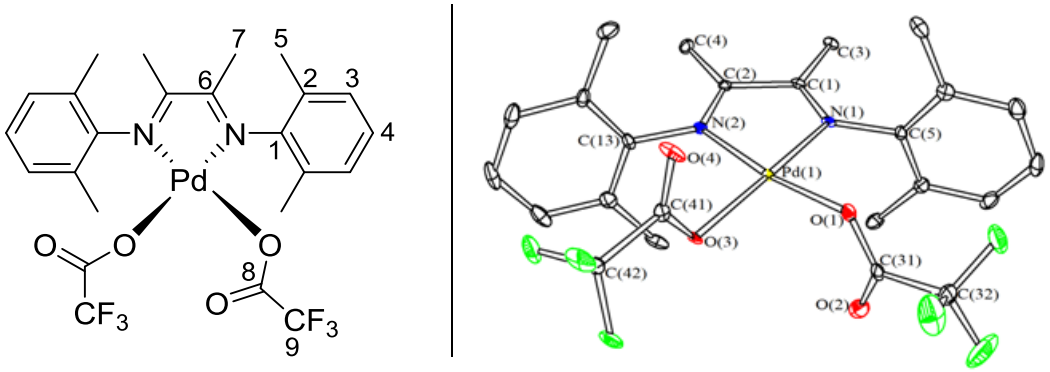


Figure 3 – Complex **A** (left) and molecular structure of complex **A** by XRD analysis (right. Displacement of ellipsoids are at 30% probability level. Hydrogens atoms have been omitted for clarity)

From the ^{1}H NMR spectrum it appears that the signals of the protons *H4*, *H5* and *H7* of the complex **A** (Figure 3, left) are shifted downfield about 0.10 - 0.30 ppm respect to the free ligand **1b**, while the signal of *H3* remains constant (Table 5, entries 1-4).

Table 5 - Differences between the chemical shifts (δ) of the complex **A** and the free ligand **1b** in the ^{1}H-NMR (top) and in the ^{13}C-NMR

Entry	Signals	δ Complex A	δ Ligand 1b	Difference[a]
1	*H3*	7.15 ppm	7.14 ppm	0.01 ppm
2	*H4*	7.29 ppm	7.06 ppm	0.23 ppm
3	*H5*	2.35 ppm	2.06 ppm	0.29 ppm
4	*H7*	2.19 ppm	2.09 ppm	0.10 ppm
5	*C1*	140.6 ppm	146.3 ppm	- 5.7 ppm
6	*C2*	129.4 ppm	126.0 ppm	3.4 ppm
7	*C3*	129.4 ppm	128.8 ppm	0.6 ppm
8	*C4*	130.0 ppm	125.3 ppm	4.7 ppm
9	*C5*	17.5 ppm	17.4 ppm	0.1 ppm
10	*C6*	180.3 ppm	171.2 ppm	9.1 ppm
11	*C7*	18.99 ppm	16.9 ppm	2.1 ppm

[a] The δ differences are calculated subtracting the chemical shifts of the ligand **1b** to the chemical shifts of complex **A**. A positive difference means that in the complex the signals are downfield shifted respect to the ligand.

In a similar way, all the carbon signals in the ^{13}C NMR spectrum are shifted downfield (about 2.1 - 9.1 ppm), with the exception of the aromatic carbon *C1*, directly linked to the nitrogen, that is shifted upfield (Table 5, entries 5-11). The observed behaviour confirmed the formation of the palladium complex and it is in agreement with the electron withdrawing effect of the metal center. Analogous complexes bearing nitrogen ligands, such as bipyridine, phenanthroline or aryl α-diimine, have been previously reported.[148]

Moreover, orange single crystals of **A·HFIP**, suitable for XRD analysis, were obtained by slow evaporation of the solvent, after dissolving the catalyst in a small amount of HFIP and adding $CHCl_3$ (Figure 3, right). Complex **A** displays the expected square-planar geometry, with two coordination sites of the Pd(II) centre occupied by the aryl α-diimine ligand and the other two sites by two trifluoroacetate ligands. The bonding parameters are similar to those previously found in analogous complexes.[148c,149] The angles between the planes of the two aromatic rings and the least-squares plane comprising Pd(1), N(1), N(2), O(1) and O(3) are 87.43(16)° and 83.68(15)°, respectively. The almost perpendicular position of the aryl rings respect to the Pd coordination plane, is probably due to the presence of substituents in the *ortho* positions.[139] We speculated that this conformation would favour the expulsion of products **3**, enhancing the efficiency of the reaction. Unfortunately, further attempts to isolate other intermediates of the catalytic cycle have been unsuccessful, mostly due to the decomposition of the complex to palladium black after the addition of MeOH and CO.

2.2.4 Isolation and Characterization of By-products 4a and 4b

In the bis-alkoxycarbonylation reaction of *cis*- and *trans*-β-methylstyrene, using isopropanol as nucleophile, in addition to the expected bis-carbonylated products **3c** (yield: 40%) and **3f** (yield: 50%), the by-products **4a** (yield: 46%) and **4b** (yield: 41%) were attained, due the ability of hydroquinone to act as a nucleophile (Scheme 36).

The structures of compounds **4a** and **4b** have been identified performing HMBC experiments in addition to ^{1}H and ^{13}C NMR. Interestingly, in both cases, only the product bearing the isopropoxy carbonyl group bounded to the CH bearing the methyl was found. This carbon-bond connectivity was also confirmed by XRD analysis of single crystals of **4b**, obtained upon slow diffusion of *n*-hexane into a dichloromethane solution of the compound (Figure 4).

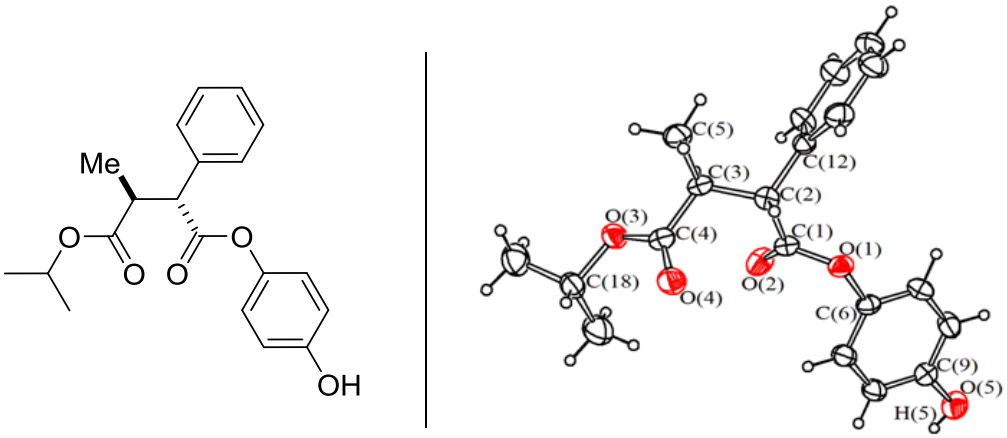
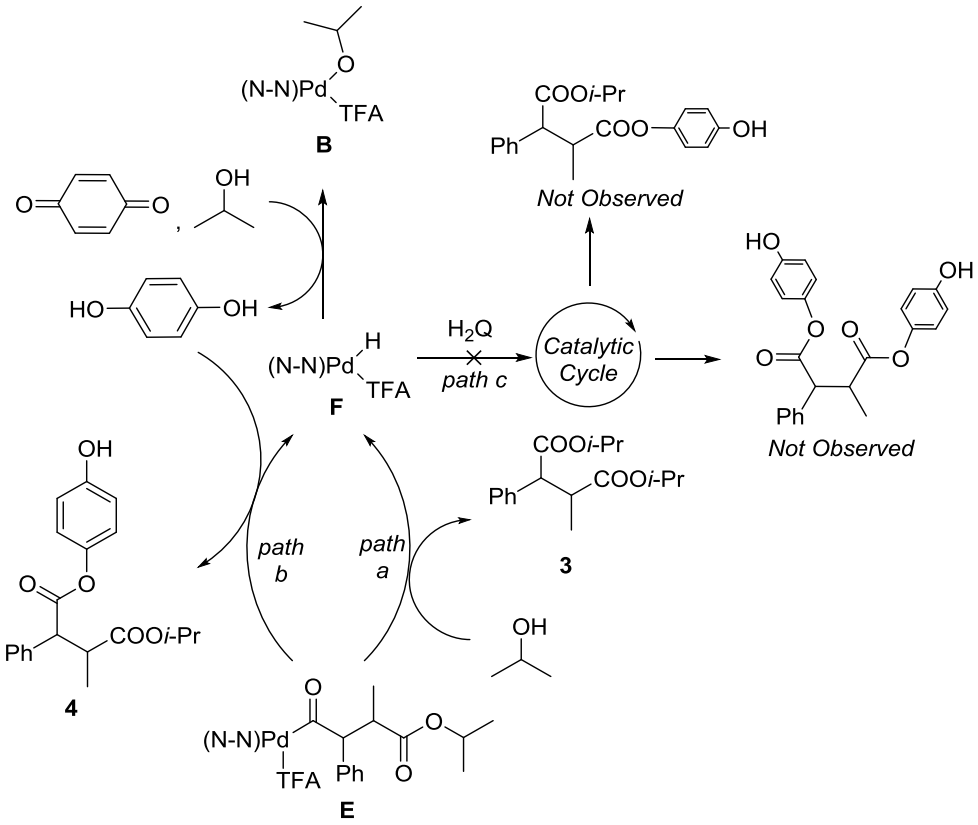


Figure 4 – Compound **4b** (left) and molecular structure of **4b** by XRD analysis (right. Displacement ellipsoids are at the 30% probability level).

The identification of structure of compounds **4a** and **4b** provided further details on the catalytic cycle. We hypothesized that the smaller steric hindrance of hydroquinone compared to isopropanol makes the first one more reactive, but being the *i*-PrOH present in great excess, the succinate esters **3c** and **3f** and the by-products **4** are formed in almost equal quantities. Considering the 2,1 regioselectivity of the insertion of the β-methylstyrenes[140a] into the Pd-alkoxycarbonyl bond of complex **C** (Scheme 37), the formation of both compounds **3** and **4** resulted from a competition between isopropanol and hydroquinone to act as nucleophiles only towards the intermediate **E**. Probably, while in the highly hindered intermediate **E** the competition between the two nucleophiles is present, in the intermediate **F** only the *i*-PrOH, present in greater amounts, reacts regenerating the active species **B** (Scheme 40). As a matter of fact, the other possible by-product, bearing the isopropoxy carbonyl group bounded to the CH linked to the phenyl, has not been detected. We think that this information on the catalytic cycle can be really useful to design the synthesis of succinates bearing two different esteric functionalities, that may have a diverse reactivity in further reactions.



Scheme 40 - Proposed pathways for the formation of the products **3** (*path a*) and **4** (*path b*), using *i*-PrOH as alcohol. The expected products deriving from the *path c* were not observed.

2.3 Conclusion

In conclusion, an efficient method for the bis-alkoxycarbonylation of 1,2-disubstituted olefins to give 2,3-disubstituted-succinic esters has been developed, using $Pd(TFA)_2$ as palladium source, bis-(2,6-dimethylphenyl)-2,3-dimethyl-1,4-diazabutadiene as ligand and *p*-benzoquinone as oxidant. The process turned out to be diastereospecific, due to the *syn* addition of the olefinic double bond to the alkoxycarbonyl palladium intermediate **C**. The high efficiency of our catalytic system has been demonstrated by the high selectivity of the reaction and the nearly quantitative yields obtained with aromatic, cyclic and aliphatic olefins using methanol or benzyl alcohol as nucleophiles, operating under particularly mild reaction conditions (4 bar of CO at 20°C). For the first time the bis-alkoxycarbonylation reaction of 1,2-dialkyl substituted olefins and of unsaturated fatty acid methyl esters has been successfully realized, obtaining the corresponding products stereospecifically, in good to excellent yields.

While with internal olefins bearing a methyl or an ethyl group as substituent on the double bond, excellent yields were generally achieved, using alkenes bearing a more internal double bond, slightly less satisfactory results were obtained and *trans* olefins resulted to be more reactive than the *cis* ones. Interestingly, under our reaction conditions, olefin isomerization was not observed, as often happens in Pd catalyzed processes. In conclusion, our bis-alkoxycarbonylation reaction is very general since it can be applied to a wide range of variously 1,2-disubstituted olefins.

Based on these results and on palladium intermediates previously isolated in model reactions, a catalytic cycle, explaining the complete diastereoselectivity of the process, has been proposed. Moreover, the structure of the complex **A** has been fully identified. The high reactivity of the catalytic system is probably due to the structure of the palladium intermediates having the aryl rings of the ligand **1b** almost perpendicular to the Pd coordination plane, due to the presence of *ortho* substituents. This conformation probably favours the leaving of succinic ester products **3**, enhancing the efficiency of the reaction. Eventually, the use of the bulky isopropyl alcohol as nucleophile allowed us to draw some additional conclusions about the mechanism of the catalytic cycle.

2.4 Experimental Section

2.4.1 General Information

All reactions were carried out under nitrogen atmosphere with dry solvents under anhydrous conditions, in a stainless steel autoclave, by using Schlenk technique. Reactions were monitored by ^{1}H NMR taking a direct sample of the crude mixture. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance 400 spectrometer (^{1}H: 400 MHz, ^{13}C: 101 MHz), using $CDCl_3$ as solvent. Chemical shifts are reported in the δ scale relative to residual $CHCl_3$ (7.26 ppm) for ^{1}H NMR and to the central line of $CDCl_3$ (77.16 ppm) for ^{13}C NMR. ^{13}C NMR was recorded with ^{1}H broadband decoupling. ^{19}F NMR were recorder on a Varian Mercury Plus VX 400 (^{19}F: 376 MHz), using $CDCl_3$ as solvent. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet, dd = double doublets, dq = double quartets, td = triple doublets. Mass spectra were recorded on a LC-MS apparatus Agilent Ion-Trap 6310A 2795, using electrospray (ES+ or ES-) ionisation techniques. Carbon monoxide (Cp grade 99.99%) was supplied by Air Liquide, *p*-benzoquinone was purchased by Sigma-Aldrich and was recrystallized from *n*-heptane/EtOH mixture, olefins **2a**-**2j** were purchased from Sigma-Aldrich, Alfa Aesar or TCI, filtered off a plug of neutral Al_2O_3 and used without further purification. Anhydrous THF was distilled from sodium-benzophenone, methanol was distilled from $Mg(OMe)_2$ and isopropyl alcohol was distilled from CaH_2. $Pd(TFA)_2$ was weighted in an analytical balance without excluding moist and air. All other chemicals were purchased from Sigma-Aldrich and used without further purification. Ligand **1a** was synthesized by our group according to a previously reported procedure.[128c] Ligands **1b** and **1g**, used in the optimization reaction, were synthesized according to previously reported procedure.[150]

2.4.2 Typical Procedure for the Bis-Alkoxycarbonylation of 1,2-Disubstituted Olefins

In a nitrogen flushed Schlenk tube, equipped with a magnetic stirring bar, the respective olefins **2a–j** (2 mmol) and the alcohol R^3OH (3.5 mL) were added in sequence. The mixture was left under stirring for 10 min. In another nitrogen flushed Schlenk tube, equipped with a magnetic stirring bar, the $Pd(TFA)_2$ (13.3 mg, 0.04 mmol) and THF (0.5 mL) were added in sequence. After the mixture turned in a red/brown color (20 min), the ligand **1b** (12.8 mg, 0.044 mmol) was added. The mixture was left under stirring for 10

min, turning in a dark orange color. The olefin solution and the formed catalyst was injected in sequence in a nitrogen flushed autoclave, equipped with a magnetic stirring bar, containing *p*-benzoquinone (325 mg, 3 mmol) and *p*-TSA·H_2O (7.6 mg, 0.04 mmol). After 10 min of stirring, the autoclave was flushed three times with CO and pressurized with 4 bar of carbon monoxide. The reaction was vigorously stirred at 20 °C for 66 h. The autoclave was vented off, flushed with nitrogen and the reaction mixture was directly analyzed by ^{1}H NMR to determine the conversion of the olefins **2**. The crude was then dried under reduced pressure and filtered off a plug of silica gel, washing with CH_2Cl_2/Et_2O 1:1 (150 mL) finally the solution was dried up in vacuum. Then NaOH 1M (30 mL) was added and the solution was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic solution was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The product was eventually obtained after column chromatography on silica gel (Petroleum ether/CH_2Cl_2 50:50 then 20:80; if benzyl alcohol was used as nucleophiles: Petroleum ether/CH_2Cl_2 70:30 then 50:50).

(2R*,3R*)-Dimethyl-2-methyl-3-phenylsuccinate (3a): Following the general procedure, compound **3a** was obtained as a white powder, yield: 87% (0.411 g). Spectral data were identical to the previously reported literature data.[129]

(2R*,3R*)-Dibenzyl 2-methyl-3-phenylsuccinate (3b): Following the general procedure, compound **3b** was obtained as a white powder; yield: 92% (0.715 g).
^{1}H NMR δ 7.47 – 7.27 (m, 13H), 7.14 – 7.07 (m, 2H), 5.22 (d, J = 12.4 Hz, 1H), 5.13 (d, J = 12.4 Hz, 1H), 4.94 (s, 2H), 4.02 (d, J = 11.0 Hz, 1H), 3.46 (dq, J = 11.0, 6.8 Hz, 1H), 1.40 (d, J = 6.8 Hz, 3H). ^{13}C NMR δ 173.8, 171.9, 136.5, 135.61, 135.56, 128.6, 128.5, 128.43, 128.37, 128.2, 128.0, 127.93, 127.91, 127.7, 66.6, 66.2, 54.9, 43.7, 16.4.
ESI-MS: m/z=389 $[M+H]^+$.

(2R*,3R*)-Diisopropyl 2-methyl-3-phenylsuccinate (3c): Following the general procedure, compound **3c** was obtained as a colorless oil; yield: 40% (0.232 g).
^{1}H NMR δ 7.37 – 7.31 (m, 2H), 7.30–7.19 (m, 3H), 4.99 (hept, J = 6.3 Hz, 1H), 4.72 (hept, J = 6.3 Hz, 1H), 3.71 (d, J = 11.2 Hz, 1H), 3.20 (dq, J = 11.2, 6.8 Hz, 1H), 1.28 (d, J = 6.8 Hz, 3H), 1.23 (d, J = 6.3 Hz, 3H), 1.13 (d, J = 6.3 Hz, 3H), 1.01 (d, J = 6.3 Hz, 3H), 0.83 (d, J = 6.2 Hz, 3H). ^{13}C NMR δ 173.9, 171.9, 137.1, 128.6, 128.5, 127.7, 68.5, 67.7, 55.6, 44.0, 21.9, 21.63, 21.59, 21.4, 16.5.

ESI-MS: m/z=293 $[M+H]^+$.

(2S*,3R*)-Dimethyl-2-methyl-3-phenylsuccinate (3d): Following the general procedure, compound **3d** was obtained as a pale yellow oil, yield: 93% (0.439 g). Spectral data were identical to the previously reported literature data.[129]

(2S*,3R*)-Dibenzyl 2-methyl-3-phenylsuccinate (3e): Following the general procedure, compound **3e** was obtained as a colorless oil; yield: 90% (0.699 g).
^{1}H NMR δ 7.43 – 7.26 (m, 13H), 7.20 – 7.14 (m, 2H), 5.17 (d, J = 12.4 Hz, 1H), 5.12 (d, J = 12.4 Hz, 1H), 5.08 (d, J = 12.6 Hz, 1H), 5.03 (d, J = 12.6 Hz, 1H), 3.90 (d, J = 11.4 Hz, 1H), 3.30 (dq, J = 11.4, 7.3 Hz, 1H), 1.02 (d, J = 7.3 Hz, 3H). ^{13}C NMR δ 175.4, 172.9, 136.3, 135.98, 135.89, 129.0, 128.62, 128.59, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 66.60, 66.59, 54.5, 42.5, 15.5.
ESI-MS: m/z=389 $[M+H]^+$.

(2S*,3R*)-Diisopropyl 2-methyl-3-phenylsuccinate (3f): Following the general procedure, compound **3f** was obtained as a colorless oil; yield: 50% (0.292 g).
^{1}H NMR δ 7.35 – 7.24 (m, 5H), 5.03 (hept, J = 6.3 Hz, 1H), 4.94 (hept, J = 6.3 Hz, 1H), 3.69 (d, J = 11.4 Hz, 1H), 3.09 (dq, J = 11.4, 7.3 Hz, 1H), 1.28 (d, J = 6.3 Hz, 3H), 1.24 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.3 Hz, 3H), 1.05 (d, J = 6.2 Hz, 3H), 0.94 (d, J = 7.3 Hz, 3H). ^{13}C NMR δ 175.3, 172.7, 136.9, 128.8, 128.5, 127.6, 68.3, 68.0, 54.7, 42.8, 21.9, 21.80, 21.76, 21.4, 15.6.
ESI-MS: m/z=293 $[M+H]^+$.

(1R*,2S*)-Dimethyl-cyclohexane-1,2-dicarboxylate (3g): Following the general procedure, compound **3g** was obtained as a colorless oil, yield: 85% (0.341 g). Spectral data were identical to the previously reported literature data.[151]

(1R*,2S*)-Dibenzyl cyclohexane-1,2-dicarboxylate (3h): Following the general procedure, compound **3h** was obtained as a colorless oil; yield: 80% (0.564 g).
^{1}H NMR δ 7.40 – 7.28 (m, 10H), 5.08 (d, J = 12.4 Hz, 2H), 5.03 (d, J = 12.4 Hz, 2H), 2.95–2.88 (m, 2H), 2.12–2.01 (m, 2H), 1.86–1.75 (m, 2H), 1.59–1.35 (m, 4H). ^{13}C NMR δ 173.5, 136.1, 128.5, 128.24, 128.17, 66.3, 42.7, 26.3, 23.8.
ESI-MS: m/z=353 $[M+H]^+$.

(1R*,2S*)-Diisopropyl-cyclohexane-1,2-dicarboxylate (3i): Following the general procedure, olefin **2c** were converted for 43%, obtaining compound **3i** as a pale orange oil with 49% of yield (0.108 g) over the converted olefin. Spectral data were identical to the previously reported literature data.[152]

(2R*,3S*)-Dimethyl 2-methyl-3-pentylsuccinate (3j): Following the general procedure, compound **3j** was obtained as a pale yellow oil; yield: 92% (0.423 g).
^{1}H NMR δ 3.68 (s, 3H), 3.67 (s, 3H), 2.73 – 2.62 (m, 2H), 1.70 – 1.54 (m, 1H), 1.43 – 1.31 (m, 1H), 1.31–1.17 (m, 6H), 1.12 (d, J = 6.7 Hz, 3H), 0.85 (t, J = 6.8 Hz, 3H). ^{13}C NMR δ 175.5, 174.8, 51.9, 51.7, 48.7, 42.2, 31.7, 30.8, 27.2, 22.5, 15.3, 14.1.
ESI-MS: m/z=231 $[M+H]^+$.

(2R*,3S*)-Dibenzyl 2-methyl-3-pentylsuccinate (3k): Following the general procedure, compound **3k** was obtained as a colorless oil; yield: 89% (0.681 g).
^{1}H NMR δ 7.39 – 7.28 (m, 10H), 5.14 – 5.05 (m, 4H), 2.81 – 2.69 (m, 2H), 1.69 – 1.55 (m, 1H), 1.41 – 1.30 (m, 1H), 1.26 – 1.15 (m, 6H), 1.13 (d, J = 6.6 Hz, 3H), 0.82 (t, J = 6.8 Hz, 3H). ^{13}C NMR δ 174.6, 174.0, 135.90, 135.88, 128.60, 128.58, 128.5, 128.34 (2C), 128.32, 66.5, 66.4, 48.7, 42.3, 31.5, 30.7, 27.1, 22.4, 15.1, 14.0.
ESI-MS: m/z=383 $[M+H]^+$.

(2R*,3S*)-Diisopropyl 2-methyl-3-pentylsuccinate (3l): Following the general procedure, olefin **2d** were converted for 42%, obtaining compound **3l** as a pale orange oil with 43% of yield (0.103 g) over the converted olefin.
^{1}H NMR δ 5.10 – 4.96 (m, 2H), 2.67 – 2.56 (m, 2H), 1.69 – 1.57 (m, 1H), 1.44 – 1.34 (m, 1H), 1.34 – 1.18 (m, 18H), 1.12 (d, J = 6.5 Hz, 3H), 0.86 (t, J = 6.4 Hz, 3H). ^{13}C NMR δ 174.6, 173.9, 67.9, 67.8, 48.9, 42.6, 31.7, 30.8, 27.1, 22.5, 22.0 (2C), 21.94, 21.88, 15.3, 14.1.
ESI-MS: m/z=287 $[M+H]^+$.

(2S*,3S*)-Dimethyl 2-methyl-3-pentylsuccinate (3m): Following the general procedure, compound **3m** was obtained as a pale yellow oil; yield: 96% (0.442 g).
^{1}H NMR δ 3.66 (s, 3H), 3.65 (s, 3H), 2.78 (dq, J = 7.3, 8.3 Hz, 1H), 2.67 (dt, J = 4.4, 8.6 Hz, 1H), 1.64 – 1.46 (m, 2H), 1.34 – 1.18 (m, 6H), 1.16 (d, J = 7.1 Hz, 3H), 0.86 (t, J =

6.8 Hz, 3H). ^{13}C NMR δ 175.8, 175.4, 51.9, 51.7, 47.5, 40.9, 31.8, 28.7, 26.6, 22.5, 14.3, 14.1.
ESI-MS: m/z=231 $[M+H]^+$.

(2S*,3S*)-Dibenzyl 2-methyl-3-pentylsuccinate (3n): Following the general procedure, compound **3n** was obtained as a colorless oil; yield: 97% (0.742 g).
^{1}H NMR δ 7.40 – 7.27 (m, 10H), 5.13 – 4.99 (m, 4H), 2.89 (dq, *J* = 7.1, 1.1 Hz, 1H), 2.78 (dt, *J* = 4.1, 8.7 Hz, 1H), 1.73 – 1.48 (m, 2H), 1.33 – 1.21 (m, 6H), 1.19 (d, *J* = 7.1 Hz, 3H), 0.85 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR δ 175.1, 174.6, 136.1, 136.0, 128.60, 128.57, 128.4, 128.31, 128.27, 128.25, 66.5, 66.4, 47.5, 40.95, 31.8, 28.7, 26.6, 22.5, 14.3, 14.1.
ESI-MS: m/z=383 $[M+H]^+$.

(2S*,3S*)-Diisopropyl 2-methyl-3-pentylsuccinate (3o): Following the general procedure, olefin **2e** were converted for 65%, obtaining compound **3o** as a pale orange oil with 46% of yield (0.170 g) over the converted olefin.
^{1}H NMR δ 5.07 – 4.92 (m, 2H), 2.72 (dq, *J* = 7.1, 8.3 Hz, 1H), 2.62 (td, *J* = 4.1 8.7 Hz, 1H), 1.64 – 1.46 (m, 2H), 1.38 – 1.17 (m, 18H), 1.14 (d, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR δ 174.9, 174.3, 67.8, 67.7, 47.6, 41.1, 31.8, 28.6, 26.5, 22.5, 21.87, 21.85, 21.82, 21.77, 14.3, 14.1.
ESI-MS: m/z=287 $[M+H]^+$.

(2S*,3S*)-Dimethyl 2-butyl-3-ethylsuccinate (3p): Following the general procedure, compound **3p** was obtained as a colorless oil; yield: 92% (0.424 g).
^{1}H NMR δ 3.64 (s, 3H), 3.63 (s, 3H), 2.70 – 2.57 (m, 2H), 1.75 – 1.50 (m, 4H), 1.35 – 1.09 (m, 4H), 0.84 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR δ 175.4, 175.1, 51.68, 51.67, 48.0, 46.2, 29.1, 28.9, 22.7, 22.2, 13.95, 11.3.
ESI-MS: m/z=231 $[M+H]^+$.

(2R*,3S*)-Dimethyl 2,3-dipropylsuccinate (3q): Following the general procedure, olefin **2g** were converted for 49%, obtaining compound **3q** as a colorless oil with 91% of yield (0.205 g) over the converted olefin.
^{1}H NMR δ 3.69 (s, 6H), 2.70 – 2.59 (m, 2H), 1.67 – 1.51 (m, 2H), 1.37 – 1.17 (m, 6H), 0.87 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR δ 175.1, 51.7, 48.4, 33.2, 20.8, 14.0.
ESI-MS: m/z=231 $[M+H]^+$.

(2S*,3S*)-Dimethyl 2,3-dipropylsuccinate (3r): Following the general procedure, compound **3r** was obtained as a pale yellow oil; yield: 76% (0.350 g).
^{1}H NMR δ 3.65 (s, 6H), 2.72 – 2.63 (m, 2H), 1.63 – 1.48 (m, 4H), 1.36 – 1.16 (m, 4H), 0.89 (t, J = 7.3 Hz, 6H). ^{13}C NMR δ 175.3, 51.7, 46.6, 31.4, 20.3, 14.1.
ESI-MS: m/z=231 $[M+H]^+$.

(8R*,9S*)-Trimethyl heptadecane-1,8,9-tricarboxylate (3s): Following the general procedure, compound **3s** was obtained as a colorless oil after column chromatography on silica gel (Petroleum ether/CH_2Cl_2 30:70 then CH_2Cl_2, in this case the previous extraction with NaOH 1M / CH_2Cl_2 was not carried out due to **3s** water solubility); yield: 92% (0.381g) over a conversion of 50% of methyl oleate **2i**.
^{1}H NMR δ 3.69 (s, 6H), 3.66 (s, 3H), 2.67 – 2.57 (m, 2H), 2.29 (t, J = 7.5 Hz, 2H), 1.65 – 1.52 (m, 4H), 1.38 – 1.13 (m, 22H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR δ 175.0, 174.98, 174.4, 51.7 (2C), 51.5, 48.47, 48.45, 34.1, 31.9, 30.97, 30.91, 29.40, 29.39, 29.24, 29.19, 29.0 (2C), 27.40, 27.35, 24.9, 22.7, 14.2.
ESI-MS: m/z=415 $[M+H]^+$.

(8R*,9R*)-Trimethyl heptadecane-1,8,9-tricarboxylate (3t): Following the general procedure, compound **3t** was obtained as a pale yellow oil after column chromatography on silica gel (Petroleum ether/CH_2Cl_2 30:70 then CH_2Cl_2, in this case the previous extraction with NaOH 1M / CH_2Cl_2 was not carried out due to **3t** water solubility); yield: 78% (0.647 g).
^{1}H NMR δ 3.66 (s, 9H), 2.72 – 2.61 (m, 2H), 2.29 (t, J = 7.5 Hz, 2H), 1.64 – 1.49 (m, 6H), 1.34 – 1.16 (m, 20H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR δ 175.38, 175.36, 174.4, 51.80, 51.79, 51.6, 46.82, 46.80, 34.2, 31.97, 29.7, 29.51, 29.47, 29.35, 29.28, 29.25, 29.17 (2C), 27.04, 27.01, 25.0, 22.8, 14.3.
ESI-MS: m/z=415 $[M+H]^+$.

(2R*,3R*)-1-(4-hydroxyphenyl)-4-methyl-3-methyl-2-phenylsuccinate (4a): Following the general procedure, compound **4a** was obtained as a pale yellow oil after column chromatography on silica gel (CH_2Cl_2 then Et_2O/CH_2Cl_2 5:95, in this case the previous extraction with NaOH 1M / CH_2Cl_2 was not carried out due to **4a** water solubility); yield: 46% (0.315 g).

^{1}H NMR δ 7.44 – 7.39 (m, 2H), 7.36 – 7.26 (m, 3H), 6.85–6.71 (m, 4H), 4.77 (hept, J = 6.3 Hz, 1H), 4.00 (d, J = 10.9 Hz, 1H), 3.30 (dq, J = 6.8, 10.9 Hz, 1H), 1.39 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.2 Hz, 3H). ^{13}C NMR δ 174.2, 171.9, 154.1, 143.6, 136.1, 128.8, 128.6, 128.1, 122.1, 116.1, 68.3, 55.1, 43.9, 21.5, 21.3, 16.4.
ESI-MS: m/z=341 $[M-H]^-$.

(2S*,3R*)-1-(4-hydroxyphenyl)-4-methyl-3-methyl-2-phenylsuccinate (4b): Following the general procedure, compound **4b** was obtained as a white powder after column chromatography on silica gel (CH_2Cl_2 then Et_2O/CH_2Cl_2 5:95, in this case the previous extraction with NaOH 1M / CH_2Cl_2 was not carried out due to **4b** water solubility); yield: 41% (0.281 g).
^{1}H NMR δ 7.44 – 7.29 (m, 5H), 6.82 – 6.69 (m, 4H), 5.06 (hept, J = 6.2 Hz, 1H), 3.96 (d, J = 11.4 Hz, 1H), 3.19 (dq, J = 11.4, 7.3 Hz, 1H), 1.27 (d, J = 6.5 Hz, 3H), 1.25 (d, J = 6.5 Hz, 3H), 1.01 (d, J = 7.3 Hz, 3H). ^{13}C NMR δ 175.3, 172.5, 153.4, 144.4, 136.2, 129.2, 128.7, 128.1, 122.4, 116.0, 68.4, 54.5, 42.9, 21.9, 21.8, 15.6.
ESI-MS: m/z=341 $[M-H]^-$.

2.4.3 Synthesis and Characterization of the (bis(2,6-dimethylphenyl)butane-2,3-diimine)palladium(II)bis(trifluoroacetate) catalyst A

In a nitrogen flushed Schlenk tube, equipped with a magnetic stirring bar, the $Pd(TFA)_2$ (13.3 mg, 0.04 mmol) and THF (0.5 mL) were added in sequence. After the mixture turned in a red/brown color (20 min), the ligand **1b** (11.8 mg, 0.0404 mmol) was added. The mixture was left under stirring for 10 min, turning in a dark orange color. The solvent was removed under vacuum. The complex **A** was obtained as a orange powder; yield: 91% (0.023 g). The NMR spectra are recorded dissolving the catalyst in 50μL of HFIP and then adding $CDCl_3$.
^{1}H NMR δ 7.35 – 7.23 (m, 2H), 7.15 (d, J = 7.6 Hz, 4H), 2.35 (s, 12H), 2.19 (s, 6H). ^{13}C NMR δ 180.3, 163.6 (q, $^{2}J_{CF}$ = 38 Hz), 140.6, 130.0, 129.4 (2C), 114.4 (d, $^{1}J_{CF}$ = 287 Hz), 18.99, 17.5. ^{19}F NMR δ -75.1.

2.4.4 Crystallographic Data for Complex A·HFIP and Compound 4b

Crystal data and collection details for **4b** and complex **A·HFIP** are reported in Table 6. Data were recorded on a Bruker APEX II diffractometer equipped with a PHOTON100 detector using Mo–Kα radiation. Data were corrected for Lorentz polarization and

absorption effects (empirical absorption correction SADABS).[153] The structures were solved by direct methods and refined by full-matrix least-squares based on all data using F^2.[154] Hydrogen atoms were fixed at calculated positions and refined by a riding model. All non-hydrogen atoms were refined with anisotropic displacement parameters.

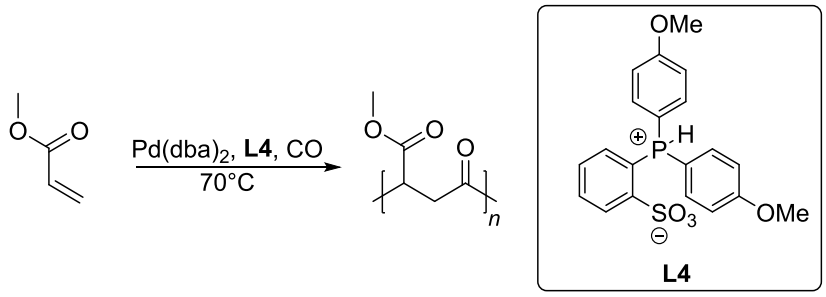
Table 6 - Crystal data and collection details **4b** and complex **A·HFIP**

	4b	**A·HFIP**
Formula	$C_{20}H_{22}O_5$	$C_{27}H_{26}F_{12}N_2O_5Pd$
Fw	342.37	792.90
T, K	294(2)	100(2)
λ, Å	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space Group	*Cc*	$P2_1/n$
a, Å	10.985(2)	8.1262(7)
b, Å	16.983(4)	27.098(2)
c, Å	10.698(4)	14.2695(12)
β, °	112.269(7)	100.185(3)
Cell Volume, Å^3	1846.9(8)	3092.7(5)
Z	4	4
D_c, g cm^{-3}	1.231	1.703
μ, mm^{-1}	0.088	0.712
F(000)	728	1584
Crystal size, mm	0.15×0.13×0.11	0.21×0.16×0.12
θ limits, °	2.335–25.994	1.633–25.049
Index ranges	-13 ≤ h ≤ 13 -20 ≤ k ≤ 20 -13 ≤ l ≤ 13	-9 ≤ h ≤ 9 -32 ≤ k ≤ 32 -16 ≤ l ≤ 16
Reflections collected	10959	31510
Independent reflections	3606 [R_{int} = 0.0922]	5456 [R_{int} = 0.0524]
Completeness to θ max	100.0%	99.8%
Data / restraints / parameters	2606 / 2 / 230	5456 / 30 / 431
Goodness on fit on F^2	0.990	1.388
R_1 (I> 2σ(I))	0.0609	0.0714
wR_2 (all data)	0.1188	0.1537
Largest diff. peak and hole, e Å^{-3}	0.132 / –0.158	1.665 / –3.178

3. Bis-Alkoxycarbonylation of Electron-Deficient Olefins

3.1 Introduction

In the field of carbonylations, the use of electron-poor alkenes has not been extensively investigated and still remains a major challenge.[112d,155] The main problems encountered with this kind of substrates are the low coordination ability of the olefinic double bond[156] and the interaction of the functional group of the electron-deficient olefin with the catalyst, resulting in a deactivation of the catalytic system.[156a,b] Moreover, only the alkoxycarbonylation of the olefinic β-carbon respect to the EWG has been reported in the literature,[157] while the α-position resulted to be not enough nucleophile to allow the insertion of the carbonyl group.[158] Using phosphine-sulfonate/Pd(II) complexes as catalysts, only Nozaki and co-workers demonstrated, in the regiocontrolled copolymerization process of methyl acrylate with CO, that it is possible to carbonylate both the α- and the β- positions of acrylic esters (Scheme 41).[159]



Scheme 41 – CO/methyl acrylate copolymerization

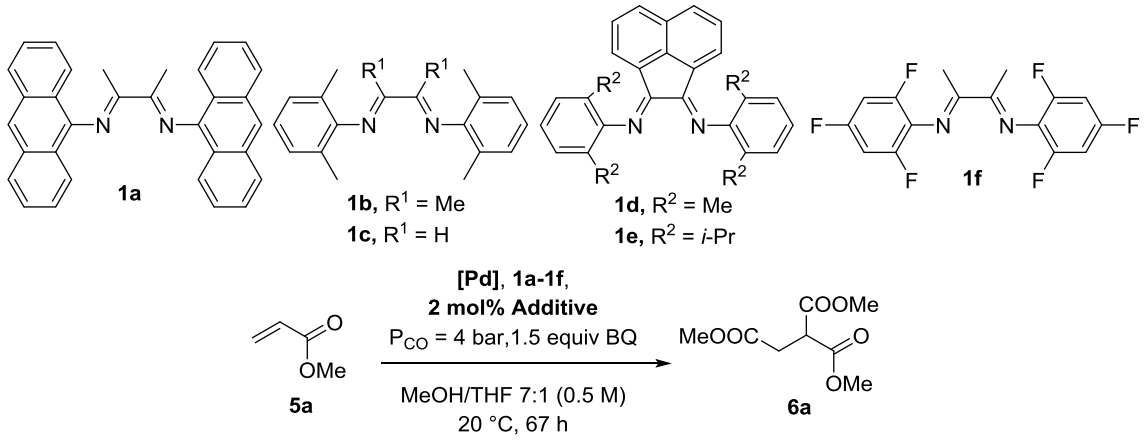
After the excellent results obtained in the bis-alkoxycarbonylation of 1,2-disubstituted olefins catalyzed by aryl α-diimine/Pd(II) complexes (*Chapter 2*), we have evaluated the possibility of employing an analogous catalytic system for effectively realize the first bis-alkoxycarbonylation of electron-deficient olefins. The envisioned bis-alkoxycarbonylation of electron-deficient alkenes should lead to 2-EWG substituted succinates. In particular, starting from acrylic esters or acrylic amides the direct synthesis of 1,1,2-ethanetricarboxylates and 2-carbamoylsuccinates, useful building blocks for medicinal[160] and organic[161] chemistry, should be possible.

3.2 Results and Discussion

3.2.1 Screening of Aryl α-Diimine Ligands and of Reaction Conditions

We started our investigation on the bis-alkoxycarbonylation of electron-deficient olefins using methyl acrylate **5a** as the model substrate (Table 7). Since in *Chapter 2.2* it has been already described the importance of the *ortho*-disubstitution on the aryls of the α-diimine ligand in order to promote an efficient olefin bis-alkoxycarbonylation reaction, we chose to test the ligands **1a-1f**, reported in Table 7, to investigate the effects of the backbone structure and of the nature of the *ortho*-substituents.

Table 7 - Optimization of the bis-methoxycarbonylation reaction of methyl acrylate **5a.**



Entry[a]	[Pd]	Ligands **1a - 1f**	Additive/Reagent	Conversion (%)[b]
1	$Pd(TFA)_2$ 3 mol%	-	*p*-TSA	< 5
2	$Pd(TFA)_2$ 0.5 mol%	**1a** 0.55 mol%	*p*-TSA	13
3	$Pd(TFA)_2$ 0.5 mol%	**1b** 0.55 mol%	*p*-TSA	22
4	$Pd(TFA)_2$ 2.0 mol%	**1a** 2.2 mol%	*p*-TSA	90
5	$Pd(TFA)_2$ 2.0 mol%	**1b** 2.2 mol%	*p*-TSA	90
6	$Pd(TFA)_2$ 2.0 mol%	**1c** 2.2 mol%	*p*-TSA	45
7	$Pd(TFA)_2$ 2.0 mol%	**1d** 2.2 mol%	*p*-TSA	85
8	$Pd(TFA)_2$ 2.0 mol%	**1e** 2.2 mol%	*p*-TSA	37
9	$Pd(TFA)_2$ 2.0 mol%	**1f** 2.2 mol%	*p*-TSA	< 5
10[c]	$PdCl_2(PhCN)_2$	**1b**	AgOTf	60

11	2.0 mol% $Pd(TFA)_2$ 2.0 mol%	2.2 mol% **1b** 2.2 mol%	-	71
12	2.0 mol% $Pd(TFA)_2$ 2.0 mol%	2.2 mol% **1b** 2.2 mol%	HFIP	73
13	2.0 mol% $Pd(TFA)_2$ 2.0 mol%	2.2 mol% **1b** 2.2 mol%	NEt_3	< 5
14[d]	2.0 mol% $Pd(TFA)_2$ 2.0 mol%	2.2 mol% **1b** 2.2 mol%	*p*-TSA	43
15[e]	2.0 mol% $Pd(TFA)_2$ 2.0 mol%	2.2 mol% **1b** 2.2 mol%	*p*-TSA	70
16[f]	2.0 mol% $Pd(TFA)_2$ 2.0 mol%	2.2 mol% **1b** 2.2 mol%	*p*-TSA	96
17[g]	2.0 mol% $Pd(TFA)_2$ 2.0 mol%	2.2 mol% **1b** 2.2 mol%	*p*-TSA	30

[a] Reaction performed in autoclave at P_{CO}=4 bar, with **5a** (2 mmol-scale), palladium salts [Pd] (0.5–3 mol%), ligands **1a–1f** (0.55–2.2 mol%), 2 mol% of additive and 1.5 equiv. of BQ, in 7:1 MeOH/THF (0.5 M) as the reaction medium, for 67 h. [b] Determined by direct ^{1}H NMR analysis on a sample of the reaction mixture. [c] Reaction performed using 4.4 mol% of AgOTf (the AgOTf has been added to the catalyst solution after the addition of the ligand and the solution was left stirring for 30 min). [d] Reaction performed using 5 mol% of *p*-TSA. [e] Reaction performed using 1.1 equiv. of BQ. [f] Reaction performed at 50 °C. [g] Reaction performed at 1 bar of CO.

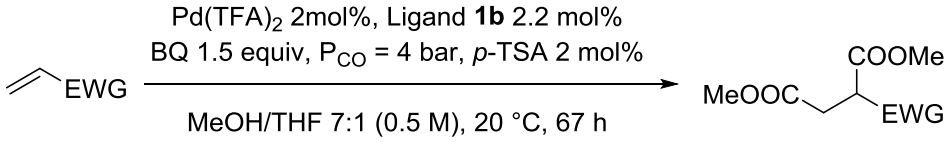
As expected, no reaction was observed without ligand (entry 1). Employing ligands **1a** and **1b** together with 0.5 mol% of $Pd(TFA)_2$ conversions of 13% and 22% were achieved respectively, attaining selectively trimethyl ethane-1,1,2-tricarboxylate **6a** (entries 2 and 3). After this poor, but encouraging results, we decided to rising up the catalyst loading to 2 mol%, obtaining 90% of olefin conversion with both ligands **1a** and **1b** (entries 4 and 5). Utilizing ligand **1c**, where the two methyl groups of the backbone are replaced with hydrogen atoms, only 45% of the starting olefin was converted. The result with the *o*-dimethyl BIAN ligand **1d**, is just slightly less satisfactory respect to those with ligands **1a** and **1b** (entry 7). On the other hand, the presence of bulky isopropyl groups on the aromatic rings in ligand **1e** drastically reduces the conversion (entry 8). Employing the ligand **1f**, with fluorine substituents in *ortho* and *para* positions, the reaction does not proceed at all (entry 9), probably due to the low basicity of the ligand that makes the catalyst less stable.[162] From these results it is clear that both the electronic character and the steric hindrance of the *ortho* substituents, together with the rigidity of the resulting catalysts, influenced by the backbone, greatly affect the reactivity. Variations on the palladium source (entry 10) did not lead to any improvement.

The use of an acidic additive was found to be crucial for this reaction, indeed without *p*-TSA the conversion of the olefin **5a** was lowered by 20% (entry 11). However, also utilizing an higher amounts of acid, a reduction on the reactivity was observed (entry 14). It is known that the main function of the protic acid is to create a free site at the metal centre[94] as well as to increase the overall conversion of the substrate, speeding up the oxidation of Pd(0) to Pd(II) by BQ.[146] On the other hand, the fact that the productivity decreases when the acid is added in relatively large amounts may be due to the possibility that the TsO^- anion competes in the coordination with the Pd species.[144a] Moreover, high amounts of monohydrated *p*-TSA bring to much H_2O in the reaction system, probably resulting in catalyst partial deactivation and therefore in a decreasing of the conversions. Interestingly, basic additives completely shut down the reaction (entry 13). Attempts to reduce the amount of *p*-benzoquinone or the pressure CO were both unsuccessful (entries 15 and 17), while rising up the temperature to 50 °C a slightly better result was achieved (entry 16, Table 7). However, we decided to continue our investigation performing the reaction at room temperature, as the conversion improvement was too small to justify an increase of 30 °C. Summarizing the best conditions turned out to be the following: the catalyst **A** is formed *in situ* by mixing $Pd(TFA)_2$ and the ligand **1b**, the reaction proceeded at 20°C under 4 bar of CO, employing *p*-benzoquinone as an oxidant and *p*-TSA as acidic additive, in a solution of methanol/THF 7:1.

3.2.2 Generality of the Bis-Alkoxycarbonylation Process with Electron-Deficient Olefins

In order to evaluate the generality of the reaction conditions found, electron-deficient olefins bearing different electron-withdrawing groups have been employed in our bis-alkoxycarbonylation process, as reported in Table 8. Interestingly, a near quantitative yield was achieved with *N*,*N*-dimethylacrylamide **7g**, which resulted to be more reactive than methyl acrylate **5a** (entries 1 and 2, Table 8). The diethyl vinyl phosphonate **9** gave less satisfactory results and the resulting dimethyl 2-(diethoxyphosphoryl)succinate product **10** was obtained in just 25 % yield (entry 3), while acrylonitrile **12** and phenyl vinyl sulfone **13** were completely unreactive under these conditions (entries 5 and 6).

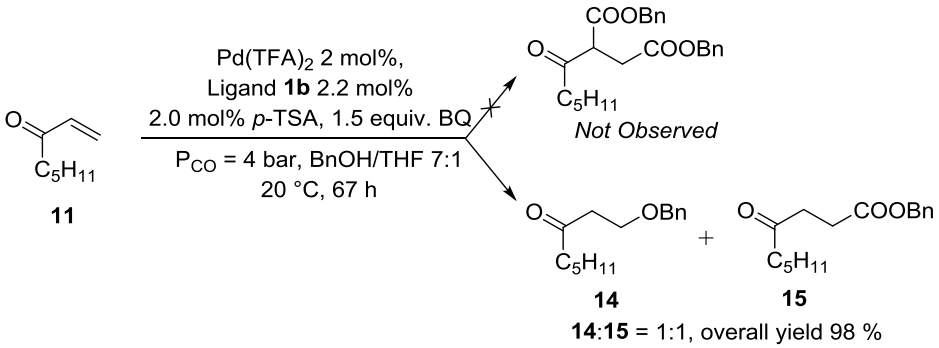
Table 8 – Bis-methoxycarbonylation of various electron-deficient olefins



Entry[a]	Olefin	EWG	Conversion (%)[b]	Yield (%)[c]
1	**5a**	COOMe	90	78
2	**7g**	$CONMe_2$	> 98	95
3	**9**	$P(O)(OEt)_2$	32	25
4	**11**	$C(O)C_5H_{11}$	100[d]	0
5	**12**	CN	< 5	-
6	**13**	SO_2Ph	< 5	-

[a] Reaction performed in autoclave at P_{CO} = 4 bar, with 2 mmol of the olefin, $Pd(TFA)_2$ (2 mol%), ligand **1b** (2.2 mol%), *p*-TSA (2 mol%) and BQ (1.5 equiv), in 7:1 MeOH/THF (4 mL) as the reaction medium, for 67 h. [b] Determined by ^1H NMR analysis of the reaction crude. [c] Isolated yields after column chromatography. [d] The olefin **11** was mainly converted into 1-methoxyoctan-3-one, together with other unidentified by-product.

Employing the α,β-unsaturated ketone **11**, no trace of the desired bis-alkoxycarbonylated product was detected (entry 4, Table 8). In this case, the olefin was mainly converted into 1-methoxyoctan-3-one, probably deriving from an acid catalyzed methoxylation reaction,[163] together with other unidentified by-products. Interestingly, using olefin **11** and benzyl alcohol as nucleophile, the mono-carbonylated benzyl 4-oxononanoate product **15** was isolated in 1:1 ratio with the corresponding mono-alkoxylated compound **14** in 98% of overall yield (Scheme 42).



Scheme 42 – Reactivity of the vinyl ketone **11** using BnOH as nucleophile.

Compounds **14** and **15** were identified in the NMR of the isolated mixture (Figure 5), and spectral data were identical to those previously reported in the literature [164]

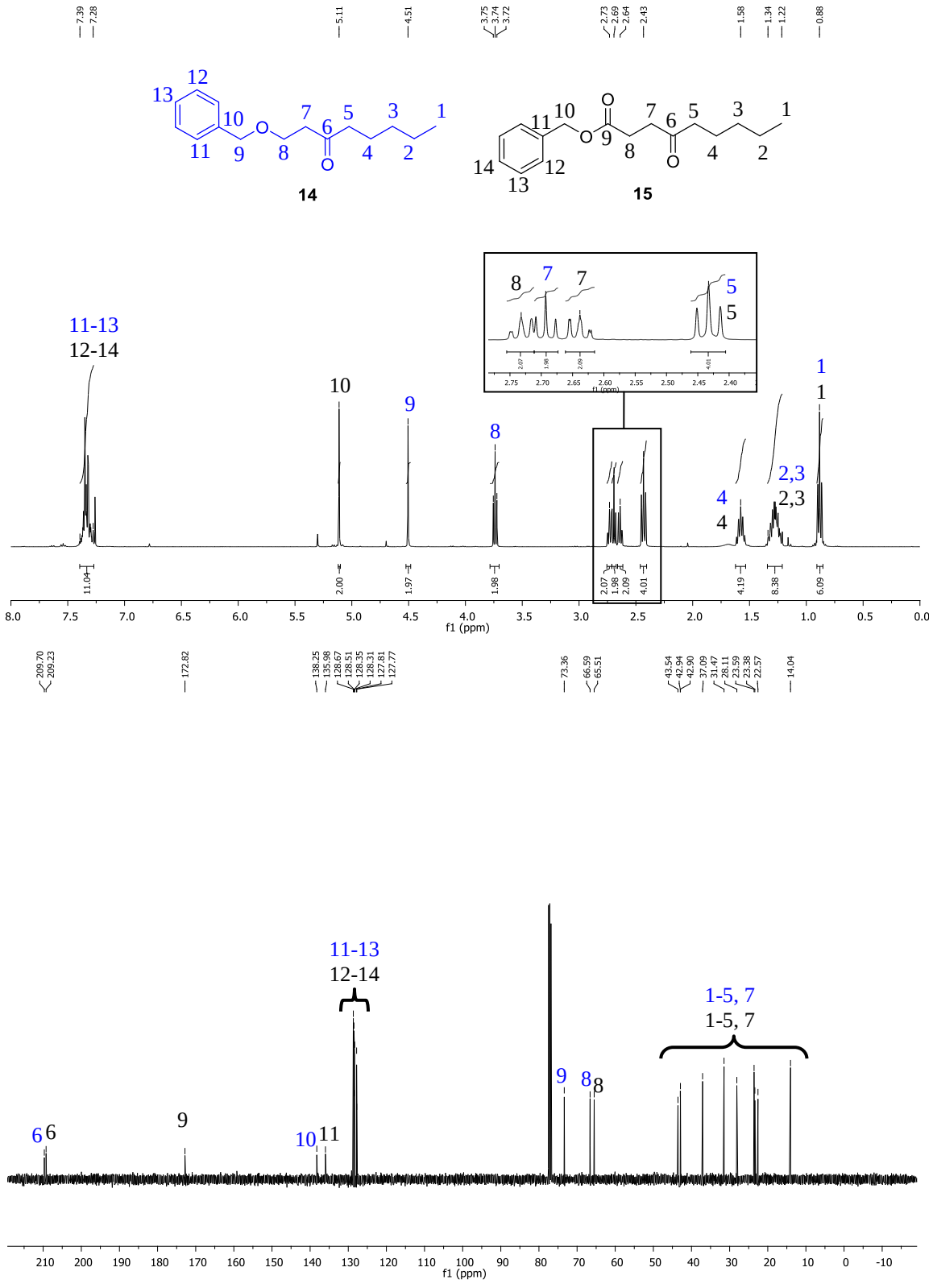


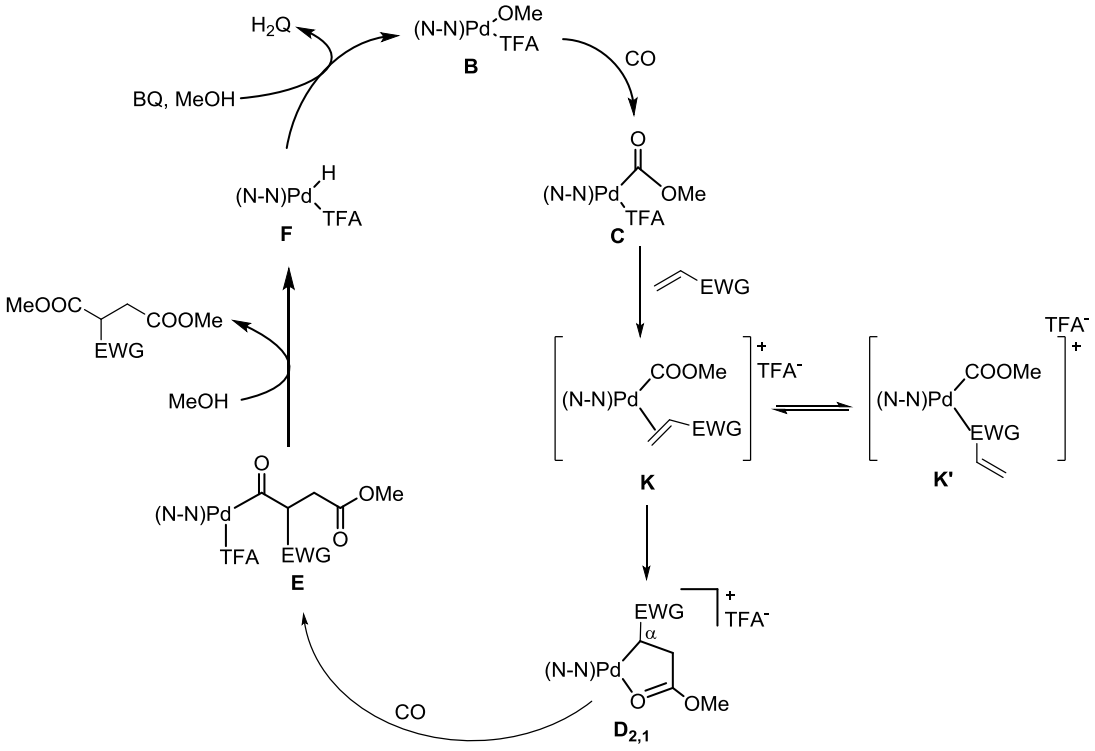
Figure 5 - ^{1}H NMR (top) and ^{13}C NMR (bottom) of the isolated mixture of **14** and **15**

Anyway, no trace of the desired bis-alkoxycarbonylated product has been detected when olefin **11** was used, even in the absence of the acidic *p*-TSA.

In conclusion, it appears that the conversions in Table 8 are correlated with the nature of the electron-withdrawing group. In particular, it seems that alkenes bearing an EWG group with a lower electron-attractor character give higher yields in the expected bis-alkoxycarbonylated product.

3.2.3 Catalytic Cycle and DFT Calculations

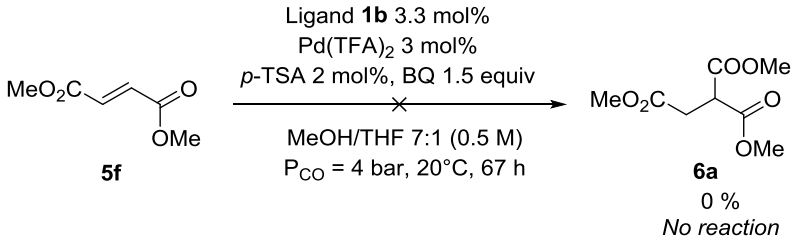
The catalytic cycle proposed for the bis-alkoxycarbonylation of electron-deficient olefins is depicted in Scheme 43 and it is similar to the one reported for the bis-alkoxycarbonylation of 1,2-disubstited olefins (Scheme 37, *Chapter 2.2.2*).



Scheme 43 – Proposed catalytic cycle for the bis-alkoxycarbonylation of electron-deficient olefins, using MeOH as nucleophile.

Palladacycles intermediates similar to $\mathbf{D_{2,1}}$ bearing an EWG group, have been previously identified in mechanistic studies concerning CO/electron-deficient olefin copolymerization.[159,165] An alternative mechanism for the formation of the bis-carbonylated product, involving β-hydride elimination from intermediate $\mathbf{D_{2,1}}$ with formation of a mono-carbonylated compound of the type EWG-CH=CH-COOR, which can be than alkoxycarbonylated again, has been excluded. Indeed, utilizing the dimethyl

fumarate **5f** as substrate, the formation of the expected product **6a** was not detected (Scheme 44).



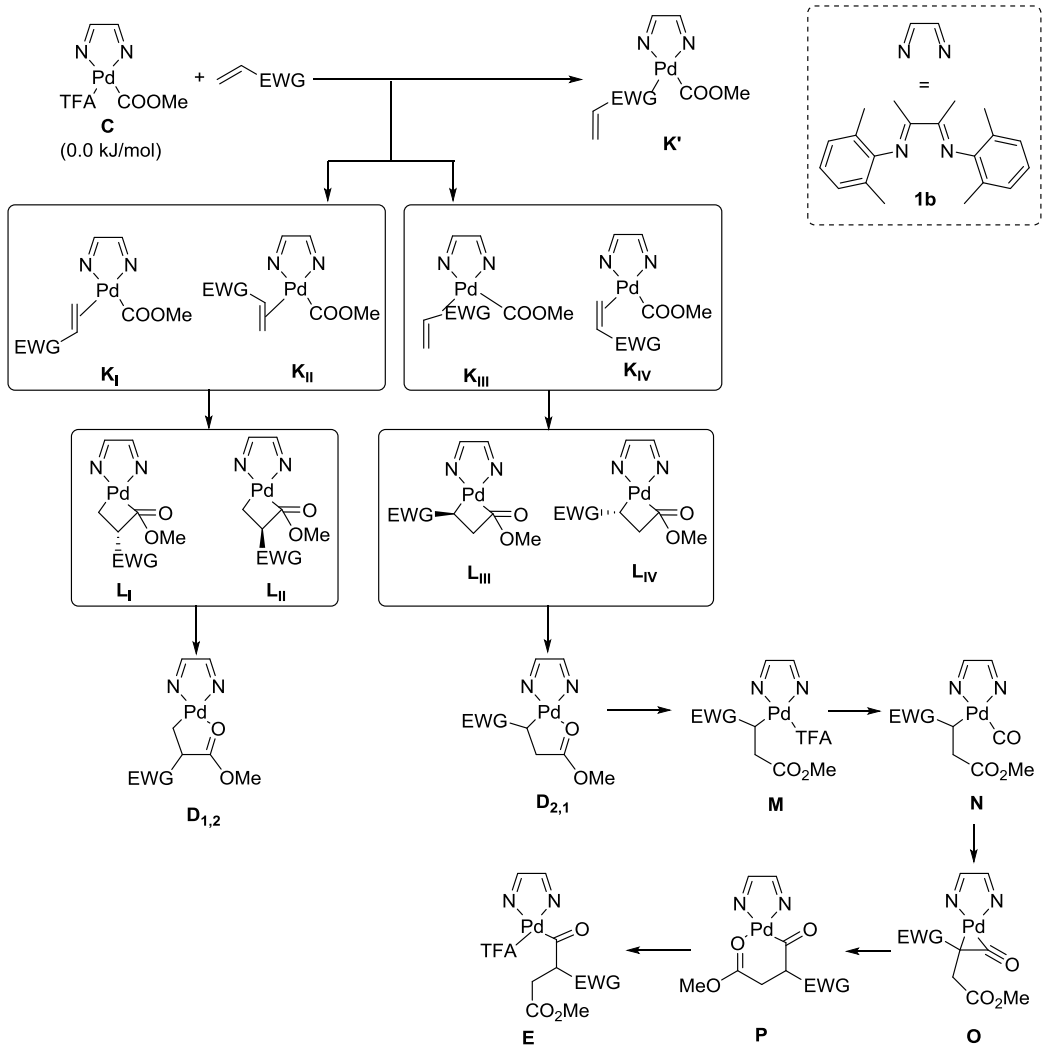
Scheme 44 - Study on the alternative mechanism involving β-H elimination in the intermediate $\mathbf{D_{2,1}}$.

Previous investigations, aimed at explaining the low reactivity of electron-deficient olefins in copolymerization reactions,[156,158,159] pointed out some drawbacks that might also inhibit our bis-alkoxycarbonylation process. These problems can be summarized in the following three points:

1) the coordination ability of the olefinic double bond is reduced by the presence of an electron-withdrawing group[156] (Scheme 43, intermediate **K**);
2) a competitive coordination by the heteroatom-containing functional group of the olefin can take place (intermediate **K'**);[156a,b]
3) the second CO insertion, forming the intermediate **E**, is inhibited by the reduced nucleophilicity of the α-carbon bearing the EWG in complex $\mathbf{D_{2,1}}$.[158,159]

In order to assess whether such effects were also at work in our catalytic cycle, and if they were responsible for the different reactivity of the EWG-substituted alkenes shown in Table 8, we performed some preliminary DFT calculations. Using alkenes **5a**, **7g**, **9**, **11**, **12** and **13**, we decided to calculate the energies only of intermediates from **K** to **E** of the catalytic cycle, because these represent the relevant steps involving the olefins (Table 9). The energy of the alkoxycarbonyl intermediate **C** (Scheme 43) has been taken as a common reference (Energy of **C** = 0.0 kJ/mol).

Table 9 – Expected species leading to the formation of intermediate **E**, starting from intermediate **K**, for olefins **5a**, **7g**, **9**, **11**-**13**, and their energy values.



Entry[a,b]	Intermediate	Energy with **5a** (kJ/mol)	Energy with **7g** (kJ/mol)	Energy with **9** (kJ/mol)	Energy with **11** (kJ/mol)	Energy with **12** (kJ/mol)	Energy with **13** (kJ/mol)
1[c]	**K'**	34.3	6.9	2.3	17.2	5.0	29.8
2	**K_I**	29.1	22.7	7.1	19.7	44.9	18.4
3	**K_{II}**	29.3	15.8	13.1	13.9	38.3	12.1
4	**K_{III}**	27.0	11.5	5.4	27.1	45.2	10.6
5	**K_{IV}**	22.5	9.7	5.9	18.1	32.9	8.5
6	**L_I**	96.8	73.2	88.5	85.2	113.2	86.2
7	**L_{II}**	97.2	75.1	83.2	85.7	102.1	84.2
8	**L_{III}**	74.7	71.4	68.2	71.8	83.6	70.9
9	**L_{IV}**	85.1	55.0	74.8	65.1	86.9	67.8

10	$\mathbf{D_{2,1}}$	-38.0	-41.0	-54.7	-49.4	-38.2	-76.7
11	$\mathbf{D_{1,2}}$	16.1	-16.1	-29.3	-16.3	7.7	-40.8
12	**M**	-47.1	-28.8	-65.6	-42.8	-49.7	-85.9
13	**N**	-60.8	-66.9	-83.9	-65.6	-64.8	-102.7
14	**O**	2.7	1.3	-24.5	-9.6	18.0	-7.6
15	**P**	-59.5	-79.8	-85.9	-74.2	-49.4	-85.4
16	**E**	-59.8	-79.6	-78.3	-54.1	-57.5	-79.3

[a] Energy of **C** = 0.0 kJ/mol. [b] The transition states are depicted in red. [c] When more than one coordination possibility on the heteroatom is possible, only the one with the lowest energy has been reported.

Graphical representations of the data of Table 9, are reported in Figures 6-11 for the olefins **5a**, **7g**, **9**, **11**, **12** and **13**.

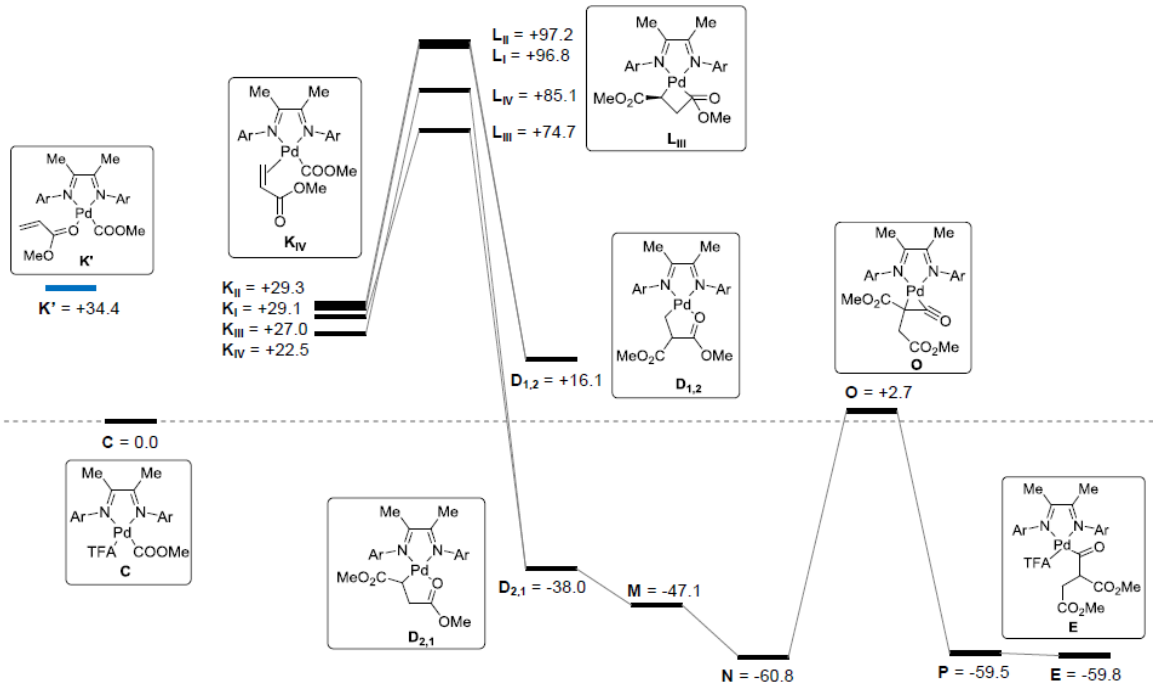


Figure 6 - Energy profile for olefin **5a**, from **K** to **E**. The energies are reported in kJ/mol (energy of **C** = 0.0 kJ/mol). Ar = (2,6-Me)C_5H_3

In particular, in Figure 6 is depicted the energy profile for the bis-alkoxycarbonylation of olefin **5a**. Starting from intermediate **K'**, in which the olefin is coordinated to the Pd by the heteroatom, it is not possible to obtain the expected bis-alkoxycarbonylated product **6a**, therefore the reaction can proceed only passing through the intermediates $\mathbf{K_{I\text{-}IV}}$,

representing the different coordinating mode of the olefinic double bond relative to the *Re* and *Si* faces of the olefin plus two rotamers. As expected, the energies related to the intermediates **K'** and $\mathbf{K_{I\text{-}IV}}$ are comparable, suggesting the presence of an equilibrium between the two possible coordination mode. The 2,1-insertion of olefin is favoured since both the isomers $\mathbf{L_{III}}$ and $\mathbf{L_{IV}}$ have a lower energy of about 10-20 kJ/mol with respect to the isomers $\mathbf{L_I}$ and $\mathbf{L_{II}}$, deriving from 1,2-insertion. Moreover the palladacycle intermediate $\mathbf{D_{2,1}}$, formed from transition states $\mathbf{L_{III}}$ and $\mathbf{L_{IV}}$, is more stable, of 54.1 kJ/mol, than complex $\mathbf{D_{1,2}}$, which is afforded from transition states $\mathbf{L_I}$ and $\mathbf{L_{II}}$. Therefore the formation of $\mathbf{D_{2,1}}$ is highly favored from both the kinetic and thermodynamic point of view, in agreement with literature data.[159] On the basis of this result, we decided to proceed by studying only the intermediates resulting from $\mathbf{D_{2,1}}$. The successive ring opening and CO coordination lead to the formation of intermediate **N** (scheme of Table 9). The subsequent CO insertion, passing through the transition state **O**, has to overcome an energy barrier to take place, yielding intermediate **P** and, eventually, the complex **E**.

Analogue considerations are applicable also to the energy profiles of olefins **7g** (Figure 7), **9** (Figure 8), **11** (Figure 9) and **13** (Figure 11).

When acrylonitrile **12** was used (Figure 10) the coordination of Pd with the nitrogen is strongly favored respect to the coordination with the olefinic double bond, by at least 28 kJ/mol, accounting for the unreactivity of this substrate. Indeed, it has been found, in Pd-catalyzed olefin/CO copolymerization reactions, that the inertia of acrylonitrile can be ascribed to a strong σ-bond between the nitrogen atom and Pd, making the π-coordination less probable.[156a]

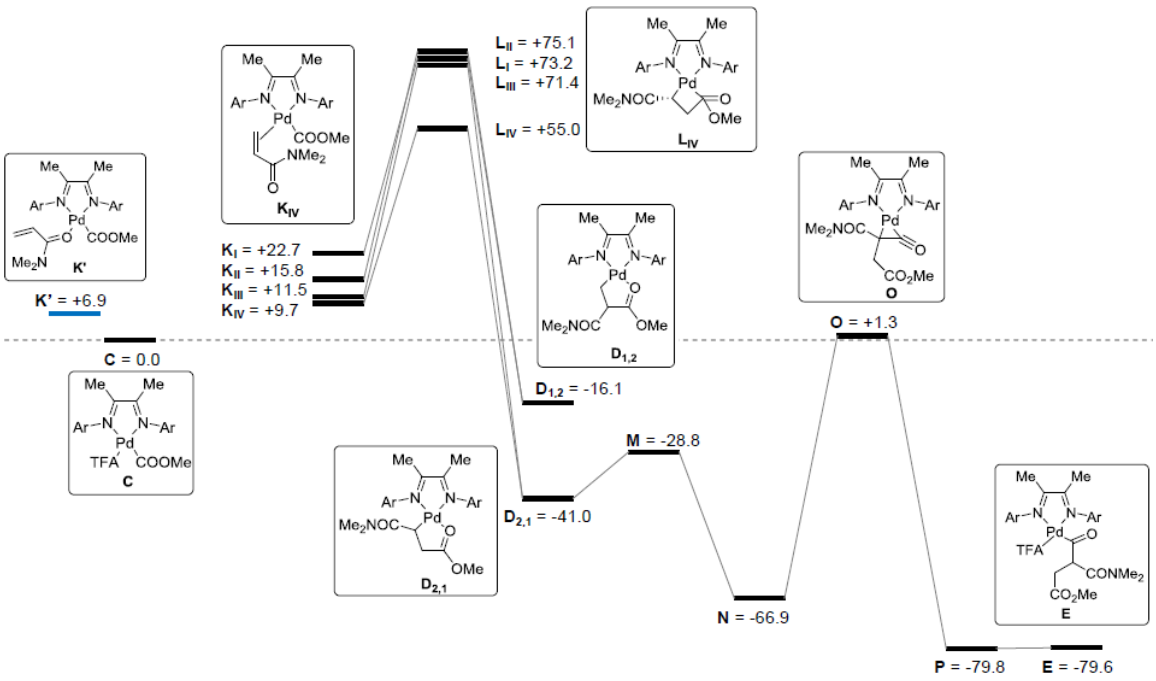


Figure 7 - Energy profile for olefin **7g**, from **K** to **E**. The energies are reported in kJ/mol (energy of **C** = 0.0 kJ/mol). Ar = (2,6-Me)C_5H_3

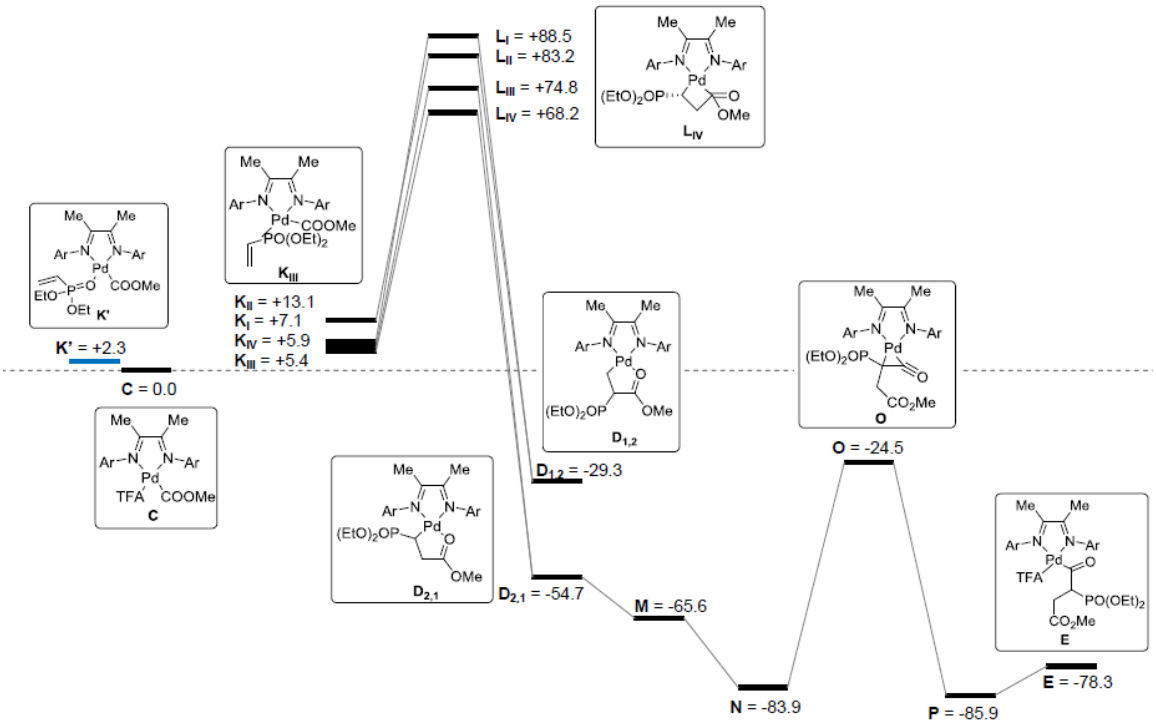


Figure 8 - Energy profile for olefin **9**, from **K** to **E**. The energies are reported in kJ/mol (energy of **C** = 0.0 kJ/mol). Ar = (2,6-Me)C_5H_3

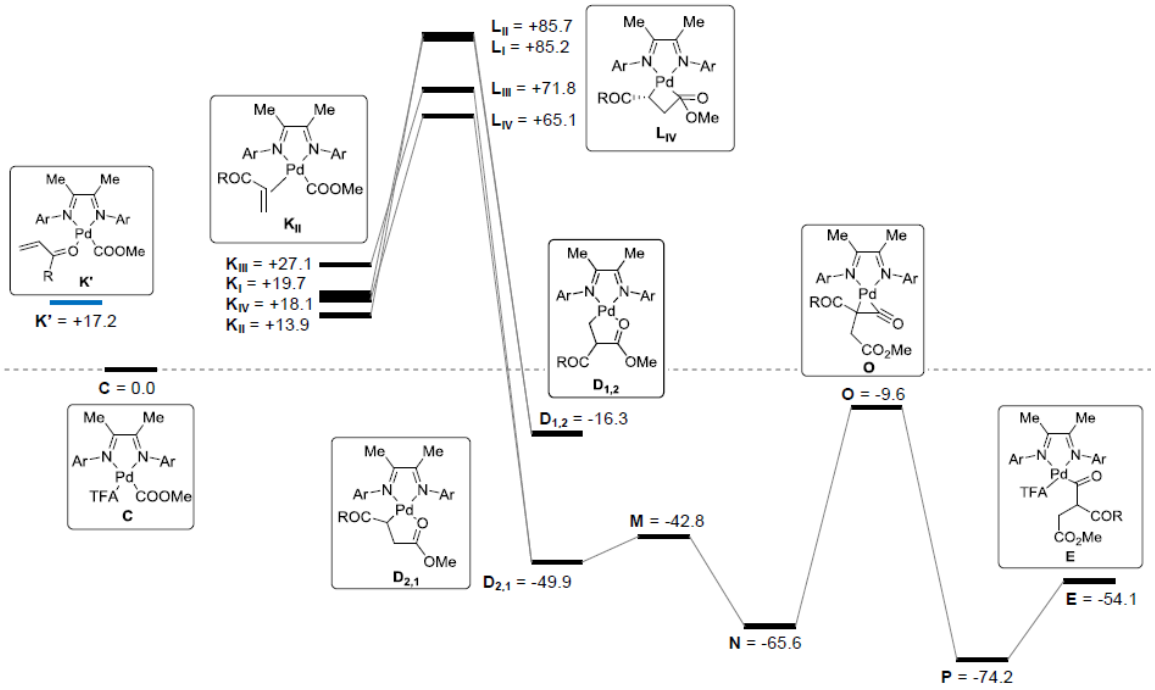


Figure 9 - Energy profile for olefin **11**, from **K** to **E**. The energies are reported in kJ/mol (energy of **C** = 0.0 kJ/mol). Ar = (2,6-Me)C_5H_3. R = C_5H_{11}.

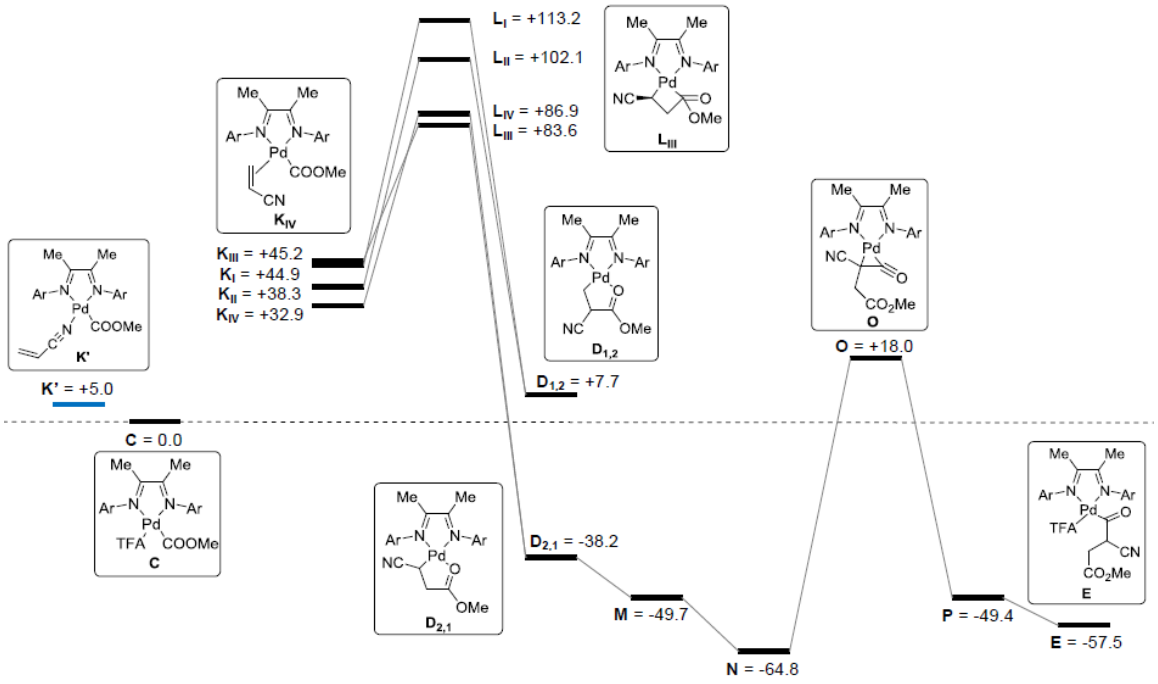


Figure 10 - Energy profile for olefin **12**, from **K** to **E**. The energies are reported in kJ/mol (energy of **C** = 0.0 kJ/mol). Ar = (2,6-Me)C_5H_3

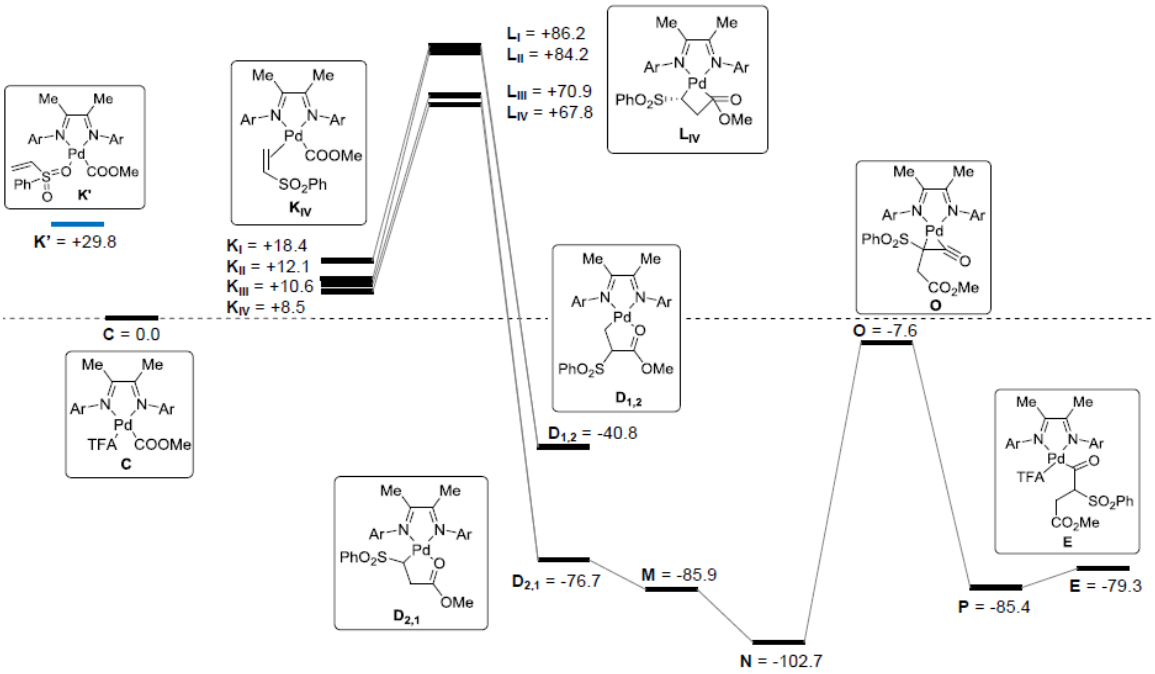


Figure 11 - Energy profile for olefin **13**, from **K** to **E**. The energies are reported in kJ/mol (energy of **C** = 0.0 kJ/mol). Ar = (2,6-Me)C_5H_3

We then decided to compare the energies of the insertion of the second molecule of CO using olefins **5a**, **7g**, **9**, **11-13** (Figure 12), because, even if several examples of 5-membered palladacycles of type $\mathbf{D_{2,1}}$ with diverse ligands and various electron-poor alkenes have been reported,[159,165] the subsequent CO insertion has never been observed.

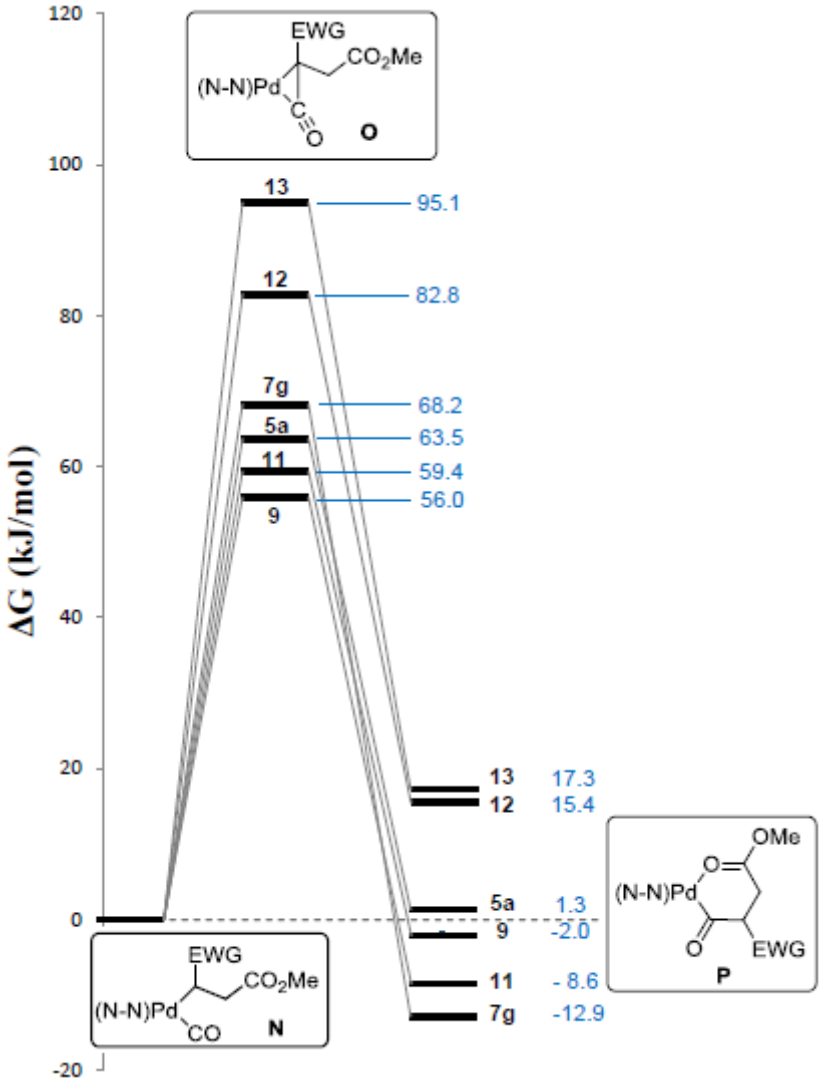


Figure 12 - Gibbs free energies (in kJ/mol) diagrams relative to the insertion of the second CO molecule, for the olefins listed in Table 8. The energy of the open chain intermediate **N**, with the CO coordinated to the Pd centre, has been taken as common reference.

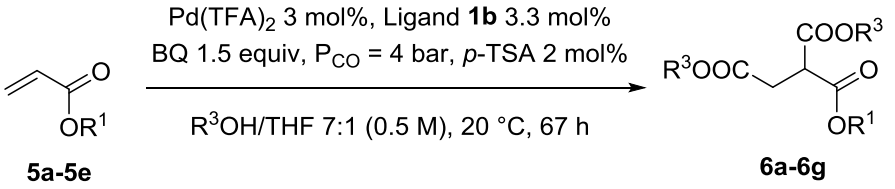
The free energy values $\Delta G^{\ddagger}$ of the transition state **O** for phenyl vinyl sulfone **13** (95.1 kJ/mol) and for acrylonitrile **12** (82.8 kJ/mol) are the highest among those calculated, while for *N*,*N*-dimethylacrylamide **7g** (68.2 kJ/mol), methyl acrylate **5a** (63.5 kJ/mol) and diethyl vinyl phosphonate **9** (59.4 kJ/mol) the values are similar and lower by at least 15 kJ/mol. The unreactivity of sulfone **13** and acrylonitrile **12** (Table 8, entries 6 and 5) can be explained considering both the very high $\Delta G^{\ddagger}$ values of **O** and the high coordination ability of sulphonic oxygens and of the –CN group towards Pd. Moreover, with these two olefins the formation of the intermediate **P** is thermodynamically disfavored. The low phosphonate conversion could be justified by the high coordination ability of the phosphonic oxygen (Figure 8), even if the $\Delta G^{\ddagger}$ value was comparable with

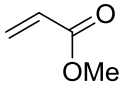
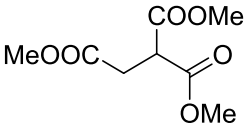
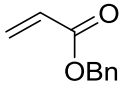
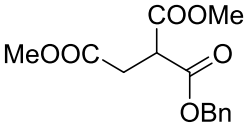
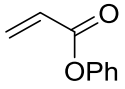
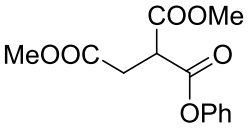
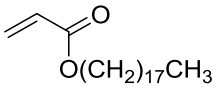
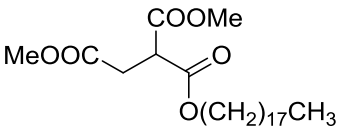
those of the much more reactive olefins **5a** and **7g**. In line with the good productivity observed, with olefins **5a** and **7g**, the values of $\Delta G^{\ddagger}$ are lower and the coordination ability of the carbonyl oxygen is similar to that of the olefinic double bond (Figures 6 and 7). The higher reactivity of the amide **7g** could be attributed to the greater stability of intermediate **P**. For the vinyl ketone **11**, the value of $\Delta G^{\ddagger}$ would be potentially favorable but, owing to its different reactivity, this step cannot be reached.

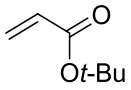
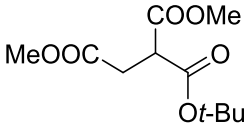
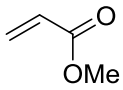
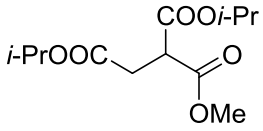
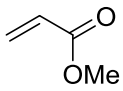
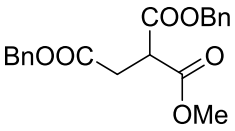
3.2.4 Scope of the Bis-Alkoxycarbonylation of Acrylic Esters

With all these data in hand, we started to investigate the scope of this unprecedent bis-alkoxycarbonylation reaction. Variously functionalized acrylic esters have been tested rising up the catalyst loading to 3 mol%, that allowed to obtain a complete conversion of the olefin **5a**, obtaining **6a** in excellent isolated yield (Table 10, entry 1).

Table 10 – Scope of the bis-alkoxycarbonylation of acrylic esters **5a**-**5e**



Entry[a]	**5**	R^3OH	**6**	Yield (%)[b]
1	 **5a**	MeOH	 **6a**	89
2	 **5b**	MeOH	 **6b**	91
3	 **5c**	MeOH	 **6c**	90 (94)[c]
4	 **5d**	MeOH	 **6d**	92

5[d]	 **5e**	MeOH	 **6e**	93 (97)[c]
6[d]	 **5a**	*i*-PrOH	 **6f**	32 (40)[c]
7	 **5a**	BnOH	 **6g**	88

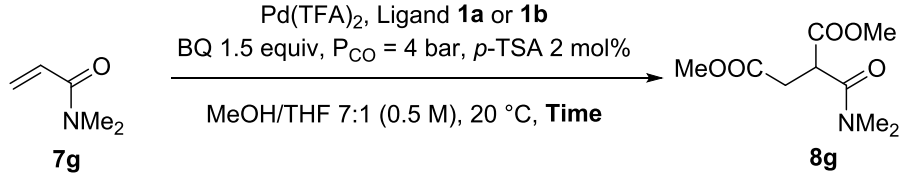
[a] Reaction performed in autoclave at P_{CO} = 4 bar, with olefins **5a**-**5e** (2 mmol), 3 mol% of $Pd(TFA)_2$, 3.3 mol% of ligand **1b**, 2 mol% of *p*-TSA and 1.5 equiv of BQ, in 7:1 R^3OH/THF (4 mL), for 67 h. [b] Isolated yields after column chromatography. [c] The conversion (%) is reported in parentheses when not complete. [d] Reaction performed with 5 mol% of catalyst loading.

Starting from benzyl acrylate **5b** and phenyl acrylate **5c**, excellent isolated yields of bis-alkoxycarbonylated compounds **6b** and **6c** were obtained (entries 2 and 3). This system can be successfully also applied to acrylic esters bearing a long alkyl side chain (entry 4) or a sterically demanding substituent (entry 5) on the oxygen, as demonstrated by the formation of the products **6d** and **6e** respectively. In particular, for olefin **5e**, a nearly quantitative conversion was achieved only when 5 mol% of catalyst loading was used. Unfortunately, utilizing the bulky and less nucleophilic isopropanol, product **6f** was formed with less satisfactory results, even with an higher amount of catalyst (entry 6). On the other hand, high yield of **6g** was achieved employing benzyl alcohol as nucleophile (entry 7, Table 10).

3.2.5 Scope of the Bis-Alkoxycarbonylation of Acrylic Amides

Before to proceed with the evaluation of the scope of the bis-alkoxycarbonylation of acrylic amides, an attempt to reduce the catalyst loading (entries 1 and 2, Table 11), the reaction time (entries 3 and 4, Table 11) or the pressure of CO (entry 6, Table 11) has been made, using **7g** as model substrate, but no improvement was observed. Therefore, we proceeded our investigation utilizing the conditions reported in Table 8.

Table 11 – Screening of the reaction conditions of the bis-methoxycarbonylation reaction using **7g**.

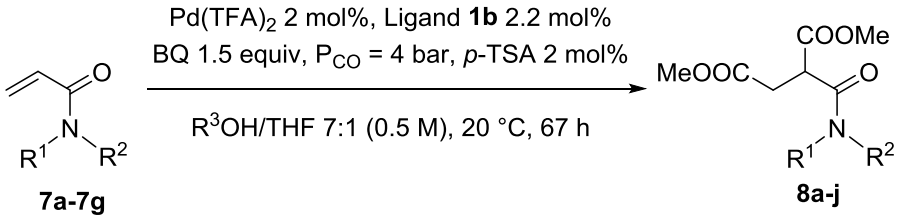


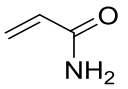
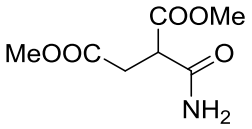
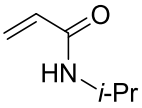
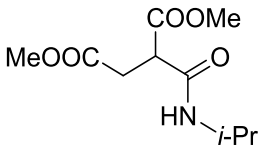
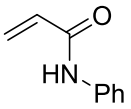
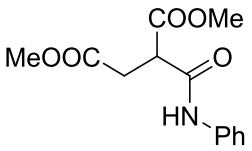
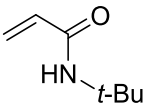
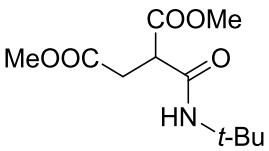
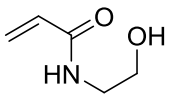
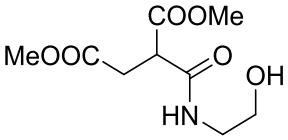
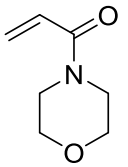
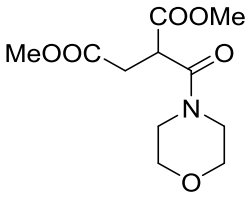
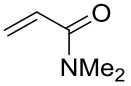
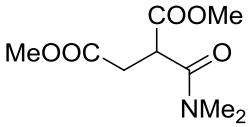
Entry[a]	$Pd(TFA)_2$ (mol %)	Ligand (mol%)	Time (h)	Conversion (%)[b]
1	0.5	**1a** 0.55	67	27
2	0.5	**1b** 0.55	67	35
3	2	**1b** 2.2	24	39
4	2	**1b** 2.2	46	72
5	2	**1b** 2.2	67	> 98
6[c]	2	**1b** 2.2	67	30

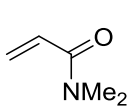
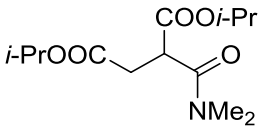
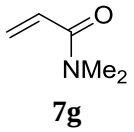
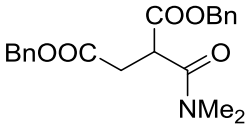
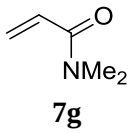
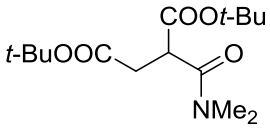
[a] Reaction performed in autoclave at P_{CO} = 4 bar, with olefin **7g** (2 mmol), $Pd(TFA)_2$ (0.55 - 2 mol%), ligand **1a** or **1b (**0.55 - 2.2 mol%), *p*-TSA (2 mol%) and BQ (1.5 equiv.), in 7:1 MeOH/THF (4 mL) as the reaction medium, for the indicated time. [b] Determined by ^{1}H NMR analysis of the reaction crude. [c] Reaction performed at 1 bar of CO.

Differently substituted acrylic amides have been successfully carbonylated, obtaining various 2-carbamoylsuccinates in high yields and total selectivity, as shown in Table 12.

Table 12 – Scope of the bis-alkoxycarbonylation of acrylic amides **7a-7g**



Entry[a]	7	R^3OH	8	Yield (%)[b]
1	 **7a**	MeOH	 **8a**	91
2	 **7b**	MeOH	 **8b**	92
3	 **7c**	MeOH	 **8c**	90
4	 **7d**	MeOH	 **8d**	78 (85)[c]
5	 **7e**	MeOH	 **8e**	98
6	 **7f**	MeOH	 **8f**	98
7	 **7g**	MeOH	 **8g**	95

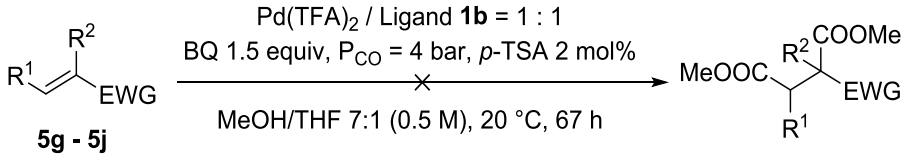
8	 **7g**	*i*-PrOH	 **8h**	88 (90)[c]
9	 **7g**	BnOH	 **8i**	93
10[d]	 **7g**	*t*-BuOH	 **8j**	40 (60)[c]

[a] Reaction performed in autoclave at P_{CO} = 4 bar, with olefins **7a-7g** (2 mmol), 2 mol% of $Pd(TFA)_2$, 2.2 mol% of ligand **1b**, 2 mol% of *p*-TSA and 1.5 equiv of BQ, in 7:1 R^3OH/THF (4 mL), for 67 h. [b] Isolated yields after column chromatography. [c] The conversion (%) is reported in parentheses when not complete. [d] Reaction performed with 5 mol% of catalyst loading at 50 °C.

Regardless the different steric hindrance and the different electronic character of the amidic substituents, olefins **7a**, **7b** and **7c** have been carbonylated in almost quantitative yields (entries 1-3). Moreover, despite the presence of the bulky *tert*-butyl group, olefin **7d** gave 78% yield of the bis-methoxycarbonylated product **8d** with 85% of conversion (entry 4). Interestingly, the acryl amide **7e**, bearing an hydroxyl group in the side chain, was well tolerated and possible by-products deriving from intra- and intermolecular reactions involving the tethered –OH group, such as cyclization reactions, were not detected (entry 5). Nearly quantitative yields were also achieved with acryl amides **7f** and **7g** showing a dialkyl-substitution on the nitrogen (entries 6 and 7). Respect to acrylic esters, here high yields have been obtained using both *i*-PrOH or BnOH as nucleophiles (entries 8 and 9). Employing the sterically demanding *tert*-butyl alcohol, just 10% of conversion of olefin **7g** was achieved. However, increasing both the catalyst loading to 5 mol% and the temperature to 50 °C, product **8j** has been isolated with a satisfactory selectivity (entry 10, Table 12).

Unfortunately, as shown in Table 13, acrylates or acrylic amides bearing a substituent group in α- or β- positions resulted to be unreactive under our reaction conditions.

Table 13 – Bis-methoxycarbonylation reaction of olefins **5g** – **5j**.



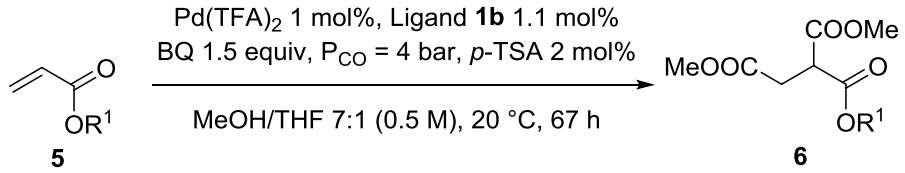
Entry[a]	Olefin	EWG	R^1	R^2	Catalyst Loading (mol%)	Conversion (%)[b]
1	**5g**	COOMe	Me	H	2	< 5
2	**5g**	COOMe	Me	H	5	< 5
3	**5h**	COOMe	H	Me	2	< 5
4	**5i**	COOEt	Ph	H	3	< 5
5	**5j**	$CONH_2$	Ph	H	3	< 5

[a] Reaction performed in autoclave at P_{CO} = 4 bar, with olefins **5g - 5j** (2 mmol-scale), catalyst loading ($Pd(TFA)_2$ / ligand **1b** = 1 : 1.1) in the indicated amount, *p*-TSA (2 mol%) and BQ (1.5 equiv.), in 7:1 MeOH/THF (4 mL) as the reaction medium, for 67 h. [b] Determined by ^{1}H NMR analysis of the reaction crude.

3.2.6 Influence of Acrylic Ester and Amide Substituents on the Reactivity of the Process

The high efficiency of our catalytic system did not allow us to appreciate the effects of the substituents on the oxygen, for acrylic esters, and on the nitrogen, for acrylic amides. Therefore, some of the reactions reported in Table 10 and Table 12, have been tested with 1 mol% of catalyst loading, in order to evaluate the different effects of the substituents.

Table 14 – Bis-methoxycarbonylation of acrylic esters using 1 mol% of catalyst loading

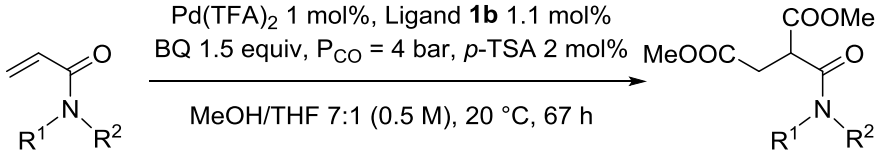


Entry[a]	Olefin **5**	R^1	Conversion (%)[b]
1	**5a**	Me	56
2	**5c**	Ph	28
3	**5d**	$(CH_2)_{17}CH_3$	47
4	**5e**	*t*-Bu	24

[a]Reaction performed in autoclave at P_{CO} = 4 bar, with olefins **5** (2 mmol), 1 mol% of $Pd(TFA)_2$, 1.1 mol% of ligand **1b**, 2 mol% of *p*-TSA and 1.5 equiv of BQ, in 7:1 MeOH/THF (4 mL), for 67 h. [b] Determined by ^{1}H NMR analysis of the reaction crude.

The results confirmed again the higher reactivity of amides respect to esters in this bis-alkoxycarbonylation reaction. Indeed, while with acrylic esters the range of conversions was between 24 % and 56 % (Table 14), with acrylic amides **4a** and **4c** the conversions were almost complete and resulted to be 90 % and 82 % respectively (Table 15, entries 1 and 3).

Table 15 – Bis-methoxycarbonylation of acrylic amides using 1 mol% of catalyst loading



7 **8**

Entry[a]	Olefin **7**	R^1	R^2	Conversion (%)[b]
1	**7a**	H	H	90
2	**7b**	H	*i*-Pr	60
3	**7c**	H	Ph	82
4	**7g**	Me	Me	68

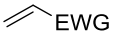
[a]Reaction performed in autoclave at P_{CO} = 4 bar, with olefins **7** (2 mmol), 1 mol% of $Pd(TFA)_2$, 1.1 mol% of ligand **1b**, 2 mol% of *p*-TSA and 1.5 equiv of BQ, in 7:1 MeOH/THF (4 mL), for 67 h. [b] Determined by ^{1}H NMR analysis of the reaction crude.

From Tables 14 and Table 15, it can be deduced that the size of the substituents negatively affects the reactivity. In particular, as the size of the substituents on the oxygen or on the nitrogen increases, the reactivity of the olefin gradually decreases. However, from the observation of the molecular models based on theoretical calculations, it appears that this trend is not so much dictated by steric effects, but rather, seems to derive from an increased inductive effect of the substituents on the esteric or amidic carbonyl, resulting in an increase of the partial charge on the oxygen. This makes the coordination of oxygen with palladium more likely, with consequent partial deactivation of the catalyst and decrease in the productivity of the reaction. In this regard, the Natural Population Analysis (NPA) partial charges on the oxygen of the carbonyl group, which can give a further evaluation of the EWG capability to coordinate the Pd center, is reported in Table 16.

These additional results suggested that the coordination ability of the oxygen to the palladium center is similar for esters (entries 1 - 5) and amides (entries 6 - 10) and, in both cases, it is lower than those of olefins **9** (entry 11) and **13** (entry 14), in line with the

productivities reported in Table 8. The slighly lower values of NPA partial charges calculated for acrylates indicate that the coordination of the olefin to the palladium through the heteroatom is more likely for amides than for esters, as already confirmed by DFT calculations (see the energies of intermediates **K'** in Table 9 and Figures 6 and 7). However, the higher reactivity of amides can be explained by: i) the low energy required for coordinating the olefinic double bond to the palladium center, which renders the formation of intermediates **K** more accessible for acrylic amides respect to acrylic esters (Table 9), and ii) the greater stability of the 6-membered palladacycle intermediate **P** (Figure 12), as already described in *Chapter 3.2.3*.

Table 16 - Natural Population Analysis (NPA) charges for the oxygen of the X=O group (X = C, P, S)

Entry	Olefin 	EWG	NPA	Entry	Olefin 	EWG	NPA
1	**5a**	COOMe	-0.566	8	**7c**	CONHPh	-0.595
2	**5b**	COOBn	-0.579	9	**7d**	CONH*t*-Bu	-0.620
3	**5c**	COOPh	-0.569	10	**7g**	$CONMe_2$	-0.591
4	**5d**	$COO(CH_2)_{17}CH_3$	-0.568	11	**9**	$P(O)(OEt)_2$	-0.995
5	**5e**	COO*t*-Bu	-0.593	12	**11**	$C(O)C_5H_{11}$	-0.521
6	**7a**	$CONH_2$	-0.581	13	**12**	CN	-0.301[a]
7	**7b**	CONH*i*-Pr	-0.619	14	**13**	SO_2Ph	-0.880[b]

[a]Partial charge on the nitrogen. [b]Average value for the two oxygens

3.3 Conclusion

Despite the low reactivity of electron-deficient olefins in carbonylation reactions, the first bis-alkoxycarbonylation of acrylic esters and acrylic amides, leading to the synthesis of the respective 1,1,2-ethanetricarboxylate compounds and 2-carbamoylsuccinate derivatives, was successfully developed. The catalytic system is constituted by $Pd(TFA)_2$ as palladium source, the aryl α-diimine ligand **1b**, *p*-benzoquinone as an oxidant and *p*-toluenesulfonic acid as additive, the reaction proceeds under mild conditions, such as 4 bar of CO at 20°C. Using methanol, isopropanol, benzyl alcohol or the bulky *tert*-butyl alcohol as nucleophiles, moderate to excellent yields of bis-carbonylated products have been obtained.

We found that slight changes on the ligand structure produced a dramatic effect on the performance of the catalytic system. From the screening carried out, the importance of the presence of methyl substituents both on the *ortho*- positions of the aryl rings and on the backbone of the ligand was evidenced, confirming the superiority of ligand **1b**. The resulting blocked conformation of the catalyst bearing this ligand probably favors the correct approach of the reagents to the catalytic center, increasing the productivity.

This selective alkoxycarbonylation reaction of both the β- and the generally non-reactive α-positions of electron-deficient olefins, was successfully applied to a wide range acrylates and acryl amides bearing different types of substituents on the oxygen or on the nitrogen, respectively. Remarkably, high yields were achieved either with sterically demanding substituents or with substituents showing a different electronic character.

To assess the generality of our bis-alkoxycarbonylation process, various electron-deficient olefins, having different electron-withdrawing groups, have been tested. The resulting trend of reactivity was rationalized on the basis of the proposed catalytic cycle and supported by DFT calculations. From these studies, it appears that two main factors determine the course of our bis-alkoxycarbonylation: 1) the competition between the olefinic double bond and the EWG's heteroatom for the coordination to the Pd catalytic center and 2) the transition state energy relative to the second insertion of the carbon monoxide.

Eventually, to better appreciate the influence of the substituents within the series of acrylic esters and amides, the catalyst loading was lowered to 1%, obtaining a scale that highlights the greater reactivity of the amides. Moreover, although the size of the substituents on the oxygen or on the nitrogen negatively influences the reactivity of the

olefins, it seems that this is mainly due to the inductive effect of the substituents on the esteric or amidic carbonyl, making it more inclined to coordinate to palladium.

3.4 Experimental Section

3.4.1 General Information

All reactions were carried out under nitrogen atmosphere with dry solvents under anhydrous conditions, in a stainless steel autoclave, by using Schlenk technique. Reactions were monitored by ^{1}H NMR taking a sample of the crude mixture. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance 400 spectrometer (^{1}H: 400 MHz, ^{13}C: 101 MHz), using $CDCl_3$ as solvent. Chemical shifts are reported in the δ scale relative to residual $CHCl_3$ (7.26 ppm) for ^{1}H NMR and to the central line of $CDCl_3$ (77.16 ppm) for ^{13}C NMR. ^{13}C NMR was recorded with ^{1}H broadband decoupling. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet, dd = double doublets, b = broad. Coupling constants (*J*) are reported in Hertz (Hz). ESI-MS spectra were recorded on Waters Micromass ZQ 4000, using electrospray ionization techniques, with samples dissolved in MeOH. Carbon monoxide (Cp grade 99.99%) was supplied by Air Liquide. The *p*-benzoquinone was purchased by Sigma-Aldrich and was filtered off a plug of silica gel washing with CH_2Cl_2, obtaining a yellow solid after drying up in vacuum the solution. Olefins **5a-5e**, **5g-5j**, **7a-7g** and **9**, **11-13** were purchased from TCI or Fluorochem. Olefin **5f** was purchased from Sigma-Aldrich. The olefins **5a-5c**, **5e**, **5g**, **5h**, **7e-7g**, **9**, **11-13** were filtered off a plug of neutral Al_2O_3 and used without further purification. The olefins **5d**, **5f**, **5i**, **5j** and **7a-7d** were used without further purification. Anhydrous THF was distilled from sodium benzophenone, methanol was distilled from $Mg(OMe)_2$. Isopropanol, benzyl alcohol and *tert*-butyl alcohol were dried over molecular sieves (Alfa Aesar, 4 Å, 1-2 mm, beads). $Pd(TFA)_2$ was purchased by Flurochem, $Pd(PhCN)_2Cl_2$ was purchased by Sigma-Aldrich and both were weighted in an analytical balance without excluding moist and air. All other chemicals were purchased from Sigma-Aldrich and used without further purification. The ligands **1b-1e** were synthesized according to a previously reported procedure,[150] as well as the ligand **1f**.[166] The ligand **1a** was synthesized according to a procedure developed by our group.[128c]

3.4.2 Computational Details

DFT calculations have been performed using the ORCA 4.01 suite of quantum chemistry programs.[167] Geometry optimizations and free energy calculations (at 298K) were done with the small def2-TZVP basis[168] and the Becke-Perdew functional.[169] Additional

single point energy calculations with the larger def2-QZVPP basis[168] and the M06 functional[170] were performed at the previously optimized geometries. Single point energies were eventually amended by inclusion of solvation effects[171] and dispersion interactions.[172] The final energy of each structure, used to evaluate the relative free energies of the various products and intermediates, was built by summing the difference between the def2-TZVP electronic and free energies to the def2-QZVPP single point electronic energy. Natural Population Analysis[173] (NPA) has been performed using the JAMPA 1.04 package.[174]

3.4.3 Typical Procedure for the Bis-Alkoxycarbonylation of Electron-Deficient Olefins

In a nitrogen flushed Schlenk tube, equipped with a magnetic stirring bar, the respective olefin **5**, **7**, **9, 11-13** (2 mmol) and methanol MeOH (3.5 mL) were added. The mixture was left under stirring for 10 min. In another nitrogen flushed Schlenk tube, equipped with a magnetic stirring bar, the $Pd(TFA)_2$ (13.3 mg, 0.04 mmol or 19.9 mg, 0.06 mmol) and THF (0.5 mL) were added. After the mixture turned in a red/brown color (25 min), the ligand **1b** (12.8 mg, 0.044 mmol or 19.3 mg, 0.066 mmol) was added. The mixture was left under stirring for 20 min, turning in a dark orange color. The olefin solution and the formed catalyst were injected in sequence in a nitrogen flushed autoclave, equipped with a magnetic stirring bar, containing *p*-benzoquinone (325 mg, 3 mmol) and *p*-TSA·H_2O (7.6 mg, 0.04 mmol). After 10 min, the autoclave was flushed three times with CO and pressurized with 4 bar of carbon monoxide. The reaction was vigorously stirred at 20 °C for 67 h. The autoclave was vented off, flushed with nitrogen and the reaction mixture was directly analyzed by ^{1}H NMR to determine the conversion of the olefin into the product. The crude was then dried under reduced pressure and filtered off a plug of silica gel eluting with CH_2Cl_2/Et_2O 1:1 and finally the solution was dried up in vacuum. The product was eventually obtained after column chromatography on silica gel.

Trimethyl ethane-1,1,2-tricarboxylate (6a): Synthesized following the general procedure. The compound **6a** has been purified by column chromatography petroleum ether/CH_2Cl_2 30:70, obtaining a colorless oil; yield: 89% (0.363 g). Spectral data were identical to the previously reported literature data.[175]

1-Benzyl 1,2-dimethyl ethane-1,1,2-tricarboxylate (6b): Synthesized following the general procedure. The compound **6b** has been purified by column chromatography petroleum ether/CH_2Cl_2 50:50 then 30:70, obtaining a colorless oil; yield: 91% (0.510 g).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H), 5.22 (d, J = 12.3 Hz, 1H), 5.17 (d, J = 12.3 Hz, 1H), 3.91 (t, J = 7.4 Hz, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 2.95 (d, J = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 168.8, 168.2, 135.3, 128.7, 128.5, 128.2, 67.6, 53.0, 52.2, 47.8, 33.0.
ESI-MS: m/z = 281 $[M+H]^+$.

1,2-dimethyl 1-phenyl ethane-1,1,2-tricarboxylate (6c): Following the general procedure, the olefin **5c** was converted for 94%. The compound **6c** has been purified by column chromatography petroleum ether/CH_2Cl_2 20:80, obtaining a pale yellow oil; yield: 90% (0.479 g).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 1H), 7.28 – 7.22 (m, 1H), 7.14 – 7.09 (m, 1H), 4.10 (dd, J = 7.8, 7.0 Hz, 1H), 3.83 (s, 1H), 3.74 (s, 1H), 3.10 (dd, J = 17.4, 7.9 Hz, 1H), 3.04 (dd, J = 17.4, 6.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 168.6, 167.2, 150.6, 129.6, 126.4, 121.4, 53.2, 52.4, 47.9, 33.1.
ESI-MS: m/z = 267 $[M+H]^+$.

1,2-Dimethyl 1-octadecyl ethane-1,1,2-tricarboxylate (6d): Synthesized following the general procedure, but adding the solid olefin **5d** directly into the autoclave together with *p*-benzoquinone and *p*-TSA. The compound **6d** has been purified by column chromatography petroleum ether/CH_2Cl_2 50:50 then 20:80, obtaining a white powder; yield: 92% (0.814 g).
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 – 4.08 (m, 2H), 3.85 (t, J = 7.4 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 2.94 (d, J = 7.4 Hz, 2H), 1.68 – 1.58 (m, 2H), 1.36 – 1.18 (m, 30H), 0.87 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 169.1, 168.5, 66.2, 52.9, 52.2, 47.8, 33.1, 32.1, 29.8 (8C), 29.72, 29.67, 29.5, 29.3, 28.6, 25.9, 22.8, 14.3.
ESI-MS: m/z = 443 $[M+H]^+$.

1-(*tert*-butyl) 1,2-Dimethyl ethane-1,1,2-tricarboxylate (6e): Following the general procedure, but using 5 mol% of catalyst loading, olefin **5e** was converted for 97%. The compound **6e** has been purified by column chromatography petroleum ether/CH_2Cl_2 30:70, obtaining a colorless oil; yield: 93% (0.460 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (t, J = 7.4 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 2.89 (d, J = 7.4 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 169.5, 167.4, 82.6, 52.8, 52.2, 48.8, 33.1, 28.0.
ESI-MS: m/z = 269 $[M+Na]^+$.

1,2-Diisopropyl 1-methyl ethane-1,1,2-tricarboxylate (6f): Following the general procedure, but using 5 mol% of catalyst loading and *i*-PrOH as nucleophile, olefin **5a** was converted for 40%. The compound **6f** has been purified by column chromatography petroleum ether/CH_2Cl_2 50:50 then 30:70, obtaining a yellow oil; yield: 32% (0.166 g).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 – 4.94 (m, 2H), 3.80 (t, J = 7.5 Hz, 1H), 3.75 (s, 3H), 2.88 (d, J = 7.5 Hz, 2H), 1.27 – 1.18 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 169.2, 168.0, 69.6, 68.7, 52.8, 48.1, 33.6, 21.9 (2C), 21.7, 21.6.
ESI-MS: m/z = 261 $[M+H]^+$.

1,2-Dibenzyl 1-methyl ethane-1,1,2-tricarboxylate (6g): Synthesized following the general procedure and using BnOH as nucleophile. The compound **6g** has been purified by column chromatography petroleum ether/CH_2Cl_2 50:50 then 20:80, obtaining a colorless oil; yield: 88% (0.627 g).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 10H), 5.20 (d, J = 12.3 Hz, 1H), 5.15 (d, J = 12.3 Hz, 1H), 5.11 (s, 2H), 3.93 (t, J = 7.4 Hz, 1H), 3.70 (s, 3H), 3.01 (d, J = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 168.8, 168.2, 135.5, 135.3, 128.7 (2C), 128.54, 128.50, 128.4, 128.3, 67.6, 67.0, 52.9, 47.8, 33.3.
ESI-MS: m/z = 379 $[M+Na]^+$.

Dimethyl 2-carbamoylsuccinate (8a): Synthesized following the general procedure, but adding the solid olefin **7a** directly into the autoclave together with *p*-benzoquinone and *p*-TSA and without filtering on a plug of silica gel. The compound **8a** has been purified by column chromatography petroleum ether/ethyl acetate 50:50 then 30:70, obtaining a white powder; yield: 91% (0.344 g).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (bs, 1H), 5.77 (bs, 1H), 3.77 (s, 3H), 3.74 (t, J = 6.8 Hz, 1H), 3.69 (s, 3H), 3.00 (d, J = 6.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 170.1, 169.0, 53.1, 52.2, 47.8, 32.5.
ESI-MS: m/z = 190 $[M+H]^+$.

Dimethyl 2-(isopropylcarbamoyl)succinate (8b): Synthesized following the general procedure, but adding the solid olefin **7b** directly into the autoclave together with *p*-benzoquinone and *p*-TSA. The compound **8b** has been purified by column chromatography petroleum ether/ethyl acetate 30:70, obtaining a white powder; yield: 92% (0.428 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (bs, 1H), 4.05 (m, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.62 (t, J = 6.9 Hz, 1H), 2.98 (d, J = 6.9 Hz, 2H), 1.16 (d, J = 6.6 Hz, 2H), 1.15 (d, J = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 170.5, 165.7, 52.9, 52.1, 48.4, 42.1, 32.7, 22.64, 22.59.

ESI-MS: m/z = 232 $[M+H]^+$.

Dimethyl 2-(phenylcarbamoyl)succinate (8c): Synthesized following the general procedure. The compound **8c** has been purified by column chromatography petroleum ether/ethyl acetate 20:80, obtaining a white powder; yield: 90% (0.477 g). Spectral data were identical to the previously reported literature data.[176]

Dimethyl 2-(*tert*-butylcarbamoyl)succinate (8d): Following the general procedure, but adding the solid olefin **7d** directly into the autoclave together with *p*-benzoquinone and *p*-TSA, a conversion of 85% has been achieved. The compound **8d** has been purified by column chromatography petroleum ether/CH_2Cl_2 50:50 then 30:70, obtaining a white powder; yield: 78% (0.383 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (bs, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.58 (t, J = 6.9 Hz, 1H), 2.95 (d, J = 6.9 Hz, 2H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 170.6, 165.6, 52.9, 52.1, 51.8, 49.0, 32.6, 28.7.

ESI-MS: m/z = 246 $[M+H]^+$.

Dimethyl 2-((2-hydroxyethyl)carbamoyl)succinate (8e): Synthesized following the general procedure, without filtering on a plug of silica gel. The compound **8e** has been purified by column chromatography petroleum ether/ethyl acetate 20:80, obtaining a pale yellow oil; yield: 98% (0.457 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (bs, 1H), 3.75 (s, 3H), 3.72 – 3.66 (m, 3H), 3.68 (s, 3H), 3.50 – 3.35 (m, 2H), 3.00 (d, J = 6.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 170.2, 167.9, 61.8, 53.1, 52.3, 48.1, 42.8, 32.7.

ESI-MS: m/z = 234 $[M+H]^+$.

Dimethyl 2-(morpholine-4-carbonyl)succinate (8f): Synthesized following the general procedure. The compound **8f** has been purified by column chromatography petroleum ether/ethyl acetate 50:50 then 40:60, obtaining a yellow oil; yield: 98% (0.508 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (dd, J = 8.3, 5.8 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.80 – 3.52 (m, 8H), 3.08 (dd, J = 17.5, 8.4 Hz, 1H), 2.97 (dd, J = 17.5, 5.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 169.1, 166.3, 66.8, 66.6, 53.0, 52.2, 46.9, 44.1, 43.0, 33.3.

ESI-MS: m/z = 260 $[M+H]^+$.

Dimethyl 2-(dimethylcarbamoyl)succinate (8g): Synthesized following the general procedure. The compound **8g** has been purified by column chromatography petroleum ether/ethyl acetate 70:30 then 50:50, obtaining a yellow oil; yield: 95% (0.414 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (dd, J = 8.3, 5.9 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.17 (s, 3H), 3.05 (dd, J = 17.5, 8.3 Hz, 1H), 3.00 (s, 3H), 2.95 (dd, J = 17.5, 5.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 169.4, 167.8, 52.8, 52.0, 44.4, 37.8, 36.2, 33.4.

ESI-MS: m/z = 218 $[M+H]^+$.

Diisopropyl 2-(dimethylcarbamoyl)succinate (8h): Following the general procedure and using *i*-PrOH as nucleophile, olefin **7g** was converted for 90%. The compound **8h** has been purified by column chromatography petroleum ether/ethyl acetate 70:30 then 50:50, obtaining a yellow oil; yield: 88% (0.481 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (hept, J = 6.3 Hz, 1H), 4.97 (hept, J = 6.3 Hz, 1H), 4.08 (dd, J = 8.3, 5.9 Hz, 1H), 3.15 (s, 3H), 2.98 (dd, J = 17.3, 8.4 Hz, 1H), 2.98 (s, 3H), 2.88 (dd, J = 17.4, 5.9 Hz, 1H), 1.24 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.3 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 168.5, 168.0, 69.4, 68.4, 45.0, 37.9, 36.2, 34.0, 21.9 (2C), 21.8, 21.7.

ESI-MS: m/z = 274 $[M+H]^+$.

Dibenzyl 2-(dimethylcarbamoyl)succinate (8i): Synthesized following the general procedure and using BnOH as nucleophile. The compound **8i** has been purified by column chromatography petroleum ether/CH_2Cl_2 50:50 then 20:80, obtaining a yellow oil; yield: 93% (0.686 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 10H), 5.18 – 5.03 (m, 4H), 4.19 (dd, J = 8.6, 5.7 Hz, 1H), 3.15 (dd, J = 17.5, 8.6 Hz, 1H), 3.06 (s, 3H), 3.01 (dd, J = 17.5, 5.7 Hz, 1H), 2.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 168.7, 167.6, 135.7, 135.4, 128.71, 128.67, 128.5, 128.4, 128.3, 128.2, 67.4, 66.9, 44.7, 37.8, 36.2, 33.7.
ESI-MS: m/z = 370 $[M+H]^+$.

Di-*tert*-butyl 2-(dimethylcarbamoyl)succinate (8j): Following the general procedure, but using *t*-BuOH as nucleophile and 5 mol% of catalyst loading at 50°C, olefin **7g** was converted for 60%. The compound **8j** has been purified by column chromatography petroleum ether/CH_2Cl_2 20:80 then pure CH_2Cl_2, obtaining a pale orange oil; yield: 40% (0.241 g).
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (dd, J = 8.2, 6.0 Hz, 1H), 3.14 (s, 3H), 2.98 (s, 3H), 2.90 (dd, J = 17.3, 8.2 Hz, 1H), 2.80 (dd, J = 17.3, 6.0 Hz, 1H), 1.43 (s, 9H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 168.4, 168.3, 82.2, 81.0, 45.9, 37.8, 36.2, 34.8, 28.2, 28.0.
ESI-MS: m/z = 302 $[M+H]^+$.

Dimethyl 2-(diethoxyphosphoryl)succinate (10): Synthesized following the general procedure, the olefin **9** was converted for 32%. The compound **10** has been purified by column chromatography petroleum ether/ethyl acetate 70:30 then 50:50, obtaining a colorless oil; yield: 25% (0.141 g). Spectral data were identical to the previously reported literature data.[177]

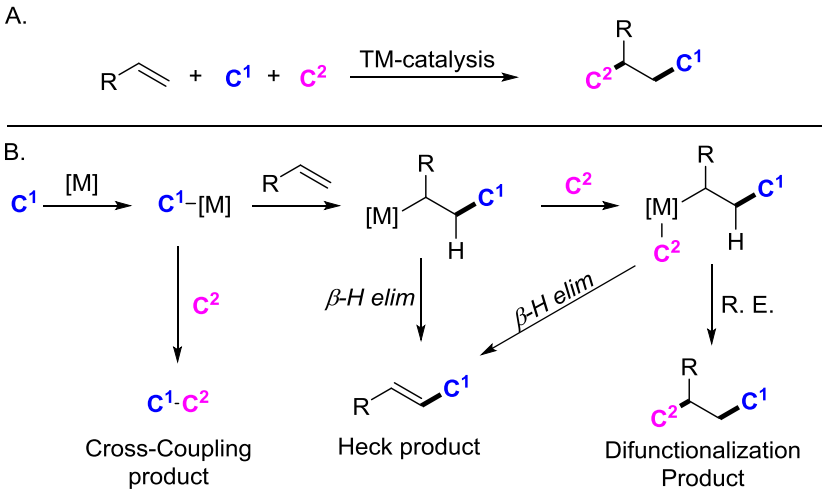
Section 2

Difunctionalization of Unactivated Alkenes Initiated by Unstabilized Ketone Enolates

4. General Introduction

4.1 Intermolecular Three Components Dicarbofunctionalization of Unactivated Alkenes

Difunctionalization of unactivated alkenes catalyzed by transition metals is a powerful synthetic method, which is generally utilized to introduce in adjacent carbons two functionalities at the same time, in order to rapidly build complex molecular architectures.[178] Dicarbofunctionalization reactions across an alkene to generate two new carbon-carbon bonds has recently gained tremendous interest in organic, pharmaceutical and synthetic chemistry (Scheme 45, A).

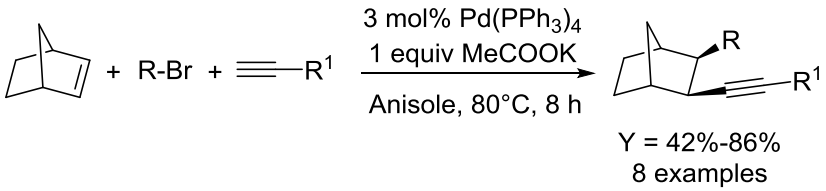


Scheme 45 – General scheme for dicarbofunctionalization of olefins (A) and simplified schematic mechanism and side reaction (B). C^1 = carbon source I; C^2 = carbon source II; [M] = metal; β-H elim = β-hydride elimination; R.E. = Reductive Elimination.

The difficulty in developing this kind of reaction is mainly derived from the challenge of avoiding β-H elimination, which generally follows a lower energy process than installing a second carbon entity C^2 (Scheme 45, B).[179]

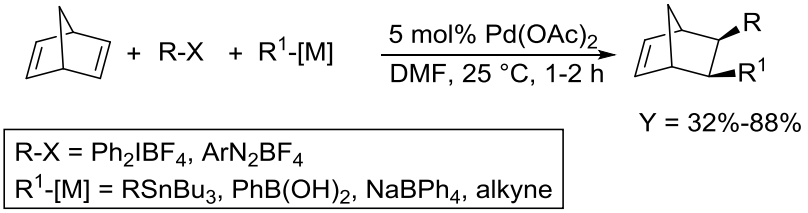
Bis-alkoxycarbonylation reaction of olefins, widely discussed in the *Section 1* of this thesis, is an example of an intermolecular dicarbofunctionalization of alkenes. However, a wide range of electrophiles, like organohalides or triflates, and nucleophiles, such as organometallic reagents or enolates, can be utilized as the carbon source instead of carbon monoxide, and different functionalities have been installed across the C-C double bond in the last few decades.

In early reports of olefin difunctionalization, geometrically strained molecules such as norbornene were utilized to avoid problems deriving from β-H elimination. In 1982, a Pd-catalyzed dicarbofunctionalization of norbornene with organobromides and alkynes (Scheme 46) has been reported by Chiusoli et al.[180]



Scheme 46 - Difunctionalization of norbornene using organobromides and alkynes

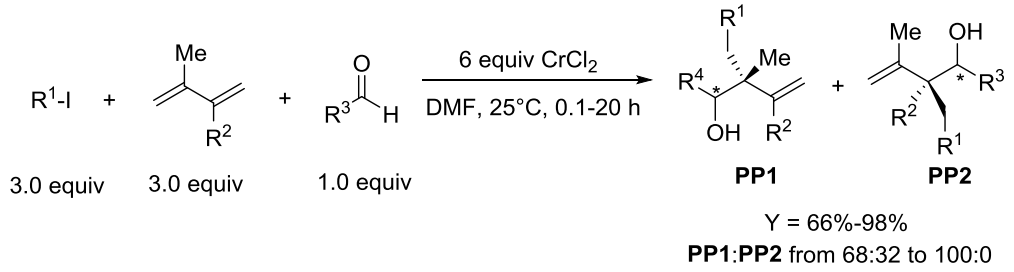
Cis-exo-difunctionalized products have been achieved in good to excellent yields. Later, the same transformation was published by the same authors using Ni catalysis.[181] After this initial discovery, norbornene type molecules has been difunctionalized with a large number of electrophiles and nucleophiles, generally affording *cis-exo*-products, usually employing Pd catalysts.[182] Norbornadiene has also been utilized in such reaction, as demonstrated by Kang et al. in 1998, in which Pd-catalysts could catalyze the selective difunctionalization of just one olefin in norbornadiene with a variety of nucleophiles such as alkynes, organostannes and organoborates, utilizing ArN_2BF_4 or Ph_2IBF_4 as electrophiles (Scheme 47).[183]



Scheme 47 – Difunctionalization of on olefin in norbornadiene

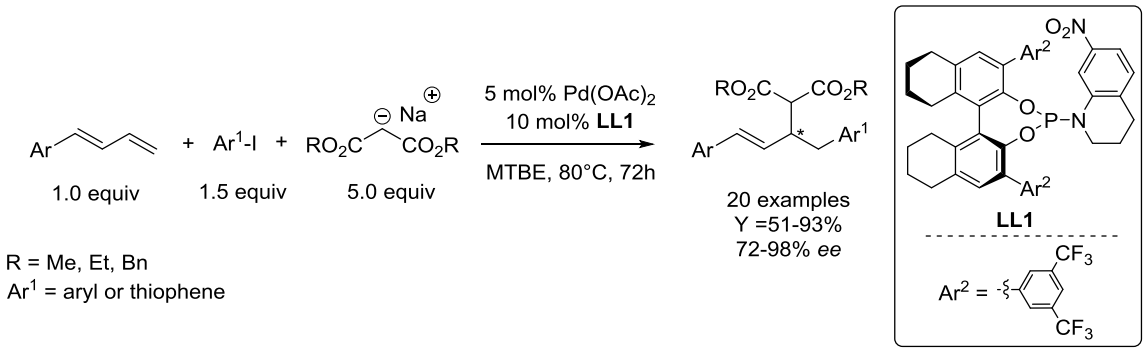
A similar reaction, was reported later by Goodson and coworkers, using aryl halides and aryl boronic acids.[184]

In 1998, Takai and coworkers reported a 1,2-difunctionalization of 1,3-dienes with alkyl halides and benzaldehyde. Unfortunately the reaction required a great excess of $CrCl_2$ in order to achieve good yields of products (Scheme 48).[185]



Scheme 48 – 1,2-difunctionalization of 1,3-dienes using $CrCl_2$

After that, many examples concerning 1,3-dienes have also been published.[186] More recently, dialkyl malonates and aryl iodides were used in the 1,2-difunctionalization of 1,3-dienes (Scheme 49).[187]

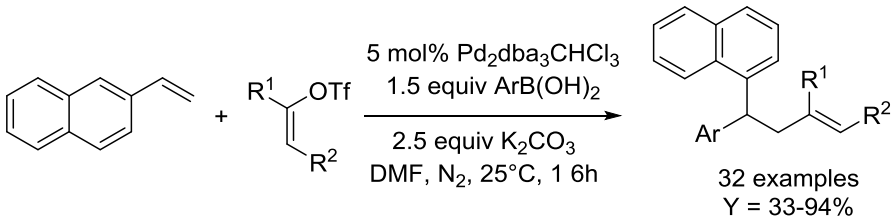


Scheme 49 – Pd-catalyzed 1,2-difunctialization of 1,3-dienes using malonates and aryl iodides

This reaction proceeded *via* a Pd-catalyzed cascade arylation and asymmetric allylic alkylation reaction. A moderate to high degree of enantioselectivity was obtained using a H_8-BINOL-based phosphoramidite ligand (**LL1**, Scheme 49).

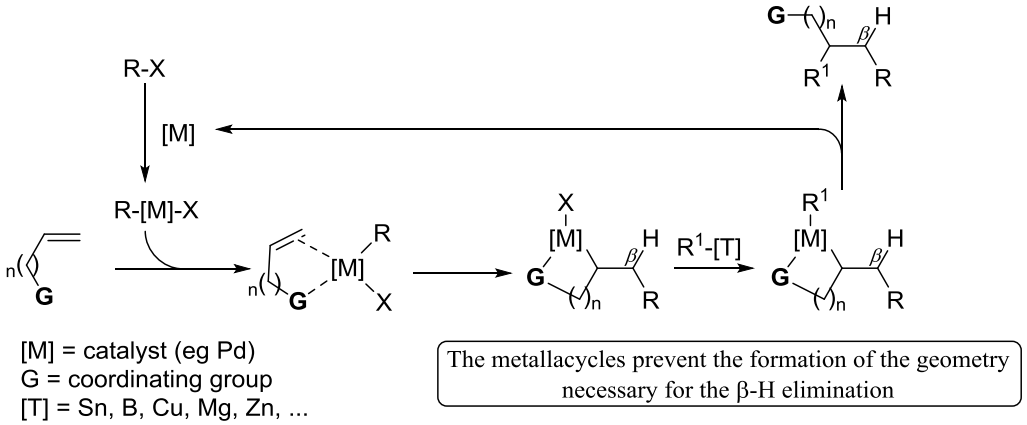
However, in some cases, difunctionalization of 1,3-dienes can lead to the formation of 1,4-functionalized products.[188]

The vinyl group of styrene derivatives can also participate in difunctionalization reactions, as reported by Song and co-workers. Here, vinyl triflates and arylboronic acids were employed and $Pd_2(dba)_3$ was used as catalyst, in the presence of styrenes (Scheme 50).[189]



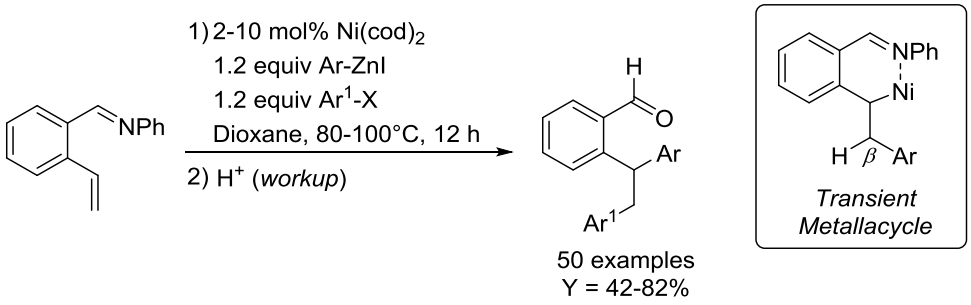
Scheme 50 – Difunctionalization of styrene derivatives

Recently, the possibility to use a removable coordinating group to prevent β-H elimination through the formation of transient metallacycles has been reported (Scheme 51)[190].



Scheme 51 - General olefin's difunctionalization pathway, using a removable coordinating group (**G**).

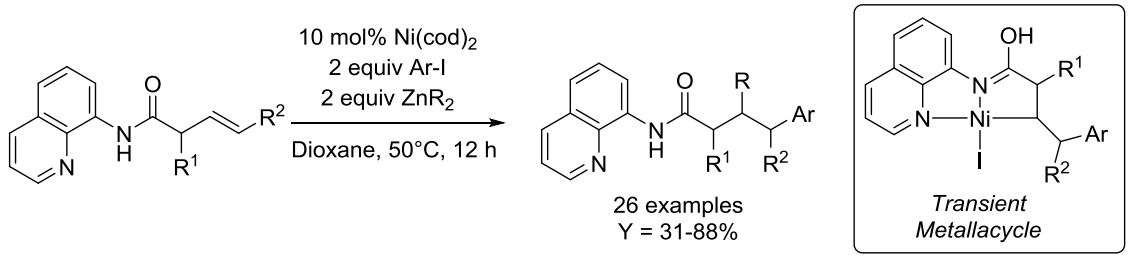
Based on this idea, the Giri group reported the 1,2-dicarbofunctionalization of 2-vinylbenzaldehyde derivatives using aryl halides or triflates (Ar^1-X) together with arylzinc reagents (Ar-ZnI) under Ni catalysis (Scheme 52).[191]



Scheme 52 - Ni-catalyzed diarylation of olefins in styrenes via coordination-assisted formation of transient metallacycles

Here, aldehydes were first converted into imines, which, upon coordination to the metal, facilitate the migratory insertion of Ar^1 on the olefin and transiently stabilized the resulting metallacycle intermediate, favoring the transmetalation/reductive elimination steps respect to the β-H elimination. Eventually, after the dicarbofunctionalization reaction was complete, through a simple acidic workup at room temperature, diarylated aldehyde products were obtained. The same authors reported an analogous strategy, using pyridine functionality as a coordinating group.[192]

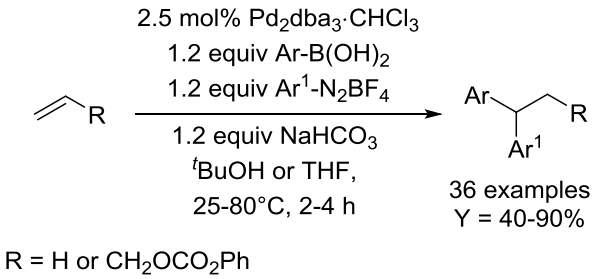
The use of the Daugulis auxiliary (8-aminoquinoline) has also been demonstrated to be a powerful bidentate coordination platform to form stable intermediates that resist β-H elimination.[193] For example, in a recent study, Engle and coworkers reported the Ni-catalyzed dicarbofunctionalization of olefins contained in 8-aminoquinolinamides (scheme 53), using aryl iodides as electrophiles and dialkylzinc reagents as nucleophiles. [194]



Scheme 53 – Alkylarylation of olefins in 8-aminoquinolinamides catalyzed by Ni

Different methods have been reported using such strategies.[195]

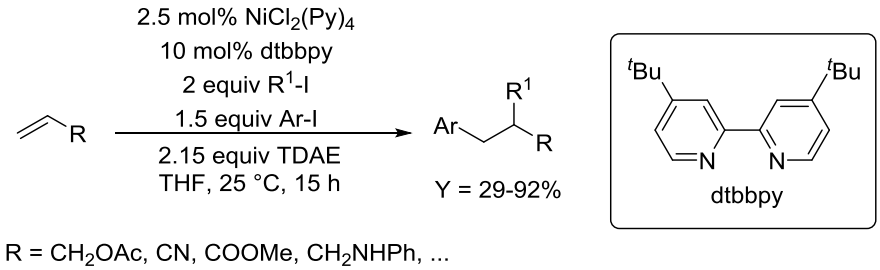
Difunctionalization of unactivated olefins in simple alkenes are also known, however, these types of substrates generally lead to the formation of 1,1-difunctionalized products[196] or 1,3-difunctionalizated products[197] For example, Sigman and coworkers employed ArN_2BF_4 and $ArB(OH)_2$ to 1,1-difunctionalize unactivated olefins in allyl carbonates using $Pd_2(dba)_3$ as a catalyst (Scheme 54).[198]



Scheme 54 - 1,1-Difunctionalization of terminal olefins with aryldiazonium salts and arylboronic acids.

Other dicarbofunctionalization reactions involving other transition metals, such as copper[199] and iron,[200] have been reported in the last five years. The use of these metals, as well as nickel, is particularly interesting due to the possibility of involving one-electron radical mechanisms.

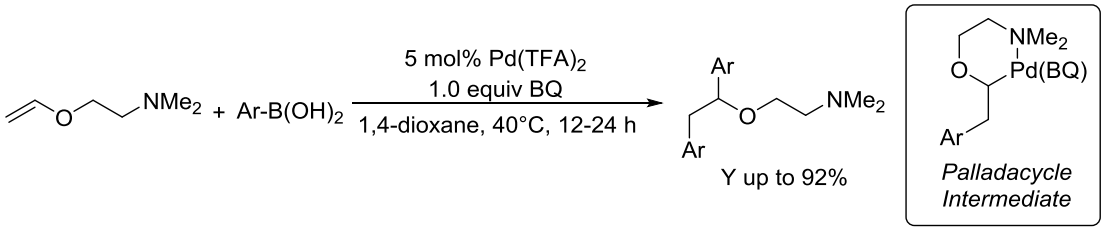
Some efforts in the difunctionalization of olefins by reductive couplings, in which both carbon entities are derived from organohalides, have been made.[201] For example, Nevado et al. recently reported a Ni-catalyzed reductive difunctionalization of unactivated or mildly activated olefins in allylic compounds, vinylcarboxylates and enamides (Scheme 55).[202]



Scheme 55 - Ni-catalyzed reductive alkylarylation of alkenes.

The reaction was proposed to proceed *via* a radical process and a stoichiometric reductant (TDAE) was required to reduce Ni(II) to Ni(0) after a catalytic cycle.

On the other hand, in few cases organometallic reagents could be used as a sole carbon source. Similarly to the oxidative carbonylations, an oxidant is required to regenerate the active metal species after the reductive elimination of the product,[203] as reported, for example, by Larhed and coworkers.[204] Here a Pd-catalyzed oxidative 1,2-diarylation of terminal olefins in vinyl ethers with arylboronic acids was developed, in the presence of stoichiometric amount of benzoquinone (Scheme 56).

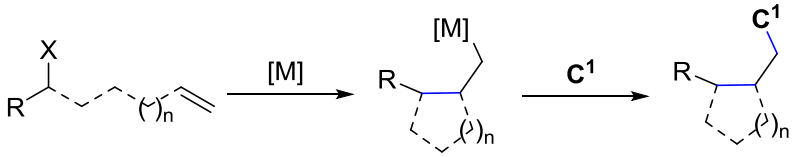


Scheme 56 - Coordination-assisted oxidative diarylation of vinyl ethers catalyzed by $Pd(TFA)_2$

The presence of the coordinating *N*,*N*-dialkylamino group in the reagents was found to be crucial in order to prevent β-H elimination pathways.

4.2 Difunctionalization of Unactivated Tethered Alkenes through Cyclization Reactions

The presence of carbocycles and heterocycles in drugs, drug targets and natural products.[205] clearly account for the interest that cyclization reactions have gained in the last decade. Transition metal-catalyzed cyclization/cross-coupling provides a noteworthy pathway to from complex cyclic architectures, allowing the use of tethered olefins for cyclization *via* radical or migratory insertion processes.[206] Generally, after cyclization upon tethered olefins, the generated C(sp^3)-[M] intermediate is intercepted, before the β-H elimination, with organohalides, enolates or organometallic reagents to realize 1,2-dicarbofunctionalization, leading to the more complex cyclic scaffold (Scheme 57).



Scheme 57 – General scheme for difunctionalization of unactivated tethered alkenes. C^1 = carbon source I. X could be a metal or an halide.

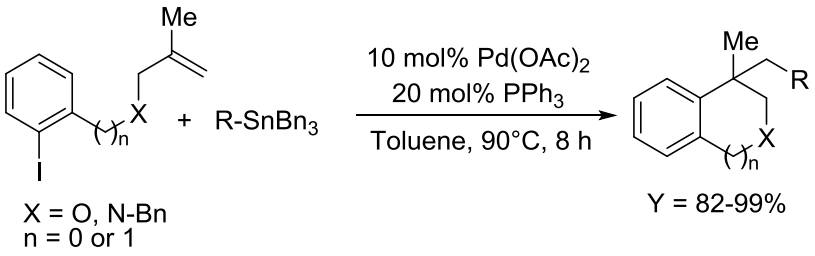
In the following chapters these reaction will be discussed based on the functional group tethered to the olefin functionality.

4.2.1 Addition to Olefins Tethered to Electrophiles

Different strategies have been developed during the years, mainly based on the designs of favorable reaction conditions and catalysts, in order to disfavor the β-H elimination pathway with respect to the difunctionalization. One of these strategies is to conduct the reaction in the presence of carbon monoxide, which can efficiently intercept the C(sp^3)-[M] intermediates by insertion of CO before the β-H elimination occurs, leading to the formation of a C(sp^3)CO-[M] species, which cannot undergoes β-H elimination anymore. Then, different nucleophiles, such as amines, alcohols or organometallic reagents, can react with this acyl-[M] species, affording the difunctionalized product. However carbonylation reactions are generally reported apart and have been widely described in the *Section 1* of this thesis.

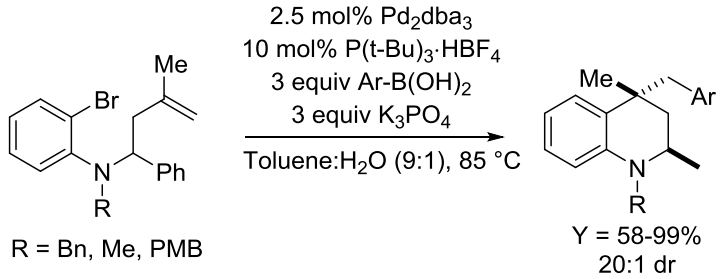
An alternative strategy is to generate C(sp^3)-[M] intermediates lacking β-hydrogens, which cannot undergo a β-H elimination, such as using 2,2-disubstituted tethered olefins.

In a pioneering paper from Grigg et al., reported in 1988, such idea was demonstrated. Here, starting from olefins tethered to aryl halides, the C(sp^3)-PdX species were intercepted directly by organotin reagents, achieving 5- and 6-membered cyclization/cross-coupling products (Scheme 58).[207]



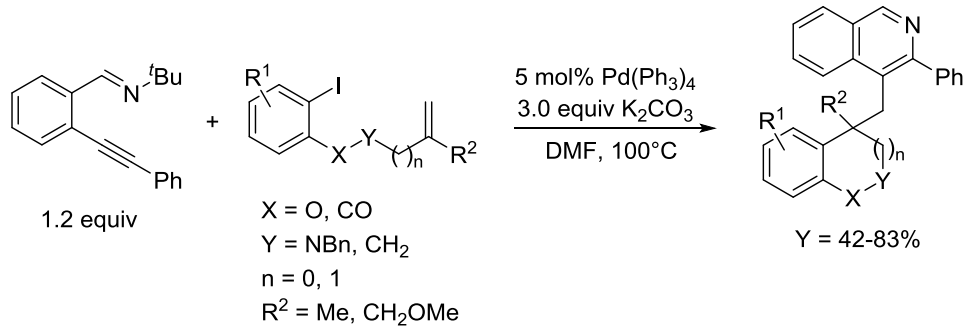
Scheme 58 - Cyclization/cross-coupling with organotin reagents

Later, they further expanded the scope of cyclization/cross-coupling of olefins tethered to aryl iodides by utilizing aryl- and vinylboronic acids instead of organotin compounds.[208] Wilson disclosed a diastereoselective dicarbofunctionalization of olefins tethered to aryl bromides with arylboronic acids, for the selective formation of six-membered products catalyzed by Pd(0)/P(*t*-Bu)$_3$ complexes (Scheme 59).[209]



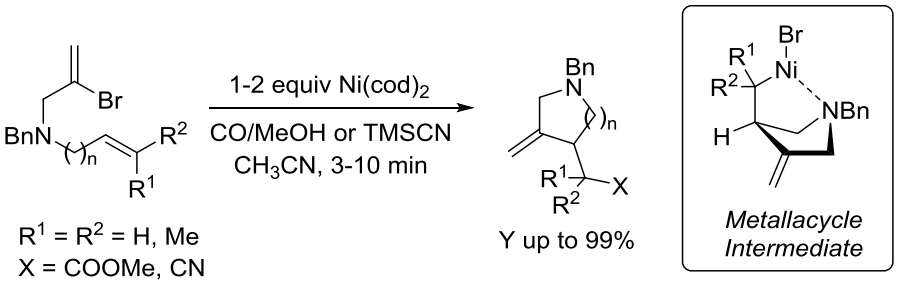
Scheme 59 - Cyclization/cross-coupling with ArB(OH)$_2$ to generate 6-membered ring.

Besides organometallic reagents, other species have been employed with 2,2-disubstituted olefins tethered to electrophiles, such as (hetero)arenes, alkenes or alkynes.[210] For example, Yao and coworkers have been recently employed a Pd catalyst with 2-alkynylbenzylimines to form differently substituted isoquinolines (Scheme 60).[211]



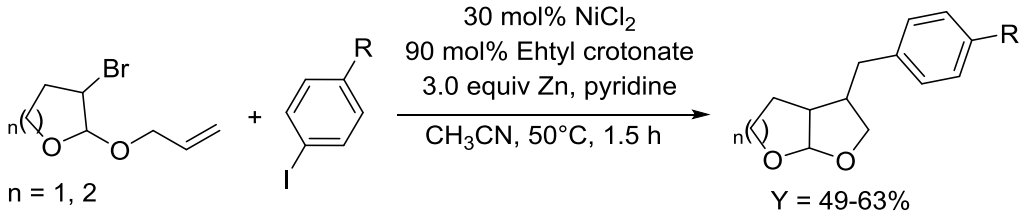
Scheme 60 - Cyclization/coupling with alkynes.

However, dicarbofunctionalization of olefins tethered to substrates that would generate C(sp^3)-[M] intermediates containing β-hydrogens, is also possible. In this case, usually appropriately located relative to the olefin, an heteroatom can stabilize the C(sp^3)-[M] intermediate by coordination, avoiding otherwise geometrically favorable β-H elimination. After the first example reported by Delgado et al. in 1994, in which cyclization/carbonylation and cyclization/cyanation of olefins tethered to *N*-benzylated vinyl bromides proceeded in presence of stoichiometric amount of Ni (Scheme 61),[212] different examples have been reported, utilizing various nucleophiles and electrophiles.[213]



Scheme 61 - Coordination-assisted Ni-promoted cyclization/cyanation and carbonylation.

Interestingly, Peng and coworkers demonstrated that a cyclization/cross-coupling could also be performed reductively by utilizing olefin-tethered alkyl bromides with aryl iodides (Scheme 62).[214]



Scheme 62 - Reductive cyclization/cross-coupling

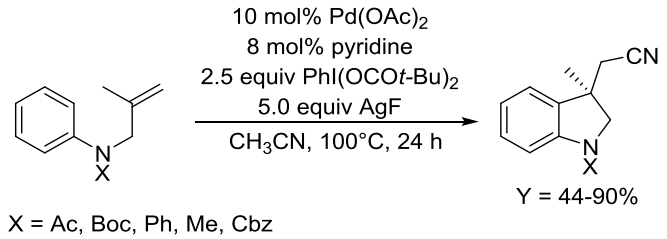
The reaction, catalyzed by $NiCl_2$ (30 mol%), was proposed to proceed *via* cyclization of alkyl radicals (with the formation of a Ni(I)Br species), which then, by radical recombination, generate an alkyl-Ni(II)-Br intermediate. This species was further reduced to alkyl-Ni(I) intermediates by the zinc, before reacting with aryl iodides. More than a stoichiometric amount of Zn as reductant was necessary.

4.2.2 Addition to Olefin by C-H bond Cleavage

Recently, several examples have revealed that aryl C-H bonds can be utilized as carbon nucleophiles for addition to alkenes by electrophilic carbometalation or by C-H activation, in order to generate a C(sp^3)-[M] intermediate *in situ* which can be then trapped with various reagents.

As already described, in 2004 Liu and coworkers, reported a Pd-catalyzed cyclization/carbonylation of indoles bearing tethered olefins (Scheme 14).[54] The reaction proceeded by activating the terminal olefin with Pd(II) (which also acts as a Lewis acid[215]) followed by the attack of the coordinated olefin by the indole at C-3, generating a C(sp^3)-PdX species which react with CO faster than the β-H elimination pathway.

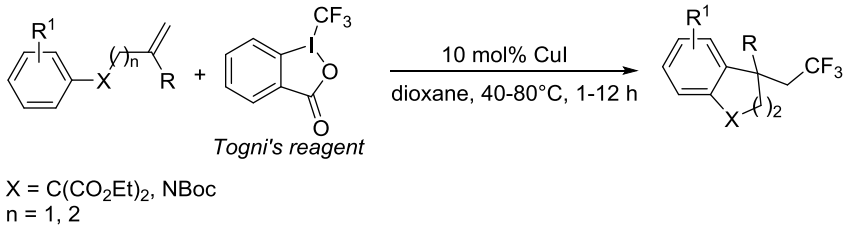
Later, the difunctionalization of *N*-allylaniline derivatives using CH_3CN, as CN source, was described. Here, the *N*-group was in *ortho* position respect to the activated aromatic C-H bond (Scheme 63).[216]



Scheme 63 - Pd-catalyzed aryl C-H cyclization/cyanomethylation.

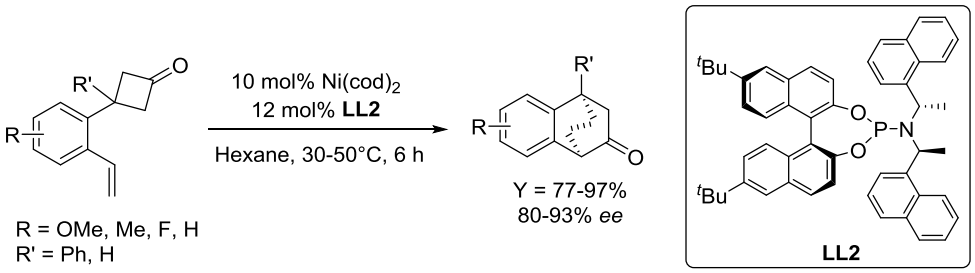
Since in this study has been shown that the rate determining step was the cleavage of the C-H bond in acetonitrile, the presence of $PhI(OPiv)_2$ and AgF was necessary to achieve high selectivity and yields (up to 90%).

Terminal olefins tethered to arenes and anilines were also employed by Sodeoka et al. in a Cu-catalyzed cyclization/trifluoromethylation reaction. Here, Togni's reagent was used as CF_3 source and various 5- and 6-membered (hetero)cycles were achieved (Scheme 64).[217]



Scheme 64 - Cu-catalyzed aryl C-H cyclization/trifluoromethylation

Interestingly, few examples have been reported on the difunctionalization of tethered olefins through C-C[218] and C-N[219] bond cleavage. For example, in 2012 a Ni-catalyst bearing a chiral phosphoramidite ligand, has shown to be efficient in breaking a C-C bond in cyclobutanone, followed by the stereoselective addition of the carbon fragments across the vinyl group of tethered styrene derivatives, leading to chiral benzobicyclo[2.2.2]octenones (Scheme 65).[220]

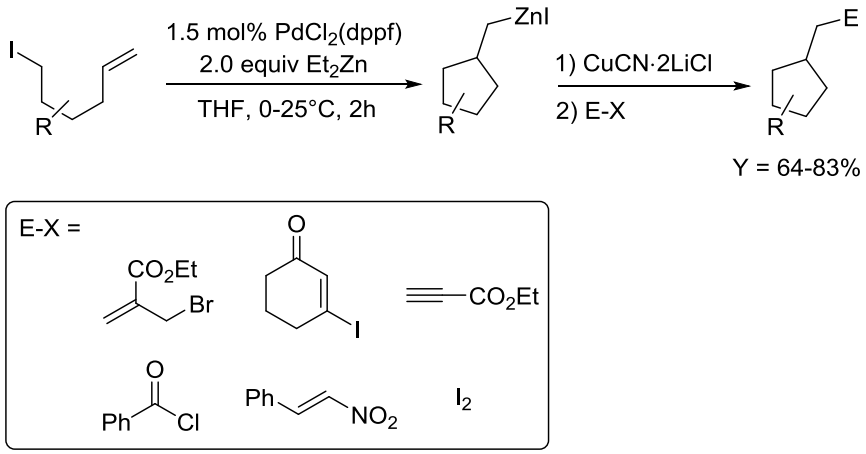


Scheme 65- Ni-catalyzed asymmetric intramolecular alkene insertion reaction into cyclobutanones

4.2.3 Addition to Olefins Tethered to Nucleophiles

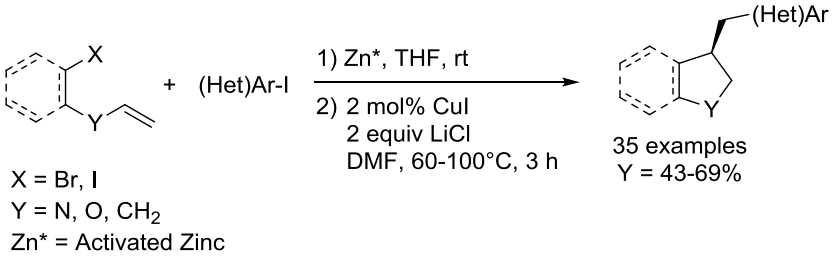
Recently, studies regarding alkenes tethered to organometallic reagents, which can be involved in cyclization/cross-coupling reactions with organohalides as intermolecular electrophiles, have been reported. In 1993, Knochel et al. demonstrated that cyclized

alkylzinc reagents, formed by a Pd-catalyzed radical cyclization of olefin-tethered alkyl halides in the presence of Et_2Zn, can react with a variety of carbon electrophiles, using a stoichiometric Cu-catalyst, to achieve dicarbofunctionalized products (Scheme 66).[221]



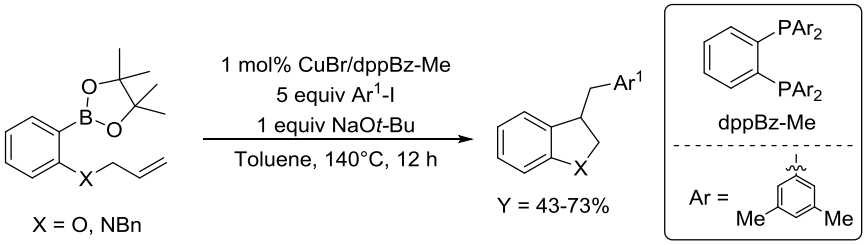
Scheme 66 - Pd-catalyzed carbozincation of alkyl iodides, followed by their Cu-mediated trapping with an electrophiles (E^+).

An analogous reaction was then developed using Ni.[222] Similarly, the Giri group developed a Cu-catalyzed cyclization/cross-coupling of aryl iodides with alkyl and arylzinc reagents derived from olefin-tethered alkyl and aryl halides leading to the synthesis of a variety of carbocycles and heterocycles (Scheme 67).[223] Mechanistic studies revealed that the reaction proceeded by radical process.



Scheme 67 - Tandem cyclization/cross-coupling of alkylzinc reagents with aryl iodides, catalyzed by CuI.

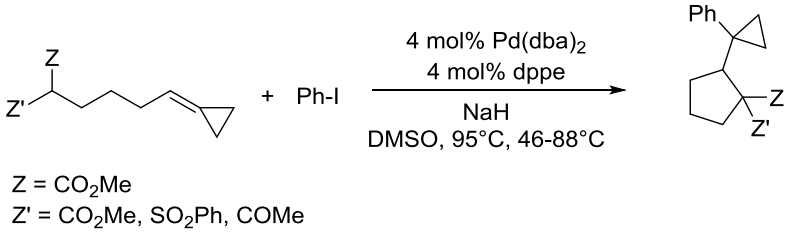
Besides alkylzinc reagents, the use of organoboron compounds have been also investigated.[224] For example, a Cu-catalyzed cyclization/cross-coupling of olefin-tethered arylboronates with aryl iodides was described in 2014 by Brown and coworkers (Scheme 68).[225]



Scheme 68 - Diarylation of alkenes by a Cu-catalyzed migratory insertion/cross-coupling cascade.

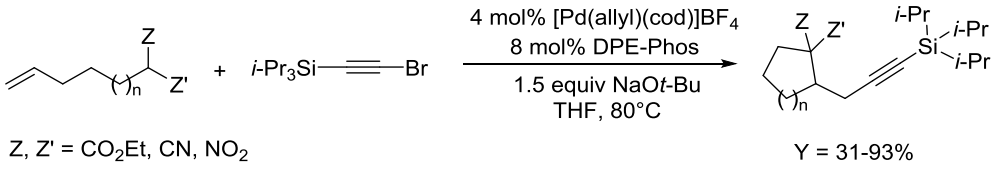
Unlike olefin-tethered arylzinc reagents, in which the cyclization is usually the first step, here, aryl-Bpin first underwent transmetalation with the Cu species, followed by migratory insertion of the tethered olefin into the aryl-Cu bond.

Enolates can also be employed as efficient nucleophiles in dicarbofunctionalization reactions. Balme et al. reported a dicarbofunctionalization of olefins tethered to dicarbonyl compounds containing an acidic α-hydrogen, using aryl iodides as electrophiles (Scheme 69).[226]



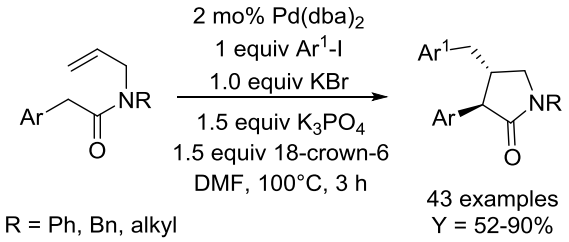
Scheme 69 - Cyclization/cross-coupling of olefin-tethered enolates with aryl iodides

In 1997 it has been reported that 3-benzyltetrahydrofuran derivatives can be obtained from the conjugate addition of allyl alcohols to α,β-unsaturated dicarbonyl compounds, with the *in situ* formation of enolate species.[227] The use of olefin-tethered dicarbonyl enolates was also reported by Waser et al. using a bromoalkynylsilane as an electrophile (Scheme 70).[228]



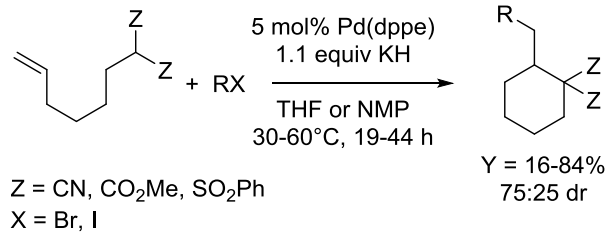
Scheme 70 - Cyclization/cross-coupling of olefin-tethered enolates with bromoalkynylsilane.

More recently, Giri developed a Pd-catalyzed regioselective 1,2- dicarbofunctionalization of unactivated olefins tethered to enolates with aryl halides (Scheme 71).[229]



Scheme 71 - Tandem Heck reaction/enolate cyclization for olefin difunctionalization.

In this study, *N*-allylarylacetamides were employed in presence of the weak base K_3PO_4 and 18-crown-6, leading to a wide range of 1,3,4-trisubstituted pyrrolidinones. Both electron-rich and deficient aryl halides were successfully utilized. Based on the reaction mechanism proposed by the authors, the Heck products, deriving from β-H elimination, were formed *in situ* and subsequently underwent cyclization with the tethered enolates.
Even if the formation of 5-membered rings is usually preferred, Balme et al. found the conditions for the cyclization/cross-coupling of olefins tethered to enolates in order to form cyclohexyl derivatives (Scheme 72).[230]



Scheme 72 - Cyclization/cross-coupling generating six-membered carbocycles

However, only olefins tethered to dinitrile, cyanoester and cyanosulfonyl groups achieved cyclohexane derivatives. Similar reaction conditions were then applied to substrates bearing both the organohalide and the enolate tethered to olefins, obtaining a bis-cyclized product.[231]

5. Dicarbofunctionalization of Unactivated Alkenes Tethered to Unstabilized Ketone Enolates

5.1 Introduction

Over the past decades, Ni catalysts have received tremendous attention for the formation of new C–C bonds due to nickel Earth abundance, and its distinct reactivity respect to palladium. These features have motivated the development of innovative transformations that add value to readily available starting materials.[54,232] In this regard, the 1,2-difunctionalization of unactivated alkenes is a powerful synthetic strategy that enables the rapid and modular construction of molecular complexity through the simultaneous installation of two new C–C bonds, and provides access to libraries of chemically diverse compounds.[178,233]

Despite the advances in nickel-catalyzed C–C bond formation, alkene difunctionalization reactions that tolerate a broad range of heterocycles remains a significant challenge,[234] due to the stronger bonds that nickel forms to basic heterocycles (relative to palladium), resulting in catalyst deactivation.[235] However, alkene vicinal difunctionalization reactions that can tolerate a diverse range of heterocycles are an important goal of particular importance for the pharmaceutical chemistry.

Alkene difunctionalization initiated by electrophiles is well-established and has led to many elegant synthetic methodologies that demonstrate the breadth of reaction partners that can be used.[178,233] More recently, reductive strategies for alkene difunctionalization employing two electrophiles have also emerged.[202,214a,236]

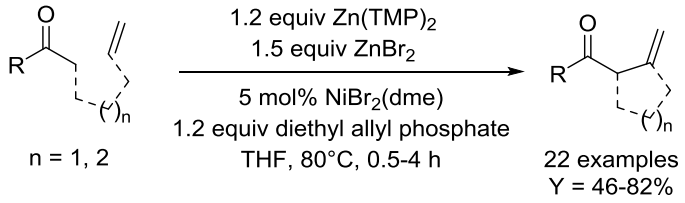
In contrast, first-row transition metal-catalyzed alkene difunctionalization initiated by nucleophiles is much less explored, and is orthogonal to approaches employing halide starting materials.[237] Fu reported an aryl-9-BBN-initiated enantioselective cyclization/alkylation reaction using a nickel/1,2-diamine catalyst system.[224a] Brown demonstrated that aryl boronic ester nucleophiles can initiate a copper-catalyzed cyclization/arylation process with a tethered alkene,[225] while Giri showed that aryl or alkylzinc halides bearing a tethered olefin can engage in a radical cyclization/arylation reaction under copper catalysis.[223] However, alkene difunctionalizations employing enolates as nucleophiles, are limited to doubly activated enolates. Moreover, they have only been achieved using Pd-catalysis.[195c,226b,229,238]

Notwithstanding these recent advances in nucleophile-initiated alkene difunctionalization, there have been no reports employing unstabilized metal enolates as

nucleophilic partners, despite their ease of preparation *via* deprotonation of the corresponding carbonyls. This synthetic strategy could expand the capabilities of alkene difunctionalization reactions by enabling the use of abundantly available ketones as nucleophiles without the need for pre-activation in a separate step.[239]

Monofunctionalization of unactivated alkenes with unstabilized enolates can be achieved via the Conia-Ene reaction,[240] but requires high temperatures and has poor functional group compatibility. Advances in transition metal catalysis have enabled α-alkylation of unstabilized enolates with unactivated olefins under much milder conditions using precious metal catalysts such as Pd,[241] Au,[242] Rh,[243] or Ir,[244] but have not led to alkene difunctionalization reactions.

Considering the results previously reported by the Newhouse group in the oxidative cycloalkenylation of ketones, using allyl-nickel catalysis to promote β-hydride elimination of a primary alkyl nickel species (Scheme 73),[245] we decided to investigate a nickel catalyzed enolate-initiated alkene difunctionalization, in particular focusing on the use of heteroarenes as electrophiles.



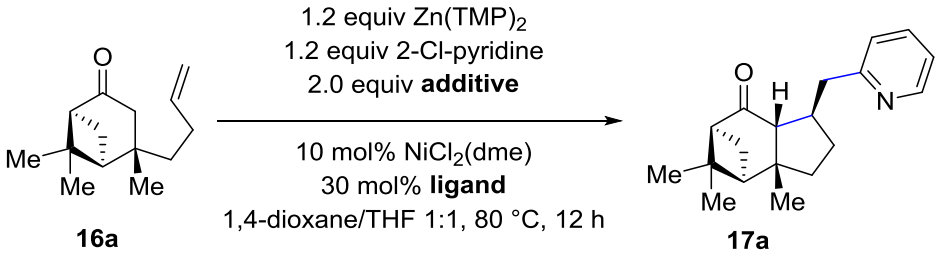
Scheme 73 - Allyl-Ni catalyst for the oxidative cycloalkenylation of ketones.

5.2 Results and Discussion

5.2.1 Optimization of the Reaction Conditions

We started to investigate the alkene difunctionalization utilizing **16a** as model substrate and 2-chloropyridine as model electrophile (Table 17).

Table 17 - Optimization of the alkene difunctionalization reaction



Entry[a]	Ligand	Additive	Yield (%)[b]
1	none	none	33 (100)
2	bpy	none	22 (63)
3	terpy	none	5 (65)
4	box[c]	none	7 (45)
5	pyrox[d]	none	32 (87)
6	pybox[e]	none	30 (68)
7	dppp	none	0 (47)
8	PCy_3	none	35 (100)
9	PPh_3	none	38 (100)
10	P(*p*-OMe-C_6H_4)$_3$	none	55 (100)
11	P(*p*-CF_3-C_6H_4)$_3$	none	60 (100)
12	P(*p*-CF_3-C_6H_4)$_3$	$ZnBr_2$	60 (100)
13	P(*p*-CF_3-C_6H_4)$_3$	$MgBr_2$	63 (100)
14	P(*p*-CF_3-C_6H_4)$_3$	LiBr	45 (75)
15	P(*p*-CF_3-C_6H_4)$_3$	TBABr	75 (92)
16	P(*p*-CF_3-C_6H_4)$_3$	TBAI	80 (95)[f]
17	P(*p*-OMe-C_6H_4)$_3$	TBAI	61 (95)
18	none	TBAI	60 (100)
19[g]	P(*p*-CF_3-C_6H_4)$_3$	TBAI	63 (79)

[a] Reaction performed using **16a** (0.2 mmol-scale), 1.2 equiv of $Zn(TMP)_2$, 1.2 equiv of 2-chloropyridine, 10 mol% of $NiCl_2$(dme), employing 2.0 equiv of the indicated additive and 30 mol% of the indicated ligand, in 1,4-dioxane/THF 1:1 as the reaction medium, at 80 °C for 12 h. [b] ^{1}H-NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. Conversion is indicated in parentheses. [c] 2,2′-Methylenebis[(4*R*,5*S*)-4,5-diphenyl-2-oxazoline]. [d] (*S*)-4-*tert*-Butyl-2-(2-pyridyl)oxazoline. [e] 2,6-Bis[(4*S*)-(−)-isopropyl-2-oxazolin-2-yl]pyridine. [f] Isolated yield. [g] 5 mol% $[Pd(allyl)Cl]_2$ was used as catalyst.

Employing $Zn(TMP)_2$ as base for the formation of the enolate and 10 mol% of $NiCl_2$(dme) as catalyst, the expected product **17a** was obtained in 33% yield in the absence of additive and ligand (entry 1). The formation of the related cycloalkenylation product in 9% yield was observed, together with the fully saturated 5-*exo* cyclization product deriving from the reaction between the enolate and alkene, which was the major by-product (yield: 52%).

We next investigated the effects of ligands and additives in order to promote reductive elimination. Employing bidentate (entries 2, 4 and 5) and tridentate (entries 3 and 6) nitrogen-based ligands, commonly utilized in Ni-catalyzed alkene functionalizations,[178,224a,233] lower yields were achieved. Using the bidentate phosphine ligand dppp, no traces of the expected product was detected (entry 7). Since monodentate trialkyl (entry 8) and triaryl (entry 9) phosphine ligands provided small but quantifiable ligand effects, we continued our study exploring the electronic effects of other commercially available triaryl phosphine ligands. Eventually, a substantial increase in yield, up to 60%, of the difunctionalization product was achieved with the electron-deficient triaryl phosphine P(*p*-CF_3-C_6H_4)$_3$ (entry 11).

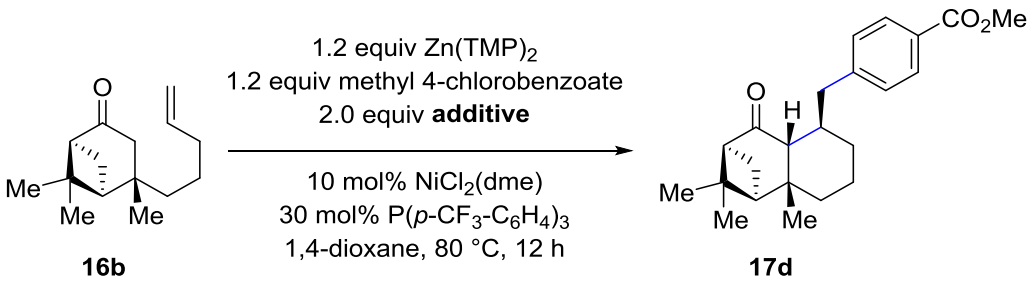
With this optimal ligand in hand and considering that dramatic changes in reactivity and selectivity have been observed when salt additives are employed in transformations involving organozinc species,[245,246] we turned our attention to such promoters.

Unfortunately, the addition of $ZnBr_2$ (entry 12) or $MgBr_2$ (entry 13) did not provide any improvement in the yield of **17a**. Furthermore, depreciation in conversion was observed employing LiBr (entry 14), probably due to a detrimental effect of lithium salts for the initial alkene carbometalation event. This result demonstrates the importance of using lithium salt-free $Zn(TMP)_2$ for this transformation, therefore, considering its limited commercial availability and its inefficient synthesis in the literature,[247] a scalable procedure for accessing this reagent in high yield and purity, has been developed (see *Chapter 5.4.3*). Kinetic enolate formation was necessary for optimal efficiency.[245] Interestingly, no reaction occurred when weak bases (Cs_2CO_3, K_2CO_3, K_3PO_4 and KO*t*Bu), which are known to promote the formation of enolates, were utilized in place of $Zn(TMP)_2$.

Turning our attention to tetrabutylammonium salts (entries 15 and 16), which have previously been demonstrated to promote nickel-catalyzed cross couplings of alkylzinc halides,[248] we found TBAI to be optimal (entry 16), providing **17a** in 80% yield and favoring the *cis*-fused bicycle product with the arene disposed on the convex face.

Interestingly, if TBAI was used without a ligand (entry 18, Table 17), a comparable result to entry 11, wherein only ligand was employed, was observed.

Table 18 – Counterion effect of tetrabutylammonium salt additives



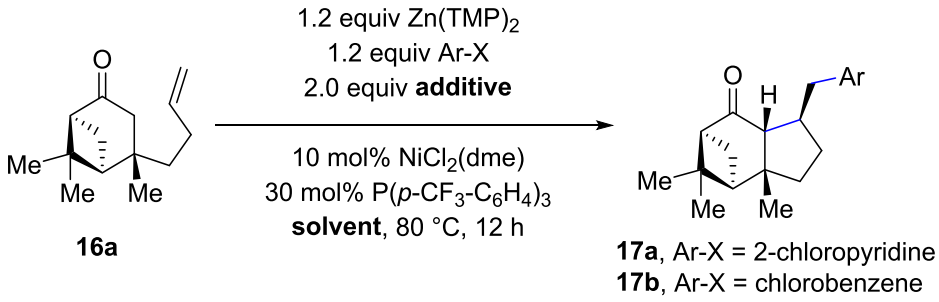
Entry[a]	Additive	Yield (%)[b]	Entry[a]	Additive	Yield (%)[b]
1[c]	TBAF	0 (0)	9	$TBANO_3$	21 (66)
2	TBACl	11 (27)	10	$TBABPh_4$	52 (72)
3	TBABr	18 (50)	11	$TBAPF_6$	56 (84)
4	TBAI	17 (62)	12	$TBAClO_4$	61 (94)
5	TBASCN, TBANCO, TBAOAc	0 (0)	13	$TBASO_3(CF_2)_3CF_3$	65 (94)
6	$TBAN_3$	3 (20)	14	$TBABF_4$	67 (87)
7	$TBAIO_4$	13 (13)	15	TBAOTf	74 (94)
8	TBAOTs	20 (61)	16	LiOTf, $Mg(OTf)_2$, $Zn(OTf)_2$, BMIMOTf[d]	0 (0)

[a] Reaction performed using **16b** (0.2 mmol-scale), 1.2 equiv of $Zn(TMP)_2$, 1.2 equiv of methyl 4-chlorobenzoate, 10 mol% of $NiCl_2(dme)$, 30 mol% of $P(p\text{-}CF_3\text{-}C_6H_4)_3$, employing 2.0 equiv of the indicated additive, in 1,4-dioxane as reaction medium, at 80 °C for 12 h. [b] ^{1}H-NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. Conversion is indicated in parentheses. [c] TBAF 1 M in THF has been used. [d] BMIMOTf = 1-butyl-3-methyl-*1H*-imidazol-3-ium triflate.

On the other hand, when tetrabutylammonium salt containing different counterion were tested in presence of ketone **16b** and methyl 4-chlorobenzoate (Table 18), the better results were achieved when weakly-coordinating anions were present (entries 10-15) and TBAOTf resulted to be the best additive (entry 15). Notably, the use of other triflate salts led to no reaction, thereby highlighting the importance of the tetrabutylammonium cation (entry 16). When aryl electrophiles were employed rather than heteroaryl electrophiles, tetrabutylammonium triflate (TBAOTf) was found to be a more effective additive, especially for the formation of 6-membered rings. We speculate that the better results achieved utilizing a tetrabutylammonium salt with a weakly-coordinating triflate anion were due to a salt metathesis that could take place at the nickel center, generating a more

cationic nickel species which would facilitate both migratory insertion and reductive elimination.[249] In addition to the low coordination ability, probably other effects, not investigated in detail, account for the high productivity observed in the presence of the triflate anion. Unfortunately, in the case of heteroaryl electrophiles, probably due to the coordinating ability of the basic groups, this phenomenon was not general.

Table 19 – Solvent/Additive effects for aryl or heteroaryl electrophiles



Entry[a]	Ar-X	Product	Solvent	Additive	Yield (%)[b]
1	2-Cl-pyridine	**17a**	1,4-dioxane	TBAI	63
2	2-Cl-pyridine	**17a**	1,4-dioxane/THF 1:1	TBAI	80
3	2-Cl-pyridine	**17a**	1,4-dioxane	TBAOTf	38
4	2-Cl-pyridine	**17a**	1,4-dioxane/THF 1:1	TBAOTf	47
5	Ph-Cl	**17b**	1,4-dioxane	TBAI	86
6	Ph-Cl	**17b**	1,4-dioxane/THF 1:1	TBAI	74
7	Ph-Cl	**17b**	1,4-dioxane	TBAOTf	87
8	Ph-Cl	**17b**	1,4-dioxane/THF 1:1	TBAOTf	87

[a] Reaction performed using **16a** (0.2 mmol-scale), 1.2 equiv of $Zn(TMP)_2$, 1.2 equiv of Ar-X (2-chloropyridine or chlorobenzene), 10 mol% of $NiCl_2(dme)$, 30 mol% of P(*p*-CF_3-C_6H_4)$_3$, employing 2.0 equiv of the indicated additive, in the indicated solvent, at 80 °C for 12 h. [b] ^{1}H-NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard.

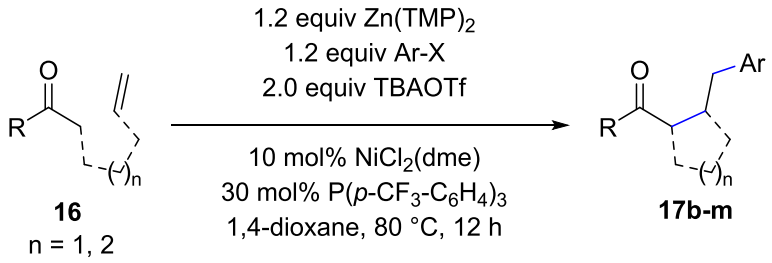
This trend is shown in Table 19, in which TABI and TBAOTf were used in different solvents, in the presence of **16a** and 2-chloropyridine or chlorobenzene. When the aryl electrophile was used, the best result was obtained with TBAOTf (entries 7 and 8) and 1,4-dioxane gave generally better results (entries 5 and 7), while with 2-chloropyridine, the best results was with TBAI utilizing a mixture of 1,4-dioxane and THF 1:1 (entry 2). Therefore, both TBAI and TBAOTf were explored as additives during our investigation of the heteroarene electrophile scope and just the best results were reported.

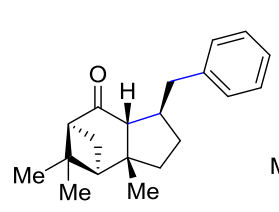
5.2.2 Scope of the Alkene Difunctionalization Reaction

We began to explore the scope of the alkene difunctionalization reaction focusing on the scope of electrophiles that can be utilized.

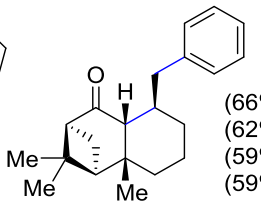
Regarding aryl electrophiles (Table 20), we first interrogated the effect of the leaving group, and found that aryl chlorides, bromides, iodides, and triflates could all be employed, obtaining the difunctionalized product **17c** with similar efficiency.

Table 20 – Scope of the alkene difunctionalization using aryl electrophiles (Ar-X).[a,b]



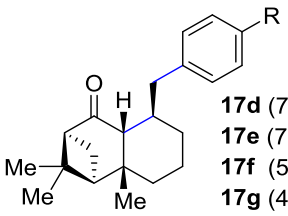


17b (82%, dr > 20:1)
X = Cl



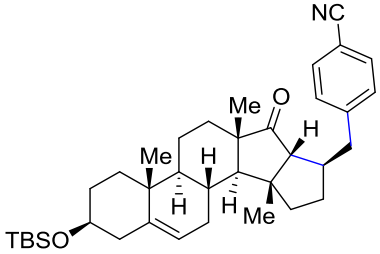
(66%) X = Cl
(62%) X = Br
(59%) X = I
(59%) X = OTf

17c (dr > 20:1)

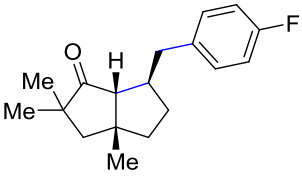


17d (71%) R = CO_2Me
17e (73%) R = CF_3
17f (55%) R = OMe
17g (45%) R = NMe_2

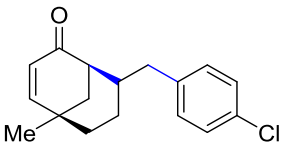
17d-g (dr > 20:1)
X = Cl



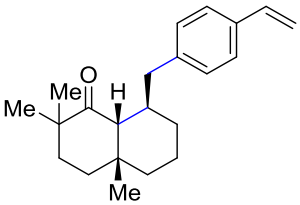
17h (51%, dr > 20:1)
X = Cl



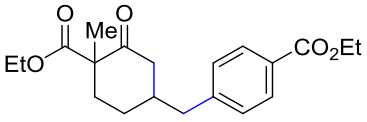
17i (55%, dr > 20:1)
X = Cl



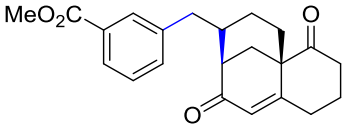
17j (63%, dr > 20:1)
X = I



17k (44%, dr > 20:1)
X = Cl



17l (35%, dr = 1:1)
X = Br



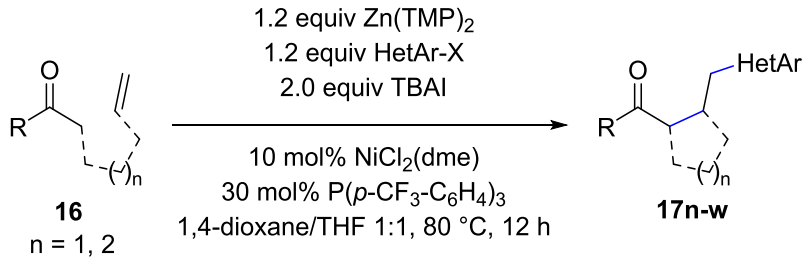
17m (21%, dr > 20:1)
X = Br

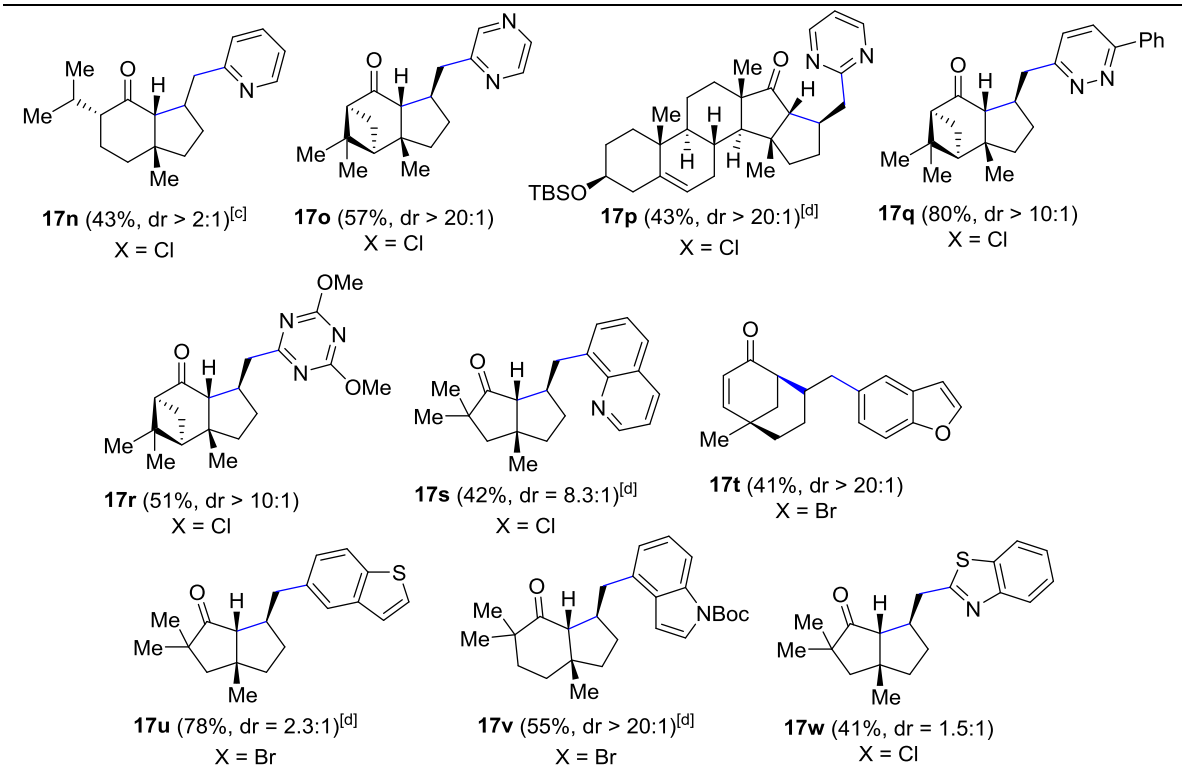
[a] Reaction performed using **16** (0.2 mmol-scale), 1.2 equiv of $Zn(TMP)_2$, 1.2 equiv of Ar-X, 10 mol% of $NiCl_2$(dme), 30 mol% of P(*p*-CF_3-C_6H_4)$_3$, employing 2.0 equiv of TBAOTf, in 1,4-dioxane as reaction medium, at 80 °C for 12 h. [b] Isolated yields reported in parentheses.

We then explored electronic effects on the benzene ring using various 4-substituted chlorobenzenes. Consistent with an accelerated reductive elimination at a more electron-deficient metal center, the use of EWG, such as -CO_2Me (**17d**) and -CF_3 (**17e**), at the *para*-position led to excellent yields. Gratifyingly, chlorobenzenes bearing electron-donating groups, like -OMe (**17f**) and -NMe_2 (**17g**), provided only slightly lower yields relative to the unsubstituted analogue. Moreover, in order to demonstrate the generality of the process, diverse ketones bearing pendant alkenes were subjected to the reaction conditions using various substituted aryl halides. Both 5- and 6-membered cyclic ketones could be employed, and both 5- and 6-membered rings could be constructed, giving access to bicyclo[4.4.0]decane, bicyclo[4.3.0]nonane, bicyclo[3.3.0]octane, and bicyclo[3.3.1]nonane ring systems.

Functionalized cyclohexanones (**17l**) can be synthesized by acyclic methyl ketones. Even aryl halides bearing potentially reactive 4-CN (**17h**) and 4-F (**17i**) functionalities were well tolerated. Using 4-chloro iodobenzene as electrophile (**17j**), the more reactive aryl iodide motif selectively participated in the cross-coupling reaction. No functionalization of the alkene moiety was observed when 4-chlorostyrene was employed, achieving **17k** in 44% of isolated yield. The use of *meta*-substituted aryl electrophile (**17m**) was also successful, although the low observed yield was a consequence of the two enolizable positions of the Wieland-Miescher ketone scaffold.

Table 21 – Scope of the alkene difunctionalization using heteroaryl electrophiles (HetAr-X).[a,b]



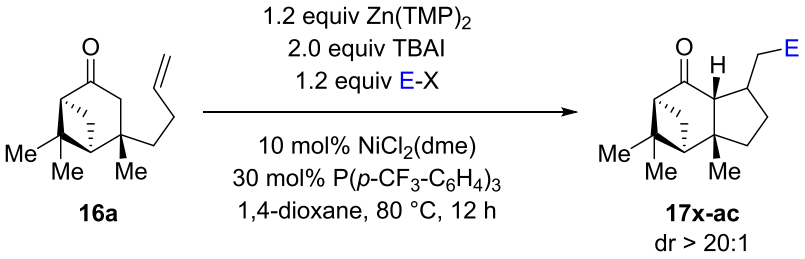


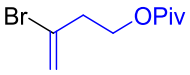
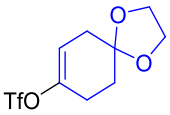
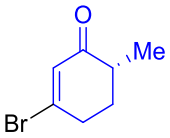
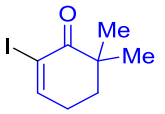
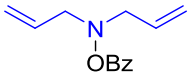
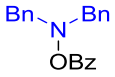
[a] Reaction performed using **16** (0.2 mmol-scale), 1.2 equiv of $Zn(TMP)_2$, 1.2 equiv of HetAr-X, 10 mol% of $NiCl_2(dme)$, 30 mol% of $P(p\text{-}CF_3\text{-}C_6H_4)_3$, employing 2.0 equiv of TBAI, in 1,4-dioxane/THF 1:1 as reaction medium, at 80 °C for 12 h.. [b] Isolated yields reported in parentheses. [c] 2.0 equiv of $Zn(TMP)_2$ was used. [d] TBAOTf was used instead of TBAI.

Next, the scope of heteroaryl electrophiles was explored (Table 21). A variety of electron-deficient heteroarenes have been successfully employed, including pyridine (**17n**), pyrazine (**17o**), pyrimidine (**17p**), pyridazine (**17q**), and 1,3,5-triazine (**17r**). The basicity of these substrates could lead to coordination to nickel, resulting in a deactivation of the catalyst. On the other hand, these substrates are also highly electron deficient, therefore a facile reductive elimination it should be expected. A variety of benzo-fused heterocyclic electrophiles were then successfully tested, such as quinoline (**17s**), benzofuran (**17t**), benzothiophene (**17u**), Boc-protected indole (**17v**), and benzothiazole

(**17w**). Remarkably, **17r**, **17t** and **17u** are additional examples of *meta*-substituted arenes whereas **17s** and **17v** represent *ortho*-substituted arenes.

Table 22 – Scope of the alkene difunctionalization using alkenyl electrophiles and electrophilic amines (E-X) .



Entry[a]	E-X	Product **17**	Yield (%)[b]
1		**17x**	42
2		**17y**	37
3		**17z**	41
4		**17aa**	28
5[c]		**17ab**	30
6[c]		**17ac**	37

[a] Reaction performed using **16a** (0.2 mmol-scale), 1.2 equiv of $Zn(TMP)_2$, 1.2 equiv of E-X, 10 mol% of $NiCl_2$(dme), 30 mol% of P(*p*-CF_3-C_6H_4)$_3$, employing 2.0 equiv of TBAI, in 1,4-dioxane as reaction medium, at 80 °C for 12 h.. [b] Isolated yield. [c] No TBAI was used.

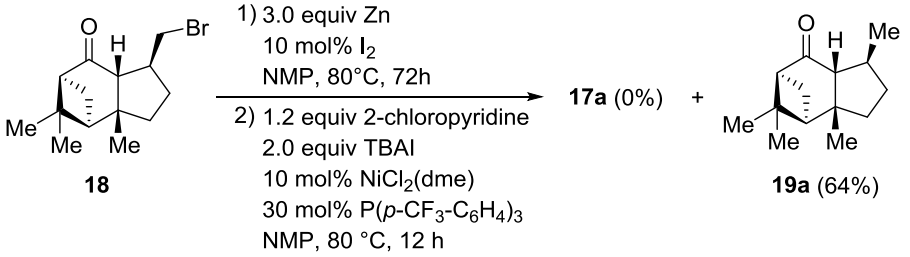
Eventually, in addition to arenes and heteroarenes, **16a** has been tested with alkenyl electrophiles and electrophilic amines (Table 22). Synthetically versatile alkenyl electrophiles could also be employed, including an -OPiv tethered 1,1-disubstituted alkenyl bromide (entry 1), an acetal containing alkenyl triflate (entry 2), a β-bromo enone (entry 3), and an α-iodo enone (entry 4). The modest yields are the result of arylation by-products, deriving from ligand degradation. Even electrophilic amines such as *N*,*N*-diallyl (entry 5) and *N*,*N*-dibenzyl *O*-benzoyl hydroxylamines (entry 6) could be utilized to give

tertiary amine products. Interestingly, the alkene carboamination reaction was more efficient without additives and enolate alkylation and alkenylation were observed to be the major by-products. Probably the catalytic system is not optimized for this transformation, and a further ligand development should be done in order improve the yields for these more challenging electrophiles.

Besides the electrophiles, under the optimized conditions, only unactivated terminal alkenes were tolerated. Polarized olefins bearing a -COOMe moiety underwent efficient cyclization, but no cross coupling. Subjecting a phenyl-substituted internal alkene to the standard conditions, no reaction was observed. Moreover, only trace product, resulting from poor conversion, is observed if a quaternary center is not present at the site of the alkene tether.

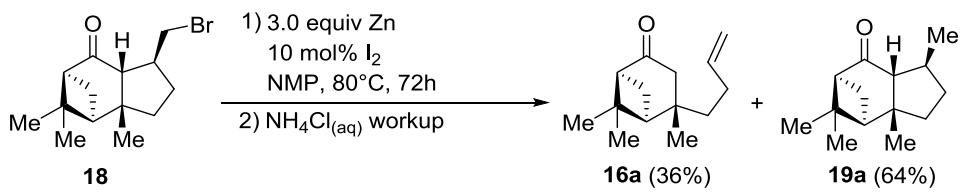
5.2.3 Mechanistic Investigations

Preliminary mechanistic studies were conducted to better understand the role of alkylzinc intermediates in this transformation. When the Negishi reagent derived from **18** was prepared by direct insertion with Zn(0) in NMP[250] and subjected to our standard conditions for nickel-catalyzed cross-coupling with 2-chloropyridine, **17a** was not observed (Scheme 74).



Scheme 74 - Cross-coupling of Negishi reagent **18**

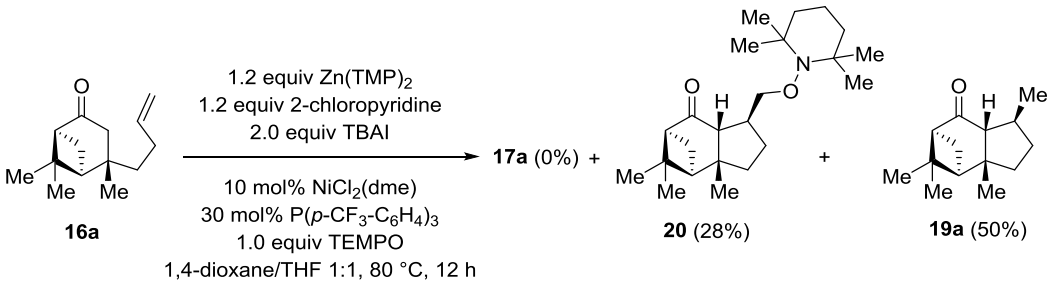
An aqueous quench of this Negishi reagent revealed that ring-opened product **16a** and hydrodehalogenation product **19a** were formed (Scheme 75).



Scheme 75 – Reversibility of zinc cyclization

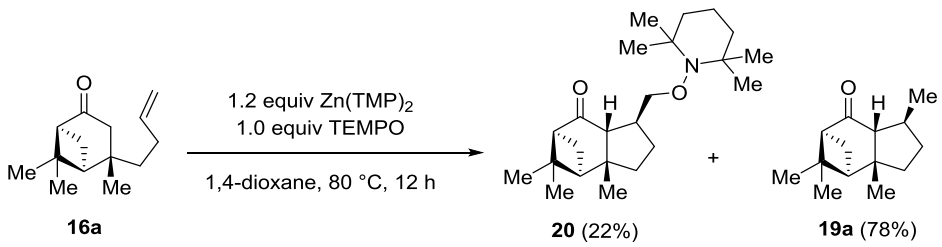
The propensity of this Negishi reagent to ring opening, *via* radical[251] or anionic process,[195c,226b,229,238] could indicate the possibility of a reversible zinc cyclization. Attempts to use other activators (such as, LiCl, TMSCl, $(CH_2Br)_2$) to prepare the Negishi reagent in ethereal solvent led to poor conversion, while the formation of the Negishi reagent using the corresponding alkyl iodide, provided similar results to those reported in Scheme 74 and Scheme 75, but with higher conversion. These results demonstrates the utility of our methodology in order to avoid the synthetic challenging preparation/functionalization of Negishi reagents at that position.

In order to investigate the involvement of single electron pathways, model substrate **16a** was subjected to the standard conditions in the presence of a stoichiometric amount of TEMPO (2,2,6,6-tetramethylpiperidinoxyl) (Scheme 76).



Scheme 76 – Experiment with TEMPO under standard reaction conditions

While formation of cross-coupling product **17a** was inhibited, cyclization product **19a** (50% yield) and TEMPO-adduct **20** (28% yield) were obtained as the major products. Even in absence of nickel-catalyst, TEMPO-adduct **20** could be obtained, indicating that the alkyl-zinc species generated from the zinc-mediated cyclization was probably responsible for the formation of product **20** (Scheme 77).

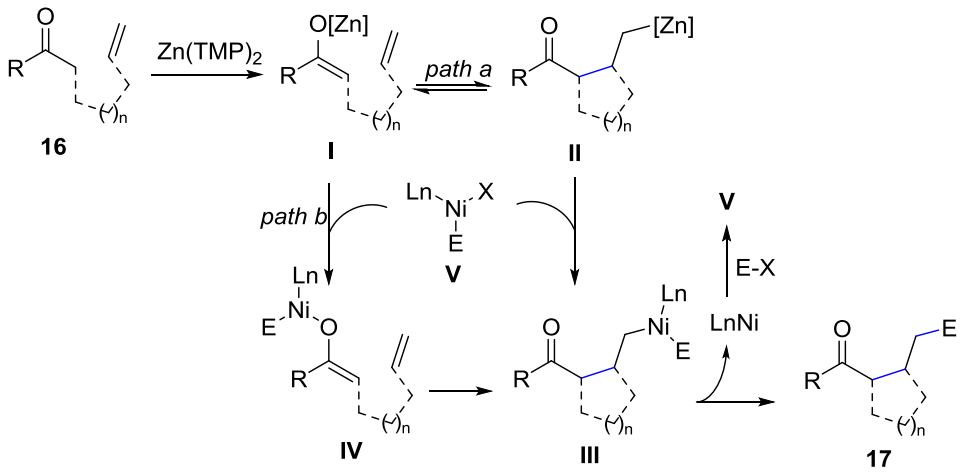


Scheme 77 - Experiment with TEMPO

These results indicate that either a radical cyclization is not operative or the rate of the C-C bond forming cyclization proceeds faster than the rate of trapping with TEMPO (10^9 M^{-1} s^{-1}).[252] Furthermore, these results indicate that the alkyl-zinc species formed under our conditions can participate in single-electron pathways.[221,253,254]

Despite these studies on the zinc-mediated cyclization, cyclization via a nickel-mediated migratory insertion cannot be excluded. The diastereoselectivity of the C–C bond forming cyclization was observed to be electrophile dependent, as exemplified by products **17s** (8.3:1 dr) and **17u** (2.3:1 dr), which were otherwise prepared under identical conditions. A compelling explanation for this variable selectivity is that the coordination sphere at nickel differs for the migratory insertion step. If olefin migratory insertion occurs with an aryl nickel enolate, the diastereoselectivity observed should be a function of the aryl group bound to nickel. Alternatively, if C-C bond forming cyclization were reversible and occurred at a rate competitive with C-C bond forming reductive elimination, variable diastereoselectivities could be the result of a compromise between kinetic and thermodynamic cyclization stereoselectivity. However, the influence of the aryl halides on diastereoselectivity is complicated to identify, due to the reversibility of the cyclization process and the differences between the ketone scaffolds.

Considering the above results, a proposed catalytic cycle is reported in Scheme 78.



Scheme 78 – Proposed catalytic cycle for the alkene difunctionalization process (n = 1 or 2) using a generic electrophile E-X.

After the formation of the Zn-enolate **I**, two pathaways are possible: in the first one, a directly carbometalation from **I** forms the alkyl-Zn intermediate **II**, which undergoes transmetalation with the aryl-Ni complex **V**, obtaining the alkyl-Ni intermediate **III** (*path*

a, Scheme 78). The latter could be also achieved starting from the Ni-enolate **IV**, generated by transmetalation of the Zn-enolate **I** with **V**, followed by a migratory insertion reaction (*path b*, Scheme 78). In any case, the complex **III** undergoes reductive elimination to form the product **17**.

5.3 Conclusion

In conclusion, the first nickel-catalyzed vicinal difunctionalization of unactivated alkenes initiated by unstabilized ketone enolates has been developed, allowing the formation of various bicyclic architectures with concomitant incorporation of a diverse range of pharmaceutically relevant electrophiles. Indeed, different aryl and heteroaryl electrophiles have been successfully tested, and this method has shown to be efficient also when alkenyl electrophiles or electrophilic amines were employed.

The use of an appropriate tetrabutyl ammonium salt and of an electron-deficient triaryl phosphine ligand was found to be crucial for the process.

Moreover, less reactive but more abundantly available aryl chlorides gave the same results as those obtained with bromides, iodides or triflate, without a decrease in reaction efficiency.

5.4 Experimental Section

5.4.1 List of ketones 16

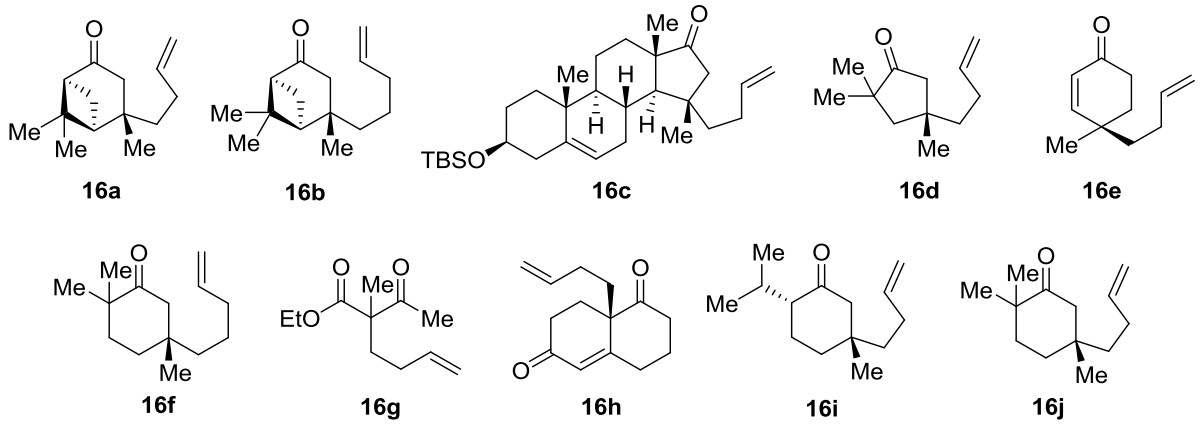


Figure 13 – Olefins utilized in the alkene difunctionalization reaction

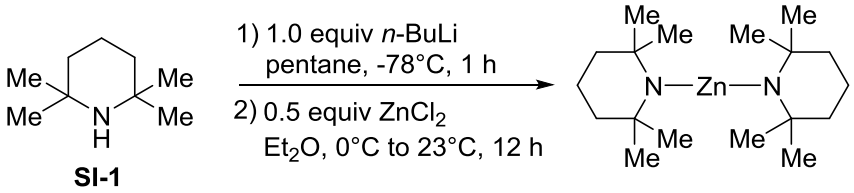
5.4.2 General Information

All reactions were carried out under an inert nitrogen atmosphere with dry solvents under anhydrous conditions unless otherwise stated. All reactions were capped with a rubber septum, or Teflon-coated silicon microwave cap unless otherwise stated. Stainless steel cannula or syringe was used to transfer solvent, and air- and moisture sensitive liquid reagents. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as the visualizing agent and potassium permanganate, an acidic solution of *p*-anisaldehyde, phosphomolybdic acid, or I_2 on SiO_2 as developing agents. Flash column chromatography employed SiliaFlash® P60 (40-60 μm, 230-400 mesh) silica gel purchased from SiliCycle, Inc. Solvents were purified using a Seca solvent purification system by Glass contour. *N*,*N*-diisopropylamine, 2,2,6,6-tetramethylpiperidine, and TMSCl were distilled over CaH_2. $CuBr•SMe_2$ was prepared and purified according to the literature procedure.[255] $NiCl_2$(dme) was purchased from Strem and stored in a glovebox. Tris(4-trifluoromethylphenyl) phosphine was prepared according to the literature procedure.[256] $Zn(TMP)_2$ (0.5 M in toluene), *n*-BuLi (2.5 M in hexanes), tetrabutylammonium iodide (TBAI), and $ZnCl_2$ were purchased from Sigma Aldrich. Tetrabutylammonium trifluoromethanesulfonate (TBAOTf) was purchased from Alfa Aesar and stored in a glovebox. 4-bromo-1-butene was purchased from Oakwood Products, Inc and purified via neat filtration through a 2 cm pad of dry silica in a 5.75 inch pipette prior to use. All other reagents were used as received without further purification, unless otherwise stated.

NMR spectra were recorded using a Varian 400 MHz NMR spectrometer, Varian 500 MHz NMR spectrometer, or a Varian 600 MHz NMR spectrometer. All ^{1}H-NMR data are reported in δ units, parts per million (ppm), and were calibrated relative to the signals for residual chloroform (7.26 ppm) in deuterochloroform ($CDCl_3$). All ^{13}C-NMR data are reported in ppm relative to $CDCl_3$ (77.16 ppm) and were obtained with ^{1}H decoupling unless otherwise stated. The following abbreviations or combinations thereof were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, abq = ab quartet, br = broad, m = multiplet, and a = apparent. All IR spectra were taken on an FT-IR/Raman Thermo Nicolet 6700. Gas chromatography mass spectra (GCMS) were recorded on an Agilent Technologies 6890N Network Gas Chromatograph System with an Agilent Technologies 5973N Mass Selective Detector. High resolution mass spectra (HRMS) were recorded on a Waters Xevo high resolution mass spectrometer using Qtof (quadrupole-time of flight). Optical rotation data was obtained using a Perkin-Elmer 341 polarimeter.

Compounds **16a, 16e, 16g, 16h, 16i, 16j** and **18** were prepared according to the literature procedure.[245]

5.4.3 Preparation of $Zn(TMP)_2$



To a flame-dried 500 mL three-necked, round-bottomed flask equipped with a dropping funnel and a magnetic stir bar was added 2,2,6,6-tetramethylpiperidine **SI-1** (20.0 g, 141.6 mmol, 1.0 equiv) and pentane (200 mL, 0.7 M). The reaction vessel was moved to a -78 °C dry ice/acetone bath and stirred for 10 minutes. To the cooled reaction mixture was added *n*-BuLi (56.6 mL, 2.5 M in hexanes, 141.6 mmol, 1.0 equiv) dropwise via dropping funnel and the reaction mixture was stirred for 1 hour at –78 °C to give a light-yellow suspension. To the reaction mixture was added a vigorously stirred (at least 1 hour) solution of $ZnCl_2$[257] (9.65 g, 70.8 mmol, 0.5 equiv) in Et_2O (50 mL, 1.4 M) via cannula at -78 °C. The transfer was quantitated by rinsing with Et_2O (5 mL). The reaction vessel was moved to a 0 °C ice bath and stirred for 12 hours and allowed to

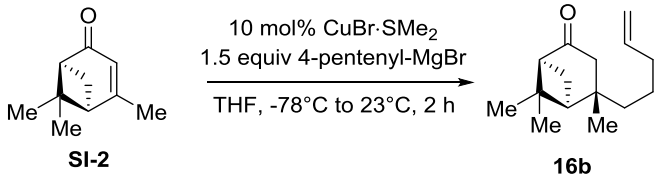
warm to ambient temperature to give a white suspension. The reaction vessel was placed under N_2 and the dropping funnel was quickly replaced with a Schlenk adapter. The solvent was completely removed under reduced pressure and the resulting residue was re-dissolved in pentane (150 mL). The resulting white suspension was filtered under vacuum via cannula transfer to an air-free, fritted filter containing a pad of oven dried celite (at least 24 h) and the filtrate was collected in a 500 mL Schlenk flask equipped with a magnetic stir bar. The Schlenk flask was placed under N_2 and the air-free fritted vacuum filter was quickly replaced with a rubber septum. The pentane was removed from the Schlenk flask under reduced pressure to give $Zn(TMP)_2$ (24.1 g, 98%) as a light-yellow solid.[258]

^{1}H NMR (400 MHz, C_6D_6) δ 1.72–1.66 (m, 4H), 1.37 (t, J = 6.0 Hz, 8H), 1.27 (s, 24H). ^{13}C NMR (126 MHz, C_6D_6): δ 53.0, 39.5, 36.9, 19.6.

Preparation and titration of a 0.5 M solution of $Zn(TMP)_2$ in toluene

The Schlenk flask was backfilled with N_2 and to the flask was added toluene (139 mL, 0.5 M) to give a light-yellow solution. The solution of $Zn(TMP)_2$ in toluene was titrated[259] with a 0 °C solution of I_2 in THF saturated with LiCl (0.5 M) (color change from dark red to light yellow) and determined to have a final concentration of 0.5-0.55 M. One molar equivalent of I_2 should react with one molar equivalent of $Zn(TMP)_2$.

5.4.4 Synthesis of (1*S*,4*S*,5*S*)-4,6,6-trimethyl-4-(pent-4-en-1-yl)bicyclo[3.1.1]heptan-2-one (16b)



To a flame-dried 100 mL three-necked flask equipped with a magnetic stir bar and an oven dried reflux condenser was added magnesium turnings (955 mg, 39.1 mmol, 2.0 equiv) and a catalytic amount of I_2 (*ca.* 5.0 mg). The reaction vessel was evacuated, and backfilled with N_2 and THF (20 mL, 1.46 M) was added to the reaction vessel. The

reaction vessel was then moved to a 70 °C pre-heated oil bath and stirred for 10 minutes. The reaction vessel was then removed from the oil bath and to the reaction mixture was added 5-bromo-1-pentene (3.5 mL, 29.4 mmol, 1.5 equiv) dropwise over 15 minutes as to maintain a gentle reflux. The reaction vessel was then moved back to a 70 °C oil bath and stirred for 30 minutes. The reaction vessel was then removed from the oil bath and cooled to ambient temperature. In a separate flame-dried 100 mL round-bottomed flask equipped with a magnetic stir bar was added CuBr•SMe_2 (411 mg, 2.0 mmol, 10 mol %). The flask was evacuated and backfilled with N_2 before THF (20 mL, 1.0 M) was added to the reaction vessel. The reaction mixture was then cooled to −40 °CC in a dry ice-acetonitrile bath and the previously prepared 4-pentenylmagnesium bromide solution was added dropwise over 15 minutes. The reaction mixture was stirred at −40 °C for 30 minutes before it was cooled to −78 °C in a dry ice-acetone bath and (−)-verbenone **SI-2** (3.0 mL, 19.6 mmol, 1.0 equiv) was added dropwise. The reaction mixture was stirred for 2 hours and slowly warmed to ambient temperature. To the reaction mixture was added sat. aq. NH_4Cl (50 mL) and Et_2O (50 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (10% Et_2O/hexanes) afforded **16b** (2.85 g, 66%) as a colorless oil. The characterization data match those previously reported in the literature.[260]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, J = 16.8, 10.0, 6.4 Hz, 1H), 5.02–4.94 (m, 2H), 2.53 (at, J = 5.2 Hz, 1H), 2.46 (adt, J = 10.8, 6.0 Hz, 1H), 2.36 (d, J = 19.6 Hz, 1H), 2.27 (d, J = 19.6 Hz, 1H), 2.04–1.96 (m, 3H), 1.63 (d, J = 10.8 Hz, 1H), 1.38–1.29 (m, 4H), 1.36 (s, 3H), 1.14 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.7, 138.8, 114.8, 58.3, 51.8, 48.3, 43.7, 41.1, 34.5, 27.6, 26.0, 25.7, 24.9, 23.1

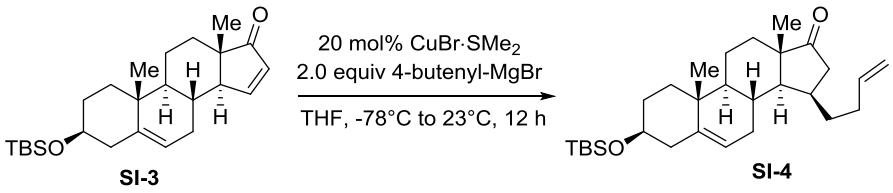
IR (cm^{-1}): 2934, 1705, 1641, 1473, 1458, 1387, 1266, 1251, 1202, 987, 908, 741, 514.

GCMS (m/z): calc'd for $C_{15}H_{24}O$: 220.2; found: 220.2.

Rf: 0.47 (10% EtOAc/hexanes)

$[\alpha]_D^{20.0}$: –24.0° (*c* 1.0, $CHCl_3$)

5.4.5 Synthesis of (3*S*,8*R*,9*S*,10*R*,13*S*,14*S*,15*R*)-15-(but-3-en-1-yl)-3-((*tert*-butyldimethylsilyl)oxy)-10,13-dimethyl-1,2,3,4,7,8,9,10,11,12,13,14,15,16-tetradecahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (SI-4)



To a flame-dried 20 mL microwave vial equipped with a magnetic stir bar was added magnesium turnings (224 mg, 9.33 mmol, 2.2 equiv) and a catalytic amount of I_2 (*ca.* 2.0 mg). The vial was capped, evacuated, and backfilled with N_2 and THF (8.5 mL, 1.0 M) was added to the reaction vessel. The reaction vessel was then moved to a 70 °C pre-heated oil bath and stirred for 10 minutes. The reaction vessel was then removed from the oil bath and to the reaction mixture was added 4-bromo-1-butene (0.86 mL, 8.48 mmol, 2.0 equiv) dropwise over 10 minutes as to maintain a gentle reflux. The reaction vessel was then moved back to a 70 °C oil bath and stirred for 30 minutes. The reaction vessel was then removed from the oil bath and cooled to ambient temperature. In a separate flame-dried 100 mL round-bottomed flask equipped with a magnetic stir bar was added CuBr•SMe_2 (175 mg, 0.85 mmol, 20 mol %). The flask was evacuated and backfilled with N_2 before THF (20 mL, 0.2 M) was added to the reaction vessel. The reaction mixture was then cooled to −40 °C in a dry ice-acetonitrile bath and the previously prepared 3-butenylmagnesium bromide solution was added dropwise over 10 minutes. The reaction mixture was stirred at −40 °C for 30 minutes before it was cooled to −78 °C in a dry ice-acetone bath and a solution of **SI-3**[261] (1.70 g, 4.24 mmol, 1.0 equiv) in THF (2 mL, 2.1 M) was added dropwise. The reaction mixture was stirred for 12 hours and slowly warmed to ambient temperature. To the reaction mixture was added sat. aq. NH_4Cl (50 mL) and Et_2O (30 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (10% Et_2O/hexanes) afforded **SI-4** (1.49 g, 77%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, J = 16.8, 10.0, 6.8 Hz, 1H), 5.35–5.34 (m, 1H), 5.04–4.96 (m, 2H), 3.48 (att, J = 4.8 Hz, 1H), 2.36–2.08 (m, 7H), 1.99–1.91 (m, 1H),

1.86–1.79 (m, 2H), 1.77–1.62 (m, 5H), 1.59–1.37 (m, 5H), 1.30–1.21 (m, 2H), 1.04 (s, 3H), 0.99 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.6, 142.1, 138.3, 120.5, 115.3, 72.6, 54.3, 51.0, 46.8, 42.8, 42.6, 37.5, 37.0, 34.0, 33.8, 33.7, 32.1, 31.0, 30.4, 29.1, 26.1, 20.4, 19.5, 18.4, 17.6, −4.5.

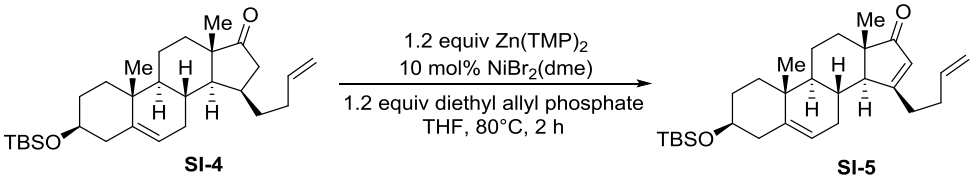
IR (cm^{-1}): 2929, 2855, 1739, 1462, 1375, 1250, 1089, 1040, 1005, 911, 888, 870, 835, 807, 773, 666.

HRMS (m/z): $[M+H]^+$ calc'd for $C_{29}H_{49}O_2Si^+$: 457.3496; found: 457.3476

Rf: 0.50 (10% EtOAc/hexanes)

$[\alpha]_D^{20.0}$: –19.1° (*c* 1.0, $CHCl_3$)

5.4.6 Synthesis of (3*S*,8*R*,9*S*,10*R*,13*S*,14*R*)-15-(but-3-en-1-yl)-3-((*tert*-butyldimethylsilyl)oxy)-10,13-dimethyl-1,2,3,4,7,8,9,10,11,12,13,14-dodecahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (SI-5)



To a flame-dried 50 mL round-bottomed flask equipped with a magnetic stir bar was added **SI-4** (1.40 g, 3.06 mmol, 1.0 equiv). The reaction vessel was capped with a rubber septum, evacuated, and backfilled with N_2 before THF (8 mL, 0.38 M) was added. To the stirred solution of **SI-4** was added $Zn(TMP)_2$ (7.35 mL, 0.5 M in toluene, 3.68 mmol, 1.2 equiv) and a solution of $NiBr_2$(dme) (94 mg, 0.31 mmol, 10 mol %) and diethyl allyl phosphate (0.65 mL, 3.68 mmol, 1.2 equiv) in THF (2 mL, 1.8 M) at ambient temperature. The rubber septum was quickly replaced with an oven-dried reflux condenser and the reaction apparatus was placed into an 80 °C pre-heated oil bath and stirred for 2 hours. To the reaction mixture was added sat. aq. NH_4Cl (30 mL) and Et_2O (20 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (10% EtOAc/hexanes) afforded **SI-5** (681 mg, 49%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (ddt, J = 16.8, 10.0, 6.4 Hz, 1H), 5.77–5.76 (m, 1H), 5.32–5.30 (m, 1H), 5.10–5.02 (m, 2H), 3.48 (att, J = 4.8 Hz, 1H), 2.52–2.40 (m, 3H), 2.38–2.17 (m, 5H), 2.05 (ddd, J = 20.8, 10.8, 5.2 Hz, 1H), 1.94–1.86 (m, 2H), 1.82 (adt, J = 13.2, 3.6 Hz, 1H), 1.78–1.70 (m, 2H), 1.68–1.47 (m, 5H), 1.08 (s, 3H), 1.07 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.5, 178.9, 142.2, 137.1, 126.6, 120.0, 115.9, 72.5, 58.4, 52.2, 51.3, 42.7, 37.4, 37.1, 33.0, 33.0, 32.2, 31.2, 30.4, 29.0, 26.1, 20.8, 20.0, 19.4, 18.4, -4.4.

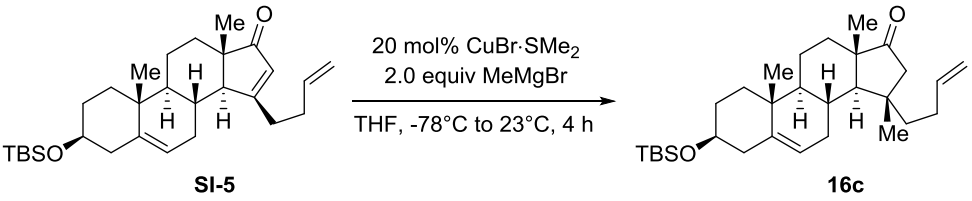
IR (cm^{-1}): 2930, 2855, 1704, 1591, 1471, 1462, 1371, 1250, 1089, 1005, 914, 888, 870, 834, 773, 735,702.

HRMS (m/z): $[M+H]^+$ calc'd for $C_{29}H_{47}O_2Si^+$: 455.3340; found: 455.3345

Rf: 0.35 (10% EtOAc/hexanes)

$[\alpha]_D^{20.0}$: –106.4° (*c* 1.0, $CHCl_3$)

5.4.7 Synthesis of (3*S*,8*R*,9*S*,10*R*,13*S*,14*R*,15*S*)-15-(but-3-en-1-yl)-3-((*tert*-butyldimethylsilyl)oxy)-10,13,15-trimethyl-1,2,3,4,7,8,9,10,11,12,13,14,15,16-tetradecahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (16c)



SI-5 **16c**

To a flame-dried 20 mL microwave vial equipped with a magnetic stir bar was added CuBr•SMe_2 (60 mg, 0.29 mmol, 20 mol %). The flask was evacuated and backfilled with N_2 before THF (10 mL, 0.15 M) was added to the reaction vessel. The reaction mixture was then cooled to −40 °C in a dry ice-acetonitrile bath and MeMgBr (2.88 mL, 1.0 M in THF, 2.88 mmol, 2.0 equiv) was added dropwise over 5 minutes. The reaction mixture was stirred at −40 °C for 30 minutes before it was cooled to −78 °C in a dry ice-acetone bath and a solution of **SI-5** (656 mg, 1.44 mmol, 1.0 equiv) in THF (1.0 mL, 1.4 M) was added dropwise. The reaction mixture was stirred for 4 hours and slowly warmed to ambient temperature. To the reaction mixture was added sat. aq. NH_4Cl (20 mL) and Et_2O (20 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with brine (50 mL),

dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (10% Et_2O/hexanes) afforded **16c** (401 mg, 61%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, J = 16.8, 10.0, 6.4 Hz, 1H), 5.33–5.32 (m, 1H), 5.03–4.93 (m, 2H), 3.48 (att, J = 4.8 Hz, 1H), 2.45 (d, J = 19.6 Hz, 1H), 2.31–2.16 (m, 4H), 2.14–2.05 (m, 1H), 1.98 (ddd, J = 21.2, 11.2, 4.8 Hz, 1H), 1.85–1.64 (m, 7H), 1.52–1.41 (m, 2H), 1.38–1.25 (m, 3H), 1.22 (s, 3H), 1.13–1.11 (m, 1H), 1.08 (s, 3H), 1.07 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (151 MHz, CDCl3) δ 220.4, 141.6, 138.9, 120.6, 114.6, 72.6, 57.6, 50.8, 49.9, 49.5, 44.9, 42.7, 39.1, 37.6, 37.2, 34.1, 33.2, 32.2, 30.8, 29.8, 26.1, 22.6, 20.1, 19.5, 18.4, 18.2, -4.4.

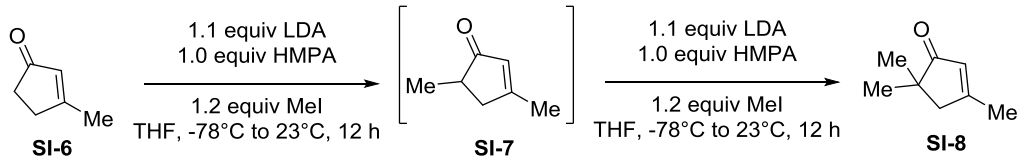
IR (cm^{-1}): 2926, 2855, 1738, 1461, 1382, 1251, 1080, 1044, 906, 890, 871, 834, 771, 665.

HRMS (m/z): $[M+H]^+$ calc'd for $C_{30}H_{51}O_2Si^+$: 471.3653; found: 471.3658.

Rf: 0.48 (10% EtOAc/hexanes)

$[\alpha]_D^{20.0}$: –30.9° (*c* 1.0, $CHCl_3$)

5.4.8 Synthesis of 3,5,5-trimethylcyclopent-2-en-1-one (SI-8)



To a 250 mL round-bottomed flask was added *N*,*N*-diisopropylamine (3.50 mL, 25.0 mmol, 1.2 equiv) and THF (40 mL, 0.52 M). The reaction vessel was placed into a 0 °C ice-water bath and stirred for 10 minutes before *n*-BuLi (9.15 mL, 2.5 M in hexanes, 22.9 mmol, 1.1 equiv) was added dropwise and the reaction mixture was stirred for 10 minutes at 0 °C. The reaction was then moved to a −78 °C dry ice-acetone bath and stirred for 10 minutes before 3-Methyl-2-cyclopentenone **SI-6** (2.0 g, 20.8 mmol, 1.0 equiv) was added dropwise and the reaction mixture was stirred for 1 hour at this temperature. To the reaction mixture was added hexamethylphosphoramide (3.62 mL, 20.8 mmol, 1.0 equiv) and MeI (1.55 mL, 25.0 mmol, 1.2 equiv) and the reaction mixture was stirred for 12 hours and slowly warmed to ambient temperature. To the reaction mixture was added sat. aq. NH_4Cl (50 mL) and Et_2O (20 mL). The organic phase was

separated and the aqueous phase was extracted with Et_2O (2 x 40 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation at 10 °C to afford crude **SI-7**. This crude mixture was resubjected to the above reaction and work-up conditions without further purification to afford crude **SI-8**. Purification by flash column chromatography on silica gel (10% Et_2O/hexanes) afforded **SI-8** (800 mg, 31% over 2 steps) as a light-yellow oil. The characterization data match those previously reported in the literature.[262]

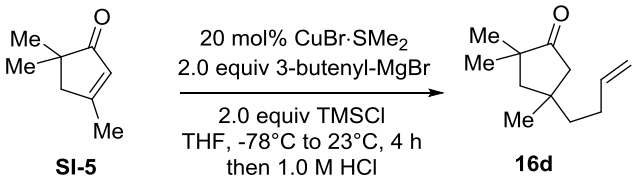
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (s, 1H), 2.43 (s, 2H), 2.11–2.09 (m, 3H), 1.10 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 214.8 175.6, 128.1, 49.8, 44.7, 25.2, 19.6.

IR (cm^{-1}): 2961, 1701, 1624, 1432, 1432, 1380, 1130, 849, 733, 435.

GCMS (m/z): calc'd for $C_8H_{12}O$: 124.1; found: 124.1

Rf: 0.25 (20% Et_2O/hexanes)

5.4.9 Synthesis of 4-(but-3-en-1-yl)-2,2,4-trimethylcyclopentan-1-one (16d)



To a flame-dried 20 mL microwave vial equipped with a magnetic stir bar was added magnesium turnings (121 mg, 5.05 mmol, 2.2 equiv) and a catalytic amount of I_2 (*ca.* 2.0 mg). The vial was capped, evacuated, and backfilled with N_2 and THF (4.6 mL, 1.0 M) was added to the reaction vessel. The reaction vessel was then moved to a 70 °C pre-heated oil bath and stirred for 10 minutes. The reaction vessel was then removed from the oil bath and to the reaction mixture was added 4-bromo-1-butene (0.47 mL, 4.59 mmol, 2.0 equiv) dropwise over 10 minutes as to maintain a gentle reflux. The reaction vessel was then moved back to a 70 °C oil bath and stirred for 30 minutes. The reaction vessel was then removed from the oil bath and cooled to ambient temperature. In a separate flame-dried 50 mL round-bottomed flask equipped with a magnetic stir bar was added CuBr•SMe_2 (95 mg, 0.46 mmol, 20 mol %). The flask was evacuated and backfilled with N_2 before THF (10 mL, 0.23 M) was added to the reaction vessel. The reaction mixture was then cooled to −40 °C in a dry ice-acetonitrile bath and the previously prepared 3-

butenylmagnesium bromide solution was added dropwise over 10 minutes. The reaction mixture was stirred at −40 °C for 30 minutes before it was cooled to −78 °C in a dry ice-acetone bath and **SI-8** (285 mg, 2.3 mmol, 1.0 equiv) was added dropwise. The reaction mixture was stirred for 12 hours and slowly warmed to ambient temperature. To the reaction mixture was added 1.0 M HCl (20 mL) and the mixture was stirred for 1 hour at ambient temperature. To the reaction mixture was added Et_2O (20 mL) and the organic phase was separated. The aqueous phase was extracted with Et_2O (2 x 20 mL) and the combined organic extracts were washed with brine (60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (5% Et_2O/hexanes) afforded **16d** (264 mg, 64%) as a colorless oil.

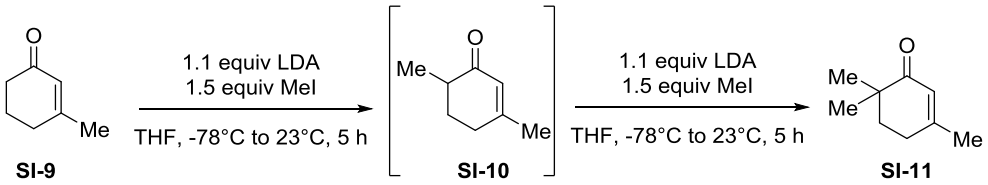
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddt, J = 16.8, 10.0, 6.4 Hz, 1H), 5.04–4.92 (m, 2H), 2.29 (d, J = 17.2 Hz, 1H), 2.15 (dd, J = 17.2, 1.2 Hz, 1H), 2.11–1.96 (m, 2H), 1.81 (d, J = 13.6, 1.2 Hz, 1H), 1.47 (at, J = 8.4 Hz, 2H), 1.12 (s, 3H), 1.08 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 223.7, 138.8, 114.6, 51.6, 51.1, 45.0, 42.6, 36.3, 29.2, 28.0, 27.4, 27.0

IR (cm^{-1}): 2962, 2931, 2868, 1737, 1641, 1460, 1380, 1120, 995, 908, 706.

GCMS (m/z): calc'd for $C_{12}H_{20}O$: 180.2; found: 180.2

Rf: 0.50 (20% Et_2O/hexanes)

5.4.10 Synthesis of 3,6,6-trimethylcyclohex-2-en-1-one (SI-11)



To a 500 mL three-necked round-bottomed flask equipped with a magnetic stir bar and a dropping funnel was added *N*,*N*-diisopropylamine (7.63 mL, 54.5 mmol, 1.2 equiv) and THF (100 mL, 0.45 M). The reaction vessel was placed into a 0 °C ice-water bath and stirred for 10 minutes before *n*-BuLi (20.0 mL, 2.5 M in hexanes, 49.9 mmol, 1.1 equiv) was added dropwise via dropping funnel and the reaction mixture was stirred for 10 minutes at 0 °C. The reaction was then moved to a −78 °C dry ice-acetone bath and stirred for 10 minutes before 3-methyl-2-cyclohexenone **SI-9** (5.00 g, 45.4 mmol, 1.0

equiv) was added dropwise and the reaction mixture was stirred for 1 hour at this temperature. To the reaction mixture was added MeI (4.24 mL, 68.1 mmol, 1.5 equiv) and the reaction mixture was stirred for 5 hours and slowly warmed to ambient temperature. To the reaction mixture was added sat. aq. NH_4Cl (100 mL) and Et_2O (50 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation in a 10 °C ice-water bath to afford crude **SI-10**. This crude mixture was resubjected to the above reaction and work-up conditions without further purification to afford crude **SI-11**. Purification by flash column chromatography on silica gel (10% Et_2O/hexanes) afforded **SI-11** (4.71 g, 75% over 2 steps) as an orange oil. The characterization data match those previously reported in the literature.[263]

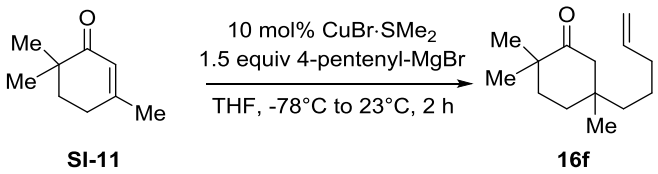
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.73 (s, 1H), 2.26 (at, J = 6.0 Hz, 2H), 1.89 (s, 3H), 1.77 (at, J = 6.0 Hz, 2H), 1.05 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 204.6, 160.5, 125.1, 40.2, 36.4, 28.5, 24.3, 24.1.

IR (cm^{-1}): 2962, 2918, 1667, 1636, 1472, 1439, 1381, 1313, 1212, 1173, 1120, 1002, 916, 863, 691.

GCMS (m/z): calc'd for $C_9H_{14}O$: 138.1; found: 138.1

Rf: 0.33 (10% EtOAc/hexanes)

5.4.11 Synthesis of 2,2,5-trimethyl-5-(pent-4-en-1-yl)cyclohexan-1-one (16f)



To a flame-dried 20 mL microwave vial equipped with a magnetic stir bar was added magnesium turnings (176 mg, 7.24 mmol, 2.0 equiv) and a catalytic amount of I_2 (*ca.* 2.0 mg). The vial was capped, evacuated, and backfilled with N_2 and THF (8.5 mL, 0.64 M) was added to the reaction vessel. The reaction vessel was then moved to a 70 °C pre-heated oil bath and stirred for 10 minutes. The reaction vessel was then removed from the oil bath and to the reaction mixture was added 5-bromo-1-pentene (0.64 mL, 5.43 mmol, 1.5 equiv) dropwise over 10 minutes as to maintain a gentle reflux. The reaction vessel

was then moved back to a 70 °C oil bath and stirred for 30 minutes. The reaction vessel was then removed from the oil bath and cooled to ambient temperature. In a separate flame-dried 100 mL round-bottomed flask equipped with a magnetic stir bar was added CuBr•SMe_2 (76 mg, 0.36 mmol, 10 mol %). The flask was evacuated and backfilled with N_2 before THF (30 mL, 0.12 M) was added to the reaction vessel. The reaction mixture was then cooled to −40 °C in a dry ice-acetonitrile bath and the previously prepared 4-pentenylmagnesium bromide solution was added dropwise over 10 minutes. The reaction mixture was stirred at −40 °C for 30 minutes before it was cooled to −78 °C in a dry ice-acetone bath and **SI-11** (500 mg, 3.62 mmol, 1.0 equiv) was added dropwise. The reaction mixture was stirred for 2 hours and slowly warmed to ambient temperature. To the reaction mixture was added sat. aq. NH_4Cl (15 mL) and Et_2O (15 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (2 x 15 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (5% Et_2O/hexanes) afforded **16f** (478 mg, 63%) as a colorless oil.

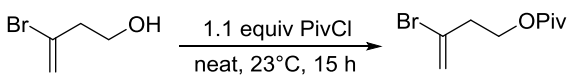
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, J = 16.8, 10.0, 6.8 Hz, 1H), 5.02–4.93 (m, 2H), 2.28 (d, J = 13.6 Hz, 1H), 2.13 (dd, J = 13.6, 1.0 Hz, 1H), 2.02 (aq, J = 7.0 Hz, 2H), 1.71–1.63 (m, 3H), 1.56–1.48 (m, 1H), 1.39–1.29 (m, 2H), 1.27–1.21 (m, 2H), 1.10 (s, 3H), 1.08 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.4, 138.8, 114.7, 50.2, 44.3, 41.3, 39.2, 36.6, 34.4, 32.6, 25.4, 25.3, 25.1, 22.9.

IR (cm^{-1}): 2961, 2931, 2861, 1704, 1641, 1462, 1385, 1302, 1105, 992, 909, 704.

GCMS (m/z): calc'd for $C_{14}H_{24}O$: 208.2; found: 208.2

Rf: 0.30 (5% Et_2O/hexanes)

5.4.12 Synthesis of 3-bromobut-3-en-1-yl pivalate (SI-13)



SI-12 **SI-13**

To a flame-dried 10 mL microwave vial was added alcohol 3-Bromo-3-buten-1-ol **SI-12** (0.50 mL, 5.04 mmol, 1.0 equiv) and pivaloyl chloride (0.68 mL, 5.54 mmol, 1.1 equiv). The neat reaction mixture was stirred at ambient temperature for 15 hours. To the

reaction mixture was added CH_2Cl_2 (25 mL) and sat. aq. $NaHCO_3$ (20 mL) and the organic phase was separated. The organic phase was washed with sat. aq. $NaHCO_3$ (2 x 20 mL) and water (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation to afford **SI-13** (1.09 g, 92%) as a yellow oil.

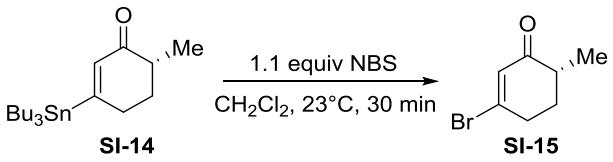
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63–5.62 (m, 1H), 5.47 (d, J = 2.0 Hz, 2H), 4.22 (t, J = 6.0 Hz, 2H), 2.72 (td, J = 6.0, 0.8 Hz, 2H), 1.16 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 129.7, 119.0, 61.6, 40.7, 38.8, 27.2.

IR (cm^{-1}): 2972, 1728, 1631, 1480, 1398, 1282, 1143, 1035, 890, 770, 533.

HRMS (m/z): $[M+H]^+$ calc'd for $C_9H_{16}BrO_2^+$: 235.0328; found: 235.0334

Rf: 0.36 (5% Et_2O/hexanes)

5.4.13 Synthesis of (*R*)-3-bromo-6-methylcyclohex-2-en-1-one (SI-15)



To a stirred solution of stannane **SI-14**[264] (2.0 g, 5.00 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL, 0.5 M) was added *N*-bromosuccinimide (980 mg, 5.50 mmol, 1.1 equiv) and the reaction mixture was stirred for 30 minutes at ambient temperature. To the reaction mixture was added water (20 mL) and CH_2Cl_2 (10 mL) and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic extracts were concentrated under reduced pressure by rotary evaporation. The crude mixture was partitioned between hexanes (10 mL) and MeCN (20 mL) and the MeCN layer was separated. The MeCN layer was further washed with hexanes (3 x 10 mL) and concentrated under reduced pressure by rotary evaporation. The crude mixture was diluted with Et_2O (20 mL) and the precipitate was removed by filtration. The filtrate was concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (10% Et_2O/hexanes) afforded **SI-15** (486 mg, 51%) as a colorless oil. The characterization data matches those reported for the racemic compound in the literature.[265]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.42 (s, 1H), 2.87 (dddd, J = 19.0, 10.0, 5.0, 2.0 Hz, 1H), 2.80 (adt, J = 19.0, 4.5 Hz, 1H), 2.35 (ddd, J = 14.0, 7.0, 5.0 Hz, 1H), 2.08 (adq, J = 13.5, 4.5 Hz, 1H), 1.80 (dddd, J = 13.5, 12.0, 10.0, 5.5 Hz, 1H), 1.13 (d, J = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.8, 149.0, 132.1, 40.3, 36.1, 31.1, 14.8.

IR (cm^{-1}): 2932, 2872, 1674, 1608, 1456, 1423, 1338, 1264, 1225, 1190, 1098, 1051, 1026, 928, 869, 767, 734, 579.

GCMS (m/z): calc'd for C_7H_9BrO: 188.0; found: 188.0

Rf: 0.23 (10% Et_2O/hexanes)

$[\alpha]_D^{20.0}$: +22.1° (*c* 1.0, $CHCl_3$)

5.4.14 General Procedure for Alkene Difunctionalization

To a flame-dried 10 mL microwave vial equipped with a magnetic stir bar was added tetrabutylammonium salt[a] (0.40 mol, 2.0 equiv), $NiCl_2$(dme) (4.4 mg, 0.02 mol, 10 mol %), and P(*p*-CF_3-C_6H_4)$_3$ (28.0 mg, 0.06 mol, 30 mol %). The vial was capped, evacuated, and backfilled with N_2 before solvent[b] (2.0 mL, 0.10 M) was added and the mixture was stirred for five minutes at ambient temperature to give a brown suspension (TBAI) or a light blue solution (TBAOTf). To the reaction mixture was added electrophile (0.24 mmol, 1.2 equiv), ketone **16** (0.20 mmol, 1.0 equiv), and $Zn(TMP)_2$ (0.48 mL, 0.50 M in toluene, 0.24 mmol, 1.2 equiv). The reaction vessel was sealed with parafilm and placed into a pre-heated 80 °C oil bath and stirred for 12 hours. The reaction mixture was removed from the oil bath and cooled to ambient temperature before sat. aq. NH_4Cl was added. The mixture was diluted with Et_2O (2 mL) and the organic phase was separated. The aqueous phase was extracted with Et_2O (2 x 2 mL) and the combined organic extracts were filtered through a pad of dry silica in a glass pipette before being concentrated under reduced pressure by rotary evaporation. The crude mixture was purified by flash column chromatography on silica gel.

[a]Either TBAI or TBAOTf was used.

[b]Either 1,4-dioxane or 1,4-dioxane/THF (1:1) was used.

(1*R*,3a*R*,4*R*,6*S*,7a*R*)-3a,5,5-trimethyl-1-(pyridin-2-ylmethyl)octahydro-7*H*-4,6-methanoinden-7-one (17a): Following the general procedure (TBAI and 1,4-dioxane/THF 1:1), using ketone **16a** (41.3 mg, 0.2 mmol, 1.0 equiv) and 2-chloropyridine (22.7 μL, 0.24 mmol, 1.2 equiv) as electrophile, compound **17a** has been

purified by column chromatography (50% EtOAc/hexanes), obtaining an off-white solid; yield: 80 % (45.2 mg, 14:1 dr).

Major diastereomer only. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 4.8 Hz, 1H), 7.57 (atd, J = 7.6, 1.6 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 7.09 (dd, J = 7.2, 5.6 Hz, 1H), 3.60 (dd, J = 13.2, 3.6 Hz, 1H), 2.72 (dd, J = 13.2, 10.4 Hz, 1H), 2.54 (at, J = 5.2 Hz, 1H), 2.44 (adt, J = 11.2, 6.0 Hz, 1H), 2.37–2.26 (m, 1H), 2.08 (d, J = 10.0 Hz, 1H), 2.01 (at, J = 5.2 Hz, 1H), 1.70–1.59 (m, 3H), 1.52–1.38 (m, 2H), 1.36 (s, 3H), 1.21 (s, 3H), 1.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.0, 161.2, 149.2, 136.3, 123.6, 121.1, 60.8, 58.5, 52.2, 49.6, 44.8, 44.2, 42.9, 40.7, 31.4, 29.2, 27.4, 25.9, 25.3.

IR (cm^{-1}): 2950, 1695, 1590, 1474, 1322, 1269, 1133, 1062, 734, 606, 520.

GCMS (m/z): calc'd for $C_{19}H_{25}NO$: 283.2; found: 283.2

Rf: 0.21 (15% EtOAc/hexanes)

(1*R*,3a*R*,4*R*,6*S*,7a*R*)-1-benzyl-3a,5,5-trimethyloctahydro-7*H*-4,6-methanoinden-7-one (17b): Following the general procedure (TBAOTf and 1,4-dioxane), using ketone **16a** (41.3 mg, 0.2 mmol, 1.0 equiv) and chlorobenzene (24.4 μL, 0.24 mmol, 1.2 equiv) as electrophile, compound **17b** has been purified by column chromatography (5% Et_2O/hexanes), obtaining a light-yellow solid; yield: 82 % (46.6 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2H), 7.21–7.17 (m, 3H), 3.48 (dd, J = 13.2, 2.8 Hz, 1H), 2.57 (at, J = 5.2 Hz, 1H), 2.51 (dd, J = 13.2, 10.0 Hz, 1H), 2.48–2.43 (m, 1H), 2.16–2.01 (m, 3H), 1.72–1.56 (m, 3H), 1.47–1.36 (m, 2H), 1.39 (s, 3H), 1.22 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.2, 141.3, 129.2, 128.3, 125.9, 60.6, 58.5, 52.2, 51.3, 44.2, 42.8, 42.6, 40.5, 31.3, 29.1, 27.4, 25.9, 25.2.

IR (cm^{-1}): 2947, 2872, 1697, 1454, 1269, 1202, 981, 762, 699, 521

GCMS (m/z): calc'd for $C_{20}H_{26}O$: 282.2; found: 282.2

Rf: 0.46 (10% EtOAc/hexanes)

$[\alpha]_D^{20.0}$: -40.9° (*c* 1.0, $CHCl_3$)

(1*R*,3*S*,4a*R*,5*R*,8a*R*)-5-benzyl-2,2,8a-trimethyloctahydro-1,3-methanonaphthalen-4(1*H*)-one (17c): Following the general procedure (TBAOTf and 1,4-dioxane), using ketone **16b** (44.1 mg, 0.2 mmol, 1.0 equiv) and chlorobenzene (24.4 μL, 0.24 mmol, 1.2 equiv) as electrophile, compound **17c** has been purified by column chromatography (3% Et_2O/hexanes), obtaining a white solid; yield: 66 % (39.0 mg).

The yield of **17c** using other aryl electrophiles:

Bromobenzene (36.9 mg, 62%)

Iodobenzene (35.0 mg, 59%)

Phenyl trifluoromethansulfonate (34.9 mg, 59%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2H), 7.22–7.16 (m, 3H), 3.32 (dd, *J* = 13.2, 5.2 Hz, 1H), 2.60 (at, *J* = 5.6 Hz, 1H), 2.56–2.48 (m, 2H), 2.41–2.31 (m, 1H), 2.08 (d, *J* = 7.2 Hz, 1H), 1.83 (at, *J* = 5.6 Hz, 1H), 1.76–1.61 (m, 3H), 1.53–1.44 (m, 2H), 1.37 (s, 3H), 1.27 (s, 3H), 1.24–1.20 (m, 1H), 1.10–1.04 (m, 1H), 1.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.1, 141.4, 129.5, 128.3, 125.9, 59.0, 55.5, 55.5, 41.8, 40.0, 36.2, 36.2, 33.6, 28.6, 27.8, 26.5, 26.5, 25.7, 16.5.

IR (cm^{-1}): 2943, 2873, 1698, 1453, 1203, 909, 744, 700, 521.

GCMS (m/z): calc'd for $C_{21}H_{28}O$: 296.2; found: 296.2

Rf: 0.32 (20% Et_2O/hexanes)

$[\alpha]_D^{20.0}$: -33.3° (*c* 1.0, $CHCl_3$)

Methyl 4-(((1*R*,3*S*,4a*R*,5*R*,8a*R*)-2,2,8a-trimethyl-4-oxodecahydro-1,3-methanonaphthalen-5-yl)methyl)benzoate (17d) Following the general procedure (TBAOTf and 1,4-dioxane), using ketone **16b** (44.1 mg, 0.2 mmol, 1.0 equiv) and methyl 4-chlorobenzoate (40.9 mg, 0.24 mmol, 1.2 equiv) as electrophile, compound **17d** has been purified by column chromatography (10% Et_2O/hexanes), affording a mixture of **17d** and homocoupled electrophile by-product. This mixture was further purified by the addition of hexanes to precipitate out the homocoupling by-product, which was removed by filtration to afford **17d** as an off-white solid; yield: 71 % (50.3 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 3.89 (s, 3H), 3.38 (dd, *J* = 13.2, 5.2 Hz, 1H), 2.59–2.49 (m, 3H), 2.36–2.27 (m, 1H), 2.02 (d, *J* = 8.0 Hz, 1H), 1.82 (at, *J* = 5.8 Hz, 1H), 1.66–1.59 (m, 3H), 1.52–1.40 (m, 2H), 1.35 (s, 3H), 1.24 (s, 3H), 1.22–1.17 (m, 1H), 1.06–1.02 (m, 1H), 1.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.1, 167.4, 147.1, 129.6, 129.6, 127.9, 59.0, 55.5, 55.4, 52.1, 41.9, 40.0, 36.4, 36.3, 33.2, 28.5, 27.8, 26.5, 26.4, 25.7, 16.5.

IR (cm^{-1}): 2947, 2871, 1719, 1695, 1609, 1435, 1274, 1178, 1108, 1021, 760, 710.

GCMS (m/z): calc'd for $C_{23}H_{30}O_3$: 354.2; found: 354.3

Rf: 0.37 (20% EtOAc/hexanes)

$[\alpha]_D^{20.0}$: -30.2° (*c* 1.0, $CHCl_3$)

(1*R*,3*S*,4a*R*,5*R*,8a*R*)-2,2,8a-trimethyl-5-(4-(trifluoromethyl)benzyl)octahydro-1,3-methanonaphthalen-4(1*H*)-one (17e): Following the general procedure (TBAOTf and 1,4-dioxane), using ketone **16b** (44.1 mg, 0.2 mmol, 1.0 equiv) and 4-chlorobenzotrifluoride (32.0 μL, 0.24 mmol, 1.2 equiv) as electrophile, compound **17e** has been purified by column chromatography (3% Et_2O/hexanes), obtaining a white crystalline solid; yield: 73 % (53.3 mg). Recrystallization in hot hexanes afforded large white needles.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 3.40 (dd, J = 13.2, 5.2 Hz, 1H), 2.60–2.40 (m, 3H), 2.33–2.24 (m, 1H), 2.02 (d, J = 8.0 Hz, 1H), 1.82 (at, J = 5.8 Hz, 1H), 1.74–1.59 (m, 3H), 1.53–1.41 (m, 2H), 1.35 (s, 3H), 1.24 (s, 3H), 1.22–1.16 (m, 1H), 1.08–1.02 (m, 1H), 1.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.2, 145.5, 129.8, 128.2 (q, $J_{C\text{-}F}$ = 32.3 Hz) 125.1 (q, $J_{C\text{-}F}$ = 4.0 Hz), 124.6 (q, $J_{C\text{-}F}$ = 272.7 Hz) 59.0, 55.6, 55.3, 41.7, 40.0, 36.5, 36.2, 33.1, 28.4, 27.7, 26.3, 26.3, 25.7, 16.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.3.

IR (cm^{-1}): 2951, 1699, 1379, 1275, 1169, 1127, 895, 683, 522.

GCMS (m/z): calc'd for $C_{22}H_{27}F_3O$: 364.2; found: 364.2

Rf: 0.28 (20% Et_2O/hexanes)

$[\alpha]_D^{20.0}$: -25.0° (*c* 1.0, $CHCl_3$)

(1*R*,3*S*,4a*R*,5*R*,8a*R*)-5-(4-methoxybenzyl)-2,2,8a-trimethyloctahydro-1,3-methanonaphthalen-4(1*H*)-one (17f): Following the general procedure (TBAOTf and 1,4-dioxane), using ketone **16b** (44.1 mg, 0.2 mmol, 1.0 equiv) and 4-chloroanisole (29.4 μL, 0.24 mmol, 1.2 equiv) as electrophile, compound **17f** has been purified by column chromatography (5% Et_2O/hexanes), followed by removal of volatile impurities under reduced pressure for 4 days, obtaining a colorless oil; yield: 55 % (36.0 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 3.78 (s, 3H), 3.19 (dd, J = 13.6, 5.6 Hz, 1H), 2.57 (at, J = 5.6 Hz, 1H), 2.54–2.44 (m, 2H), 2.35–2.27 (m, 1H), 2.06 (d, J = 7.2 Hz, 1H), 1.80 (at, J = 5.6 Hz, 1H), 1.73–1.59 (m, 3H), 1.52–1.43 (m, 2H), 1.35 (s, 3H), 1.24 (s, 3H), 1.21–1.13 (m, 1H), 1.07–1.02 (m, 1H), 1.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.1, 157.8, 133.3, 130.4, 113.6, 59.0, 55.5, 55.3, 55.3, 40.8, 39.9, 36.3, 36.2, 33.7, 28.6, 27.8, 26.6, 26.5, 25.7, 16.5.

IR (cm^{-1}): 2942, 2870, 1697, 1511, 1464, 1244, 1176, 1036, 818, 514.

GCMS (m/z): calc'd for $C_{22}H_{30}O_2$: 326.2; found: 326.3

Rf: 0.48 (20% EtOAc/hexanes)

$[\alpha]_D^{20.0}$: -25.2° (*c* 1.0, $CHCl_3$)

(1*R*,3*S*,4a*R*,5*R*,8a*R*)-5-(4-(dimethylamino)benzyl)-2,2,8a-trimethyloctahydro-1,3-methanonaphthalen-4(1*H*)-one (17g): Following the general procedure (TBAOTf and 1,4-dioxane), using ketone **16b** (44.1 mg, 0.2 mmol, 1.0 equiv) and 4-chloro-*N*,*N*-dimethylaniline[266] (37.4 mg, 0.24 mmol, 1.2 equiv) as electrophile, compound **17g** has been purified by column chromatography (10% Et_2O/hexanes), obtaining a yellow solid; yield: 45 % (30.4 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.4 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 3.15 (dd, *J* = 13.2, 5.2 Hz, 1H), 2.91 (s, 6H), 2.58 (at, *J* = 5.6 Hz, 1H), 2.51 (adt, *J* = 11.2, 6.0 Hz, 1H), 2.43 (dd, *J* = 13.6, 9.2 Hz, 1H), 2.35–2.27 (m, 1H), 2.08 (d, *J* = 7.2 Hz, 1H), 1.80 (at, *J* = 5.6 Hz, 1H), 1.72–1.57 (m, 3H), 1.52–1.44 (m, 2H), 1.35 (s, 3H), 1.25 (s, 3H), 1.23–1.10 (m, 1H), 1.10–1.06 (m, 1H), 1.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 215.1, 149.0, 130.1, 129.5, 112.9, 59.0, 55.5, 55.4, 41.0, 40.7, 39.9, 36.3, 36.2, 33.8, 28.6, 27.8, 26.6, 26.5, 25.7, 16.5.

IR (cm^{-1}): 2940, 2869, 2800, 1697, 1615, 1519, 1475, 1344, 1203, 947, 805, 520.

GCMS (m/z): calc'd for $C_{23}H_{33}NO$: 339.3; found: 339.3

Rf: 0.41 (20% EtOAc/hexanes)

$[\alpha]_D^{20.0}$: -20.6° (*c* 1.0, $CHCl_3$)

4-(((2*S*,4a*R*,4b*S*,6a*S*,7a*R*,8*R*,10a*R*,10b*R*,10c*R*)-2-((*tert*-butyldimethylsilyl)oxy)-4a,6a,10a-trimethyl-7-oxo-1,2,3,4,4a,4b,5,6,6a,7,7a,8,9,10,10a,10b,10c,11-octadecahydropentaleno[1,2-*a*]phenanthren-8-yl)methyl)benzonitrile (17h): Following the general procedure (TBAOTf and 1,4-dioxane), using ketone **16c** (47.1 mg, 0.1 mmol, 1.0 equiv) and 4-chlorobenzonitrile (16.5 mg, 0.12 mmol, 1.2 equiv) as electrophile, compound **17h** has been purified by column chromatography (10% Et_2O/hexanes), obtaining a white solid; yield: 51 % (29.0 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 5.35–5.33 (m, 1H), 3.52–3.44 (m, 1H), 3.37 (dd, *J* = 15.2, 6.4 Hz, 1H), 2.65 (dd, *J* = 13.6, 9.2 Hz, 1H), 2.59 (d, *J* = 8.8 Hz, 1H), 2.30–2.16 (m, 4H), 1.93 (ddd, *J* = 21.2, 10.8, 4.4 Hz, 1H), 1.85–1.78 (m, 3H), 1.76–1.72 (m, 2H), 1.68–1.63 (m, 1H), 1.56–1.39 (m, 3H), 1.27

(s, 3H), 1.25–1.19 (m, 3H), 1.12–1.08 (m, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 0.89 (s, 9H), -0.06 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.4, 148.6, 141.6, 132.2, 129.7, 120.6, 119.4, 109.6, 72.6, 59.7, 56.0, 50.9, 50.1, 47.7, 44.5, 42.7, 42.4, 37.6, 37.2, 36.2, 33.3, 33.1, 32.1, 32.1, 30.5, 26.1, 24.6, 20.0, 19.5, 18.4, 18.4, -4.5.

IR (cm^{-1}): 2929, 2856, 2228, 1729, 1462, 1251, 1088, 835, 774, 736, 546.

HRMS (m/z): $[M+H]^+$ calc'd for $C_{37}H_{54}NO_2Si^+$: 572.3918; found: 572.3914.

Rf: 0.46 (15% EtOAc/hexanes)

$[\alpha]_D^{20.0}$: -23.5° (*c* 1.0, $CHCl_3$)

6-(4-fluorobenzyl)-2,2,3a-trimethylhexahydropentalen-1(2*H*)-one (17i): Following the general procedure (TBAOTf and 1,4-dioxane), using ketone **16d** (36.1 mg, 0.2 mmol, 1.0 equiv) and 1-chloro-4-fluorobenzene (25.6 μL, 0.24 mmol, 1.2 equiv) as electrophile, compound **17i** has been purified by column chromatography (2% Et_2O/hexanes), obtaining a colorless oil; yield: 55 % (30.1 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.14 (m, 2H), 6.98–6.94 (m, 2H), 2.85 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.57 (dd, *J* = 13.6, 9.2 Hz, 1H), 2.48–2.40 (m, 1H), 2.15 (d, *J* = 4.4 Hz, 1H), 1.79 (1/2 abq, *J* = 13.6 Hz, 1H), 1.72 (1/2 abq, *J* = 13.6 Hz, 1H), 1.69–1.65 (m, 1H), 1.62–1.50 (m, 2H), 1.47–1.41 (m, 1H), 1.29 (s, 3H), 1.09 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 225.6, 161.5 (d, $J_{C\text{-}F}$ = 244.4 Hz), 136.5 (d, $J_{C\text{-}F}$ = 3.1 Hz), 130.5 (d, $J_{C\text{-}F}$ = 8.1 Hz), 115.2 (d, $J_{C\text{-}F}$ = 21.2 Hz), 64.0, 51.2, 47.4, 45.9, 44.2, 42.1, 40.8, 31.3, 30.3, 27.6, 26.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.6 (m).

IR (cm^{-1}): 2931, 2866, 1730, 1509, 1457, 1221, 1157, 823.

GCMS (m/z): calc'd for $C_{18}H_{23}FO$: 274.2; found: 274.2.

Rf: 0.45 (10% EtOAc/hexanes)

8-(4-chlorobenzyl)-5-methylbicyclo[3.3.1]non-3-en-2-one (17j): Following the general procedure (TBAOTf and 1,4-dioxane), using ketone **16e** (32.8 mg, 0.2 mmol, 1.0 equiv) and 1-chloro-4-iodobenzene (57.2 mg, 0.24 mmol, 1.2 equiv) as electrophile, compound **17j** has been purified by column chromatography (7% Et_2O/hexanes), obtaining a colorless oil; yield: 63 % (34.7 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.24 (m, 2H), 7.21–7.19 (m, 2H), 6.58 (dd, *J* = 10.0, 2.0 Hz, 1H), 6.12 (d, *J* = 10.0 Hz, 1H), 2.61 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.46–2.42 (m, 1H), 2.31 (dd, *J* = 13.8, 7.0 Hz, 1H), 2.08 (adt, *J* = 12.4, 2.8 Hz, 1H), 1.77–1.68 (m, 1H),

1.60–1.56 (m, 1H), 1.51–1.36 (m, 3H), 1.30–1.19 (m, 1H), 1.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5, 157.1, 139.2, 131.7, 131.3, 130.9, 128.4, 46.6, 42.4, 41.5, 39.5, 34.6, 34.0, 28.6, 26.1.

IR (cm^{-1}): 2924, 2858, 1669, 1491, 1453, 1084, 1016, 822, 524, 501.

GCMS (m/z): calc'd for $C_{17}H_{19}ClO$: 274.1; found: 274.1.

Rf: 0.25 (20% Et_2O/hexanes)

2,2,4a-trimethyl-8-(4-vinylbenzyl)octahydronaphthalen-1(2*H*)-one (17k): Following the general procedure (TBAOTf and 1,4-dioxane), using ketone **16f** (41.7 mg, 0.2 mmol, 1.0 equiv) and 4-chlorostyrene (28.8 μL, 0.24 mmol, 1.2 equiv) as electrophile, compound **17k** has been purified by column chromatography (2% Et_2O/hexanes), obtaining a yellow solid; yield: 44 % (27.1 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.68 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.69 (d, *J* = 17.6 Hz, 1H), 5.19 (d, *J* = 11.2 Hz, 1H), 2.66 (dd, *J* = 12.8, 2.4 Hz, 1H), 2.26 (atd, *J* = 13.6, 4.8 Hz, 1H), 2.21–2.07 (m, 2H), 1.90 (dd, *J* = 10.8, 1.2 Hz, 1H), 1.83 (atd, *J* = 13.6, 4.8 Hz, 1H), 1.72–1.63 (m, 3H), 1.53–1.41 (m, 3H), 1.31 (s, 3H), 1.16 (atd, *J* = 12.4, 4.8 Hz, 1H), 1.12 (s, 3H), 0.88 (s, 3H), 0.71 (ddd, *J* = 23.6, 12.4, 4.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.4, 140.4, 136.7, 135.4, 129.6, 126.1, 113.1, 64.9, 43.8, 40.5, 40.1, 38.3, 37.1, 36.3, 31.1, 29.0, 28.0, 27.9, 26.7, 21.1.

IR (cm^{-1}): 2926, 2866, 1692, 1460, 903, 736, 505.

GCMS (m/z): calc'd for $C_{22}H_{30}O$: 310.2; found: 310.3

Rf: 0.42 (20% Et_2O/hexanes)

Ethyl 4-((4-(ethoxycarbonyl)-4-methyl-3-oxocyclohexyl)methyl)benzoate (17l): Following the general procedure (TBAOTf and 1,4-dioxane), using ketone **16g** (39.7 mg, 0.2 mmol, 1.0 equiv) and ethyl 4-bromobenzoate (39.2 μL, 0.24 mmol, 1.2 equiv) as electrophile, compound **17l** has been purified by column chromatography (15% Et_2O/hexanes), obtaining a light-yellow oil; yield: 35 % (24.1 mg, 1:1 dr).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.95 (m, 2H), 7.18 (dd, *J* = 10.8, 6.4 Hz, 2H), 4.39–4.34 (m, 2H), 4.22–4.16 (m, 2H), 2.65–2.62 (m, 2H), 2.53–2.22 (m, 3H), 2.05–1.96 (m, 0.5H), 1.90–1.83 (m, 0.5H), 1.78–1.70 (m, 1H), 1.54–1.42 (m, 1H), 1.40–1.36 (m, 5H), 1.26–1.22 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.3, 207.2, 173.0, 166.7, 166.6,

145.0, 144.7, 129.9, 129.8, 129.2, 129.2, 128.8, 61.5, 61.5, 61.0, 57.2, 56.5, 47.0, 44.4, 43.4, 41.7, 40.6, 39.7, 36.9, 33.8, 29.9, 29.1, 26.5, 21.2, 20.9, 14.5, 14.2.
IR (cm^{-1}): 2980, 2933, 1710, 1448, 1273, 1177, 1100, 1020, 862, 761, 707.
GCMS (m/z): calc'd for $C_{20}H_{26}O_5$: 346.2; found: 346.2.
Rf: 0.42 (20% EtOAc/hexanes)

Methyl 3-(((4a*S*,7*S*,8*R*)-4,9-dioxo-1,3,4,5,6,7,8,9-octahydro-2*H*-4a,8-methanobenzo[8]annulen-7-yl)methyl)benzoate (17m): Following the general procedure (TBAOTf and 1,4-dioxane), using ketone **16h** (43.7 mg, 0.2 mmol, 1.0 equiv) and methyl 3-bromobenzoate (51.6 mg, 0.24 mmol, 1.2 equiv) as electrophile, compound **17m** has been purified by column chromatography (25% EtOAc/hexanes), followed by preparatory thin layer chromatography (30% EtOAc/benzene), obtaining a white solid; yield: 21 % (14.5 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.85 (m, 2H), 7.46 (adt, *J* = 7.6, 1.2 Hz, 1H), 7.35 (at, *J* = 7.6 Hz, 1H), 6.13 (s, 1H), 3.90 (s, 3H), 2.73 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.64–2.47 (m, 5H), 2.35 (dd, *J* = 13.6, 76 Hz, 1H), 2.14–2.04 (m, 3H), 1.87–1.69 (m, 3H), 1.65–1.59 (m, 1H), 1.52 (atd, *J* = 12.8, 4.0 Hz, 1H), 1.31 (atd, *J* = 13.2, 4.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.1, 200.0, 167.4, 163.4, 140.6, 134.4, 130.3, 130.3, 129.4, 128.4, 127.5, 52.2, 51.9, 46.0, 40.2, 39.8, 38.2, 35.1, 32.2, 31.7, 25.2, 22.3
IR (cm^{-1}): 2931, 1712, 1661, 1434, 1280, 1201, 1108, 731, 699, 582.
GCMS (m/z): calc'd for $C_{22}H_{24}O_4$: 352.2; found: 352.2
Rf: 0.21 (50% EtOAc/hexanes)
$[\alpha]_D^{20.0}$: +28.0° (*c* 0.5, $CHCl_3$)

(3a*R*,5*R*,7a*R*)-5-isopropyl-7a-methyl-3-(pyridin-2-ylmethyl)octahydro-4*H*-inden-4-one (17n): Following the general procedure (TBAI and 1,4-dioxane/THF 1:1), using ketone **16i** (41.7 mg, 0.2 mmol, 1.0 equiv), 2-chloropyridine (22.7 μL, 0.24 mmol, 1.2 equiv) as electrophiles and 2.0 equiv of $Zn(TMP)_2$ (0.80 mL, 0.50 M in toluene, 0.40 mmol), compound **17n** has been purified by column chromatography (20% EtOAc/hexanes), obtaining a light yellow oil; yield: 65 % (37.3 mg, 2:1 dr).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49–8.47 (m, 1H), 7.60–7.53 (m, 1H), 7.19–7.06 (m, 2H), 3.09–2.94 (m, 1H), 2.85–2.71 (m, 2H), 2.26–2.15 (m, 1H), 2.07–1.84 (m, 4H), 1.79–1.70 (m, 1H), 1.65–1.39 (m, 6H), 1.14 (s, 1H), 1.04 (s, 2H), 0.90 (d, *J* = 6.8 Hz,

1H), 0.85 (d, *J* = 6.8 Hz, 1H), 0.78 (d, *J* = 6.8 Hz, 2H), 0.74 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.1, 214.9, 161.1, 160.5, 149.1, 149.1, 136.5, 136.4, 124.0, 123.4, 121.3, 121.2, 68.0, 65.1, 55.3, 52.2, 48.8, 45.6, 44.3, 44.2, 43.2, 42.7, 40.3, 39.6, 36.0, 34.4, 30.5, 30.4, 30.4, 27.9, 26.6, 26.1, 25.2, 22.4, 21.3, 21.2, 19.2, 18.7.

IR (cm^{-1}): 2952, 2869, 1694, 1591, 1473, 1435, 1379, 1167, 993, 749.

GCMS (m/z): calc'd for $C_{19}H_{27}NO$: 285.2; found: 285.2.

Rf: 0.38 (20% EtOAc/hexanes)

(1*R*,3a*R*,4*R*,6*S*,7a*R*)-3a,5,5-trimethyl-1-(pyrazin-2-ylmethyl)octahydro-7*H*-4,6-methanoinden-7-one (17o): Following the general procedure (TBAI and 1,4-dioxane/THF 1:1), using ketone **16a** (41.3 mg, 0.2 mmol, 1.0 equiv) and 2-chloropyrazine (21.4 μL, 0.24 mmol, 1.2 equiv) as electrophiles, compound **17o** has been purified by column chromatography (50% EtOAc/hexanes), obtaining a light yellow solid; yield: 57 % (32.6 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 2H), 8.40 (s, 1H), 3.61 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.78 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.55 (at, *J* = 5.2 Hz, 1H), 2.46 (adt, *J* = 10.8, 6.4 Hz, 1H), 2.38–2.28 (m, 1H), 2.09 (d, *J* = 10.0 Hz, 1H), 2.03 (at, *J* = 5.6 Hz, 1H), 1.71–1.60 (m, 4H), 1.50–1.40 (m, 2H), 1.37 (s, 3H), 1.22 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.8, 156.8, 145.2, 144.1, 142.3, 60.6, 58.5, 52.2, 49.0, 44.2, 42.8, 41.9, 40.6, 31.4, 29.1, 27.4, 26.0, 25.3.

IR (cm^{-1}): 2946, 2873, 1696, 1474, 1402, 1251, 1017, 831, 521.

GCMS (m/z): calc'd for $C_{18}H_{24}N_2O$: 284.2; found: 284.2.

Rf: 0.25 (20% EtOAc/hexanes)

$[\alpha]_D^{20.0}$: -37.8° (*c* 1.0, $CHCl_3$)

(2*S*,4a*R*,4b*S*,6a*S*,7a*R*,8*R*,10a*R*,10b*R*,10c*R*)-2-((*tert*-butyldimethylsilyl)oxy)-4a,6a,10a-trimethyl-8-(pyrimidin-2-ylmethyl)-2,3,4,4a,4b,5,6,6a,7a,8,9,10,10a,10b,10c,11-hexadecahydropentaleno[1,2-*a*]phenanthren-7(1*H*)-one (17p): Following the general procedure (TBAOTf and 1,4-dioxane/THF 1:1), using ketone **16c** (47.1 mg, 0.1 mmol, 1.0 equiv) and 2-chloropyrimidine (13.7 mg, 0.12 mmol, 1.2 equiv) as electrophiles, compound **17p** has been purified by column chromatography (40% EtOAc/hexanes), obtaining a colorless oil; yield: 43 % (23.9 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 4.8 Hz, 2H), 7.12 (t, J = 4.8 Hz, 1H), 5.35–5.34 (m, 1H), 3.55 (dd, J = 15.2, 6.4 Hz, 1H), 3.51–3.44 (m, 1H), 3.02 (dd, J = 15.2, 9.2 Hz, 1H), 2.83 (d, J = 9.6 Hz, 1H), 2.80–2.71 (m, 1H), 2.34–2.17 (m, 3H), 1.98–1.79 (m, 4H), 1.74–1.70 (m, 2H), 1.66–1.49 (m, 8H), 1.48–1.35 (m, 1H), 1.31 (s, 3H), 1.21–1.11 (m, 1H), 1.06 (s, 3H), 1.04 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.3, 157.0, 141.6, 120.7, 72.6, 60.3, 56.0, 51.0, 50.1, 47.8, 42.7, 42.3, 41.2, 40.1, 37.6, 37.2, 33.4, 33.1, 32.2, 30.5, 26.1, 24.5, 20.0, 19.5, 18.5, 18.4, -4.5.

IR (cm^{-1}): 2930, 2856, 1730, 1561, 1422, 1251, 1088, 835, 774, 734

HRMS (m/z): $[M+H]^+$ calc'd for $C_{34}H_{53}N_2O_2Si^+$: 549.3871; found: 549.3876

Rf: 0.28 (50% EtOAc/hexanes)

$[\alpha]_D^{20.0}$: -48.6° (*c* 1.0, $CHCl_3$)

(1*R*,3a*R*,4*R*,6*S*,7a*R*)-3a,5,5-trimethyl-1-((6-phenylpyridazin-3-yl)methyl)octahydro-7*H*-4,6-methanoinden-7-one (17q): Following the general procedure (TBAI and 1,4-dioxane/THF 1:1), using ketone **16a** (41.3 mg, 0.2 mmol, 1.0 equiv) and 3-chloro-6-phenylpyridazine (45.8 mg, 0.24 mmol, 1.2 equiv) as electrophiles, compound **17q** has been purified by column chromatography (30% EtOAc/hexanes), obtaining a light brown solid; yield: 80 % (57.8 mg, 10:1 dr).

Major diastereomer only. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.08 (m, 2H), 7.79–7.77 (m, 2H), 7.53–7.45 (m, 3H), 7.42 (d, J = 8.8 Hz, 1H), 3.77 (dd, J = 14.0, 4.0 Hz, 1H), 3.03 (dd, J = 14.0, 10.4 Hz, 1H), 2.56 (at, J = 5.2 Hz, 1H), 2.52–2.38 (m, 2H), 2.12 (d, J = 10.0 Hz, 1H), 2.04 (at, J = 5.2 Hz, 1H), 1.82 (adt, J = 11.6, 5.6 Hz, 1H), 1.69 (d, J = 11.2 Hz, 1H), 1.66–1.50 (m, 1H), 1.45 (dd, J = 11.6, 6.0 Hz, 1H), 1.38 (s, 3H), 1.24 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.2, 161.1, 157.4, 136.5, 132.7, 132.6, 129.9, 129.1, 127.5, 127.0, 123.9, 60.6, 58.5, 52.2, 49.0, 44.2, 42.9, 42.2, 40.6, 31.5, 29.2, 27.4, 26.0, 25.3

IR (cm^{-1}): 2952, 2872, 1693, 1426, 1322, 1171, 1133, 1062, 735, 695.

GCMS (m/z): calc'd for $C_{24}H_{28}N_2O$: 360.2; found: 360.3.

Rf: 0.32 (50% EtOAc/hexanes)

(1*R*,3a*R*,4*R*,6*S*,7a*R*)-1-((4,6-dimethoxy-1,3,5-triazin-2-yl)methyl)-3a,5,5-trimethyloctahydro-7*H*-4,6-methanoinden-7-one (17r): Following the general procedure (TBAI and 1,4-dioxane/THF 1:1), using ketone **16a** (41.3 mg, 0.2 mmol, 1.0

equiv) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (42.1 mg, 0.24 mmol, 1.2 equiv) as electrophiles, compound **17r** has been purified by column chromatography (30% EtOAc/hexanes), obtaining a viscous light-yellow oil; yield: 51 % (35.2 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 6H), 3.49 (dd, J = 14.0, 4.4 Hz, 1H), 2.73 (dd, J = 14.2, 10.0 Hz, 1H), 2.56–2.42 (m, 3H), 2.09 (d, J = 10.0 Hz, 1H), 2.02 (at, J = 6.0 Hz, 1H), 1.82 (adt, J = 10.8, 6.4 Hz, 1H), 1.73–1.65 (m, 2H), 1.49–1.40 (m, 2H), 1.36 (s, 3H), 1.23 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.6, 182.3, 172.5, 60.6, 58.4, 55.2, 52.1, 46.9, 45.3, 44.2, 42.8, 40.7, 31.6, 29.2, 27.4, 25.9, 25.3.

IR (cm^{-1}): 2949, 1698, 1547, 1500, 1458, 1385, 1353, 1113, 1061, 821, 733, 525.

GCMS (m/z): calc'd for $C_{19}H_{27}N_3O_3$: 345.2; found: 345.2.

Rf: 0.34 (50% EtOAc/hexanes)

$[\alpha]_D^{20.0}$: -21.7° (*c* 1.0, $CHCl_3$)

2,2,3a-trimethyl-6-(quinolin-8-ylmethyl)hexahydropentalen-1(2*H*)-one (17s): Following the general procedure (TBAOTf and 1,4-dioxane/THF 1:1), using ketone **16d** (36.1 mg, 0.2 mmol, 1.0 equiv) and 8-chloroquinoline (30.7 μL, 0.24 mmol, 1.2 equiv) as electrophiles, compound **17s** has been purified by column chromatography (10% Et_2O/hexanes), obtaining a colorless oil; yield: 42 % (25.9 mg, 8.3:1 dr).

Major diastereomer only. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 2.4 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.67–7.64 (m, 2H), 7.48–7.42 (m, 1H), 7.37 (dd, J = 8.2, 4.2 Hz, 1H), 3.84 (dd, J = 13.2, 5.6 Hz, 1H), 3.10 (dd, J = 13.0, 9.4 Hz, 1H), 2.82–2.71 (m, 1H), 2.46 (d, J = 9.6 Hz, 1H), 1.80 (s, 2H), 1.67–1.63 (m, 1H), 1.59–1.54 (m, 1H), 1.41–1.36 (m, 2H), 1.22 (s, 3H), 1.14 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 226.9, 149.3, 141.0, 136.4, 129.9, 128.6, 126.3, 126.1, 120.8, 61.4, 52.0, 51.1, 47.1, 45.3, 44.8, 42.0, 32.8, 32.7, 30.6, 28.1, 25.3.

IR (cm^{-1}): 2953, 2928, 2864, 1723, 1498, 1105, 982, 790, 734, 582.

GCMS (m/z): calc'd for $C_{21}H_{25}NO$: 307.2; found: 307.2.

Rf: 0.42 (20% EtOAc/hexanes)

8-(benzofuran-5-ylmethyl)-5-methylbicyclo[3.3.1]non-3-en-2-one (17t): Following the general procedure (TBAI and 1,4-dioxane/THF 1:1), using ketone **16e** (32.8 mg, 0.2 mmol, 1.0 equiv) and 5-bromobenzofuran (30.1 μL, 0.24 mmol, 1.2 equiv) as

electrophiles, compound **17t** has been purified by column chromatography (10% Et_2O/hexanes), obtaining a yellow oil; yield: 41 % (22.9 mg).

1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 2.0 Hz, 1H), 7.49 (bs, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.18 (dd, J = 8.4, 1.6 Hz, 1H), 6.73–6.71 (m, 1H), 6.58 (dd, J = 10.0, 2.0 Hz, 1H), 6.13 (d, J = 10.0 Hz, 1H), 2.75 (dd, J = 13.6, 7.2 Hz, 1H), 2.53–2.48 (m, 1H), 2.41 (dd, J = 13.6, 7.2 Hz, 1H), 2.08 (adt, J = 12.4, 2.8 Hz, 1H), 1.83–1.74 (m, 1H), 1.64–1.56 (m, 2H), 1.49 (adt, J = 12.8, 2.0 Hz, 1H), 1.45–1.21 (m, 4H), 1.12 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.5, 156.8, 153.5, 144.9, 135.0, 131.1, 127.2, 125.7, 121.6, 110.7, 106.3, 46.6, 42.3, 41.9, 39.8, 34.5, 33.9, 28.4, 25.9.

IR (cm^{-1}): 2923, 2858, 1669, 1455, 1373, 1261, 1197, 1127, 1031, 883, 731, 421.

GCMS (m/z): calc'd for $C_{19}H_{20}O_2$: 280.1; found: 280.2.

Rf: 0.39 (20% Et_2O/hexanes)

6-(benzo[*b*]thiophen-5-ylmethyl)-2,2,3a-trimethylhexahydropentalen-1(2*H*)-one (17u): Following the general procedure (TBAOTf and 1,4-dioxane/THF 1:1), using ketone **16d** (36.1 mg, 0.2 mmol, 1.0 equiv) and 5-bromobenzothiophene (42.6 mg, 0.24 mmol, 1.2 equiv) as electrophiles, compound **17u** has been purified by column chromatography (5% Et_2O/hexanes), obtaining a pale-yellow oil; yield: 78 % (48.5 mg, 2.3:1 dr).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.71 (m, 2H), 7.37–7.34 (m, 1H), 7.29–7.23 (m, 2H), 3.37 (dd, J = 12.8, 4.4 Hz, 0.7H), 3.03 (dd, J = 13.6, 6.4 Hz, 0.3H), 2.71 (dd, J = 13.6, 9.2 Hz, 0.3H), 2.60–2.40 (m, 1.7H), 2.37 (d, J = 8.8 Hz, 0.7H), 2.23 (d, J = 4.4 Hz, 0.3H), 1.84–1.42 (m, 5.7H), 1.32 (s, 0.9H), 1.25 (s, 2.1H), 1.12–1.09 (m, 6H), 0.98–0.89 (m, 0.3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 226.7, 225.5, 140.1, 140.0, 138.8, 137.9, 137.8, 137.2, 125.9, 125.8, 125.6, 125.4, 123.7, 123.7, 123.4, 123.3, 122.5, 122.3, 64.1, 61.2, 51.9, 51.2, 47.3, 47.0, 46.8, 46.0, 44.7, 44.2, 42.1, 42.0, 41.6, 37.0, 32.7, 31.3, 30.6, 30.4, 28.0, 27.6, 26.1, 25.2.

IR (cm^{-1}): 2954, 2865, 1724, 1465, 1456, 1264, 1103, 1084, 886, 816, 735, 692, 623.

GCMS (m/z): calc'd for $C_{20}H_{24}OS$: 312.2; found: 312.2.

Rf: 0.30 (10% EtOAc/hexanes)

***tert*-butyl 4-((3a,6,6-trimethyl-7-oxooctahydro-1*H*-inden-1-yl)methyl)-1*H*-indole-1-carboxylate (17v):** Following the general procedure (TBAOTf and 1,4-dioxane/THF 1:1), using ketone **16j** (38.9 mg, 0.2 mmol, 1.0 equiv) and t*ert*-butyl 4-bromo-1*H*-indole-

1-carboxylate[267] (71.1 mg, 0.24 mmol, 1.2 equiv) as electrophiles, compound **17v** has been purified by column chromatography (5% Et_2O/hexanes), obtaining a orage oil; yield: 55 % (44.7 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.0 Hz, 1H), 7.58 (dd, J = 3.6 Hz, 1H), 7.21 (at, J = 7.6 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 6.69 (d, J = 3.6 Hz, 1H), 3.20 (dd, J = 18.0, 9.6 Hz, 1H), 2.69–2.62 (m, 1H), 2.10 (d, J = 7.6 Hz, 1H), 1.73–1.68 (m, 2H), 1.66 (s, 9H), 1.53–1.40 (m, 5H), 1.15 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.2, 150.0, 135.2, 133.8, 130.1, 125.5, 124.2, 123.0, 113.1, 106.0, 83.6, 63.3, 45.3, 44.5, 43.7, 40.4, 39.3, 35.2, 33.5, 30.9, 29.5, 28.3, 26.8, 26.8.

IR (cm^{-1}): 2931, 2866, 1732, 1690, 1428, 1323, 1154, 852, 735.

HRMS (m/z): $[M+H]^+$ calc'd for $C_{26}H_{36}NO_3^+$: 410.2690; found: 410.2695

Rf: 0.26 (10% EtOAc/hexanes)

6-(benzo[*d*]thiazol-2-ylmethyl)-2,2,3a-trimethylhexahydropentalen-1(2*H*)-one (17w): Following the general procedure (TBAI and 1,4-dioxane/THF 1:1), using ketone **16d** (36.1 mg, 0.2 mmol, 1.0 equiv) and 2-chlorobenzothiazole (31.2 μL, 0.24 mmol, 1.2 equiv) as electrophiles, compound **17w** has been purified by column chromatography (20% Et_2O/hexanes), followed by preparatory thin layer chromatography (100% CH_2Cl_2), obtaining a yellow oil; yield: 41 % (25.7 mg, 1.5:1 dr).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.95 (m, 1H), 7.86–7.82 (m, 1H), 7.47–7.42 (m, 1H), 7.37–7.32 (m, 1H), 3.67 (dd, J = 15.0, 6.6 Hz, 0.4H), 3.35 (dd, J = 14.4, 6.4 Hz, 0.6H), 3.16 (dd, J = 14.8, 8.8 Hz, 0.6H), 3.04 (dd, J = 14.8, 8.8 Hz, 0.4H), 2.84–2.70 (m, 1H), 2.48 (d, J = 9.2 Hz, 0.4H), 2.33 (d, J = 4.4 Hz, 0.6H), 1.92 (m, 4.6H), 1.65–1.51 (m, 1.4H), 1.33 (s, 1.8H), 1.29 (s, 1.2H), 1.11 (s, 1.2H), 1.10 (s, 1.8H), 1.09 (s, 1.2H), 1.08 (s, 1.8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 226.3, 224.6, 171.8, 170.6, 153.4, 153.3, 135.6, 135.5, 126.0, 125.9, 124.9, 124.7, 122.8, 122.6, 121.7, 121.6, 64.0, 60.4, 51.9, 51.1, 47.3, 47.2, 44.5, 44.3, 42.2, 42.0, 40.1, 35.2, 32.8, 31.7, 30.6, 30.2, 27.9, 27.7, 26.1, 25.0.

IR (cm^{-1}): 2955, 2865, 1725, 1455, 1436, 1100, 758, 729, 429.

GCMS (m/z): calc'd for $C_{19}H_{23}NOS$: 313.2; found: 313.2.

Rf: 0.48 (20% EtOAc/hexanes)

3-(((1*R*,3a*R*,4*R*,6*S*,7a*R*)-3a,5,5-trimethyl-7-oxooctahydro-1*H*-4,6-methanoinden-1-yl)methyl)but-3-en-1-yl pivalate (17x): Following the general procedure (TBAI and 1,4-dioxane), using ketone **16a** (41.3 mg, 0.2 mmol, 1.0 equiv) and **SI-13** (56.4 mg, 0.24

mmol, 1.2 equiv) as electrophiles, compound **17x** has been purified by column chromatography (10% Et_2O/hexanes), obtaining a colorless oil; yield: 42 % (30.2 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (s, 1H), 4.77 (s, 1H), 4.17 (t, *J* = 6.8 Hz, 2H), 2.86 (dd, *J* = 13.2, 1.6 Hz, 1H), 2.52 (t, *J* = 5.2 Hz, 1H), 2.45 (adt, *J* = 11.2, 6.0 Hz, 1H), 2.39–2.26 (m, 2H), 2.09–1.92 (m, 4H), 1.86 (adt, *J* = 12.4, 5.6 Hz, 1H), 1.70–1.62 (m, 2H), 1.44 (dd, *J* = 12.8, 6.4 Hz, 1H), 1.36 (s, 3H), 1.34–1.25 (m, 1H), 1.22 (s, 3H), 1.18 (s, 9H), 0.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.2, 178.7, 144.7, 112.2, 62.7, 61.1, 58.5, 52.3, 47.5, 44.2, 43.8, 42.7, 40.8, 38.8, 34.9, 31.8, 29.2, 27.4, 25.9, 25.3.
IR (cm^{-1}): 2955, 2872, 1726, 1699, 1284, 1150, 893, 735, 522.
GCMS (m/z): calc'd for $C_{23}H_{36}O_3$: 360.3; found: 360.3.
Rf: 0.20 (10% EtOAc/hexanes)
$[\alpha]_D^{20.0}$: -28.3° (*c* 1.0, $CHCl_3$)

(1*R*,3a*R*,4*R*,6*S*,7a*R*)-1-((1,4-dioxaspiro[4.5]dec-7-en-8-yl)methyl)-3a,5,5-trimethyloctahydro-7*H*-4,6-methanoinden-7-one (17y): Following the general procedure (TBAI and 1,4-dioxane), using ketone **16a** (41.3 mg, 0.2 mmol, 1.0 equiv) and 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate[268] (69.2 mg, 0.24 mmol, 1.2 equiv) as electrophiles, compound **17y** has been purified by column chromatography (20% Et_2O/hexanes), obtaining a yellow solid; yield: 37 % (25.7 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (s, 1H), 3.96 (s, 4H), 2.78 (d, *J* = 13.2 Hz, 1H), 2.50 (at, *J* = 5.2 Hz, 1H), 2.43 (adt, *J* = 10.8, 6.0 Hz, 1H), 2.24 (bs, 2H), 2.21–2.09 (m, 2H), 2.04–1.96 (m, 2H), 1.92–1.80 (m, 3H), 1.77–1.69 (m, 2H), 1.68–1.60 (m, 2H), 1.41 (dd, *J* = 12.4, 6.0 Hz, 1H), 1.35 (s, 3H), 1.32–1.23 (m, 1H), 1.20 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.3, 136.8, 119.3, 119.1, 108.3, 64.5, 61.2, 52.2, 47.8, 44.2, 42.8, 40.8, 35.8, 31.9, 31.3, 29.2, 27.7, 27.4, 25.8, 25.2.
IR (cm^{-1}): 2945, 1698, 1269, 1114, 1059, 857, 734, 521.
GCMS (m/z): calc'd for $C_{23}H_{32}O_3$: 344.2; found: 344.3.
Rf: 0.40 (20% EtOAc/hexanes)
$[\alpha]_D^{20.0}$: -25.3° (*c* 1.0, $CHCl_3$)

(1*R*,3a*R*,4*R*,6*S*,7a*R*)-3a,5,5-trimethyl-1-(((*R*)-4-methyl-3-oxocyclohex-1-en-1-yl)methyl)octahydro-7*H*-4,6-methanoinden-7-one (17z): Following the general procedure (TBAI and 1,4-dioxane), using ketone **16a** (41.3 mg, 0.2 mmol, 1.0 equiv) and

SI-15 (45.4 mg, 0.24 mmol, 1.2 equiv) as electrophiles, compound **17z** has been purified by column chromatography (40% Et_2O/hexanes), obtaining a orange solid; yield: 41 % (26.1 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (s, 1H), 3.03 (dd, *J* = 15.6, 11.6 Hz, 1H), 2.54 (at, *J* = 5.2 Hz, 1H), 2.47 (adt, *J* = 10.8, 6.2 Hz, 1H), 2.38–2.24 (m, 3H), 2.16–2.02 (m, 4H), 1.95 (dd, *J* = 9.0, 3.6 Hz, 1H), 1.83 (adt, *J* = 12.0, 6.0 Hz, 1H), 1.76–1.60 (m, 3H), 1.46 (dd, *J* = 12.8, 6.4 Hz, 1H), 1.37 (s, 3H), 1.35–1.27 (m, 1H), 1.23 (s, 3H), 1.13 (dd, *J* = 6.8, 2.4 Hz, 1H), 0.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.0, 202.5, 164.3, 126.1, 126.0, 60.9, 58.5, 52.2, 46.9, 46.8, 45.5, 45.0, 44.1, 42.7, 41.0, 40.7, 31.9, 31.7, 31.0, 30.9, 29.6, 29.4, 29.2, 27.4, 25.9, 25.3, 15.3, 15.3.

IR (cm^{-1}): 2933, 2873, 1697, 1666, 1457, 1371, 1206, 733, 521.

GCMS (m/z): calc'd for $C_{21}H_{30}O_2$: 314.2; found: 314.3.

Rf: 0.30 (15% EtOAc/hexanes)

$[\alpha]_D^{20.0}$: -11.2° (*c* 1.0, $CHCl_3$)

(1*R*,3a*R*,4*R*,6*S*,7a*R*)-1-((5,5-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)-3a,5,5-trimethyloctahydro-7*H*-4,6-methanoinden-7-one (17aa): Following the general procedure (TBAI and 1,4-dioxane), using ketone **16a** (41.3 mg, 0.2 mmol, 1.0 equiv) and 2-iodo-6,6-dimethylcyclohex-2-en-1-one[269] (50.2 mg, 0.20 mmol, 1.0 equiv) as electrophiles, compound **17aa** has been purified by column chromatography (10% Et_2O/hexanes), followed by preparatory thin layer chromatography (30% Et2O/hexanes), obtaining a yellow oil; yield: 28 % (18.5 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (at, *J* = 4.0 Hz, 1H), 2.86–2.82 (m, 1H), 2.50 (at, *J* = 5.6 Hz, 1H), 2.40 (adt, *J* = 11.2, 6.4 Hz, 1H), 2.36–2.32 (m, 2H), 2.20 (dd, *J* = 13.2, 8.8 Hz, 1H), 2.00–1.93 (m, 3H), 1.80 (at, *J* = 6.0 Hz, 1H), 1.65–1.54 (m, 3H), 1.42–1.36 (m, 1H), 1.34 (s, 3H), 1.31–1.23 (m, 1H), 1.18 (s, 3H), 1.09 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.0, 202.5, 164.3, 126.0, 60.9, 58.5, 52.2, 46.9, 46.8, 45.5, 45.0, 44.1, 42.7, 41.0, 40.9, 40.7, 31.9, 31.7, 31.0, 30.9, 29.6, 29.4, 29.2, 27.4, 25.9, 25.3, 15.3.

IR (cm^{-1}): 2943, 2871, 1698, 1669, 1472, 1385, 1270, 1201, 981, 733, 521.

GCMS (m/z): calc'd for $C_{22}H_{32}O_2$: 328.2; found: 328.3

Rf: 0.44 (15% EtOAc/hexanes)

$[\alpha]_D^{20.0}$: -35.0° (*c* 1.0, $CHCl_3$)

(1*S*,3a*R*,4*R*,6*S*,7a*R*)-1-((diallylamino)methyl)-3a,5,5-trimethyloctahydro-7*H*-4,6-methanoinden-7-one (17ab): Following the general procedure (no additive and 1,4-dioxane), using ketone **16a** (41.3 mg, 0.2 mmol, 1.0 equiv) and *N*,*N*-diallyl-*O*-benzoylhydroxylamine[270] (52.1 mg, 0.20 mmol, 1.0 equiv) as electrophiles, compound **17ab** has been purified by column chromatography (25% Et_2O/CH_2Cl_2), obtaining a colorless oil; yield: 30 % (18.0 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 2H), 5.19–5.10 (m, 4H), 3.21 (dd, *J* = 14.0, 5.6 Hz, 2H), 2.98 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.92 (dd, *J* = 12.6, 4.0 Hz, 1H), 2.51 (at, *J* = 5.4 Hz, 1H), 2.47–2.37 (m, 2H), 2.17–2.07 (m, 1H), 2.05–1.99 (m, 2H), 1.93 (d, *J* = 9.2 Hz, 1H), 1.71–1.65 (m, 1H), 1.62 (d, *J* = 10.8 Hz, 1H), 1.47–1.37 (m, 2H), 1.36 (s, 3H), 1.20 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.3, 136.2, 117.3, 59.5, 59.3, 58.5, 57.5, 52.4, 47.7, 44.0, 42.5, 41.0, 31.7, 29.2, 27.3, 25.9, 25.3.

IR (cm^{-1}): 2940, 2872, 2793, 1700, 1458, 1199, 995, 914, 523.

HRMS (m/z): $[M+H]^+$ calc'd for $C_{20}H_{32}NO^+$: 302.2478; found: 302.2797.

Rf: 0.36 (15% EtOAc/hexanes)

$[\alpha]_D^{20.0}$: -4.0° (*c* 1.0, $CHCl_3$)

(1*S*,3a*R*,4*R*,6*S*,7a*R*)-1-((dibenzylamino)methyl)-3a,5,5-trimethyloctahydro-7*H*-4,6-methanoinden-7-one (17ac): Following the general procedure (no additive and 1,4-dioxane), using ketone **16a** (41.3 mg, 0.2 mmol, 1.0 equiv) and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine[270] (76.2 mg, 0.20 mmol, 1.0 equiv) as electrophiles, compound **17ac** has been purified by column chromatography (10% Et_2O/hexanes), obtaining a light-yellow oil; yield: 37 % (29.4 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.37 (m, 2H), 7.32–7.28 (m, 4H), 7.23–7.19 (m, 2H), 3.77 (d, *J* = 13.6 Hz, 2H), 3.34 (d, *J* = 13.6 Hz, 2H), 2.89 (dd, *J* = 12.4, 4.4 Hz, 1H), 2.50 (at, *J* = 5.2 Hz, 1H), 2.44–2.37 (m, 2H), 2.24–2.15 (m, 1H), 2.14–2.06 (m, 1H), 1.97 (dd, *J* = 6.0, 5.2 Hz, 1H), 1.85 (d, *J* = 8.8 Hz, 1H), 1.65–1.58 (m, 1H), 1.56 (s, 2H), 1.37 (atd, *J* = 6.8, 2.0 Hz, 1H), 1.33 (s, 3H), 1.30–1.25 (m, 1H), 1.04 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.3, 140.3, 129.0, 128.2, 126.8, 60.0, 59.3, 59.0, 58.6, 52.5, 47.3, 44.1, 42.4, 40.9, 31.5, 29.1, 27.3, 25.8, 25.3.

IR (cm^{-1}): 2943, 1698, 1452, 1266, 981, 733, 697, 522

HRMS (m/z): $[M+H]^+$ calc'd for $C_{28}H_{36}NO^+$: 402.2791; found: 402.2797

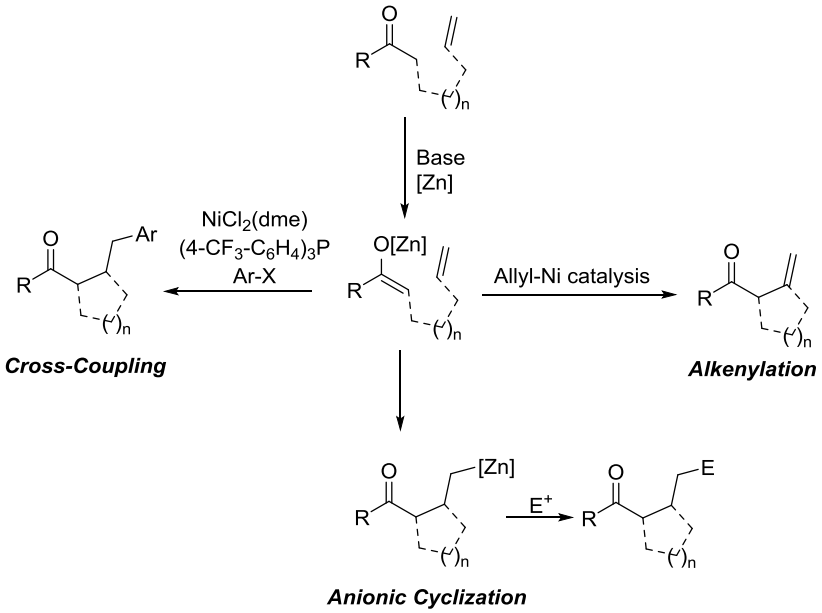
Rf: 0.25 (10% EtOAc/hexanes)

$[\alpha]_D^{20.0}$: -4.8° (*c* 1.0, $CHCl_3$)

6. Preliminary Results Obtained in the Anionic Cyclization of Zinc-Enolates Tethered to Unactivated Alkenes

6.1 Introduction

Considering the results obtained in the cycloalkenylation reaction reported by Newhouse[245] and in the alkene difunctionalization of unactivated alkenes tethered to unstabilized ketone enolates, described in *Chapter 5*, we have decided to investigate the anionic cyclization of unstabilized ketones and unactivated alkenes, through the formation of Zn-enolates (Scheme 79)

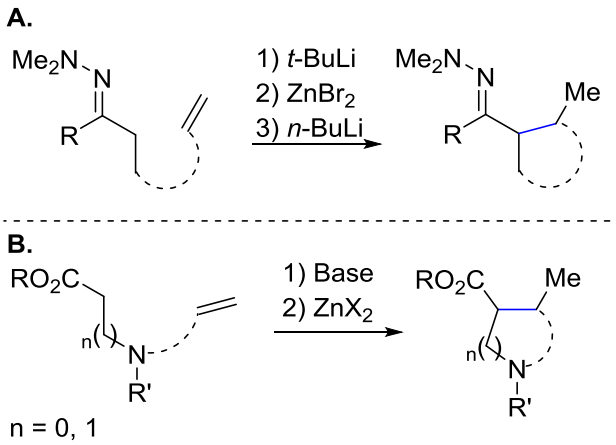


Scheme 79 – Zinc-enolates transformations investigated by Newhouse group

In the last decade, zincated nucleophiles have emerged as reagents of choice to perform carbometalations of unactivated olefins.[239] The resulting organometallic species can be used for various subsequent synthetic transformations, without problems related to the β-H elimination that are favored by transition metals.

Two different approaches are mainly developed in the carbocyclization of zinc enolates (Scheme 80). The first approach involves the use of aza-enolates (Scheme 80, A).[271] Here, the protection of the carbonyl group as the hydrazone can stabilize the zinc-enolate. The second major field of development of carbometalation reactions of unactivated olefins with Zn-enolate derivatives has involved the use of zincated α- or β-aminoesters

(Scheme 80, B). With this second strategy more examples of carbocyclization of zinc enolates are reported than with aza-enolates.[239,272]



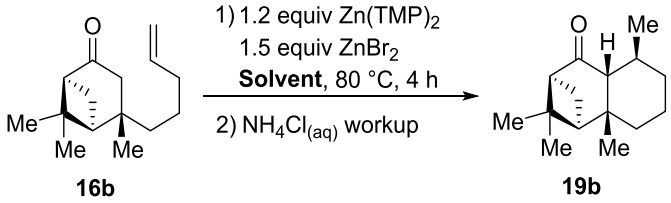
Scheme 80 – Carbocyclization of zincated hydrazones (**A**) and of α- and β-amino ester zinc enolates (**B**)

However, no examples have been reported so far employing both unstabilized zinc enolates and unactivated alkenes. This synthetic strategy could expand the capabilities of the zinc mediated carbocyclization reactions, allowing the use of abundantly available ketones without the need for pre-activation in a separate step. Here, preliminary results obtained in this transformation are reported.

6.2 Results and Discussion

We started our investigation using the ketone **16b** as model substrate. When $ZnBr_2$, in THF, was used as additive, employing $Zn(TMP)_2$ as base and heating to 80°C, only 10% of the cyclic product **19b** was obtained after the aqueous work up (Table 23, entry 1).

Table 23 – Solvent screening of the Zinc mediated anionic cyclization

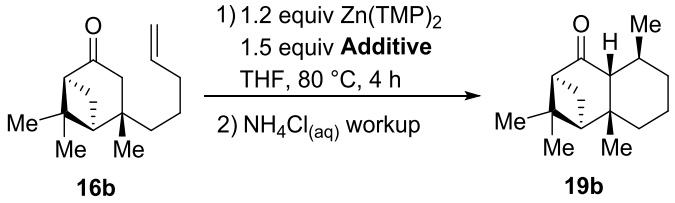


Entry[a]	Solvent	Yield (%)[b]
1	THF	10
2	DMF	6
3	Benzotrifluoride	24
4	Cyclohexane	29
5	DME	30
6	DCE	40

[a] Reactions performed using **16b** (0.1 mmol), 1.2 equiv. of $Zn(TMP)_2$, 1.5 equiv of $ZnBr_2$ in the indicate solvent (0.1 M). [b] ^1H NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard.

Since screening different solvents only modest yields were achieved (Table 23), we decided to investigate the effect of different transition metal salts and zinc derivatives (Table 24). The use of transition metals bromide salts did not lead to any improvement (entries 1 and 2), as well as the use of dialkyl-zinc derivatives (entry 3). Among the different zinc salts tested (entries 4-7) only with $Zn(OTf)_2$ 75% yield could be achieved (entry 7). Then, a set of triflates salts were tested (entries 8-10) and, while $Fe(OTf)_2$ and TBAOTf (entries 9 and 10) were able to provide the product **19b**, the best result was still obtained with $Zn(OTf)_2$. Employing 1,2-dimethoxyethane (entry 11) and 1,2-dichloroethane (entry 12) as solvents, slightly better results were obtained with DME. Interestingly, when no additive was used, 48% of yield was obtained (entry 13), achieving better results than with $ZnBr_2$ (Table 23, entry 5). As expected, no reaction was observed when no base was employed, confirming the necessity of the formation of a zinc enolate in order to achieve this transformation (Table 24, entry 14).

Table 24 – Optimization of the Zinc mediated anionic cyclization



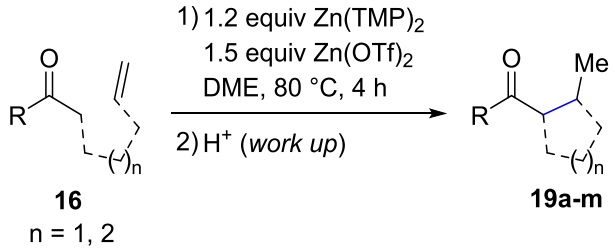
16b **19b**

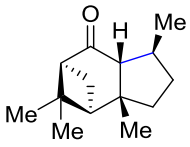
Entry[a]	Additive	Yield (%)[b]
1	$FeBr_2$, $FeBr_3$, $CoBr_2$, $MnBr_2$	0
2	CuBr	20
3	$ZnMe_2$, $ZnEt_2$	0
4	$Zn(OAc)_2$, $Zn(BF)_4$	0
5	ZnI_2	13
6	$ZnCl_2$	20
7	$Zn(OTf)_2$	75
8	$Fe(OTf)_3$, $Cu(OTf)\cdot Ph$, $Cu(OTf)_2$, $Sc(OTf)_3$	0
9	$Fe(OTf)_2$	38
10	TBAOTf	40
11[c]	$Zn(OTf)_2$	92
12[d]	$Zn(OTf)_2$	87
13	-	48
14[e]	$Zn(OTf)_2$	0
15[f]	$Zn(OTf)_2$	80

[a] Reactions performed using **16b** (0.1 mmol), 1.2 equiv. of $Zn(TMP)_2$, 1.5 equiv of the indicate additive in THF (0.1 M). [b] ^1H NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. [c] 1,2-dimethoxyethane (DME) was used as solvent. [d] 1,2-dichloroethane (DCE) was used as solvent. [e] No $Zn(TMP)_2$ was used. [f] 0.5 equiv of $Zn(OTf)_2$ were used.

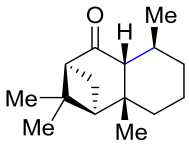
With this optimized conditions in hand, we proceeded to evaluate the generality of the process (Table 25). Different fused bicycles were obtained from moderate to excellent yields (**19a**-**19m**). Verbenone derivatives have been obtained in good to excellent yields (**19a**-**19c**), allowing for the formation of new 5- and 6 membered rings. Moreover, bridged bicyclic ring systems (**19e** and **19j**) and spirocyclic motifs (**19f** and **19g**) can be generated. Acyclic ketones could efficiently cyclize with a pendant homoallyl group, leading to compounds **19h** and **19i**. It is important to notice that products **19l** and **19m** have been obtained with good yields, despite the presence of two identical enolizable positions. Probably, the formation of a more thermodynamically stable and accessible 6- and 5-membered rings account for the formation of these bicycles species.

Table 25 – Scope of the Zinc mediated anionic cyclization reaction.[a,b]

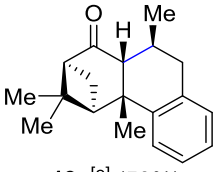




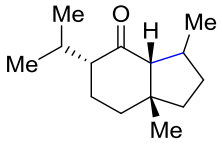
19a[c] (96%)



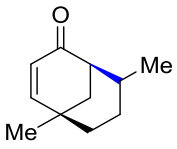
19b (92%)



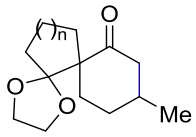
19c[e] (53%)



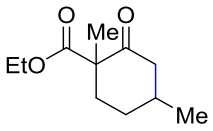
19d (66%, dr 2:1)



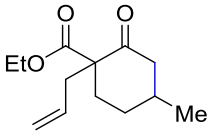
19e (43%)



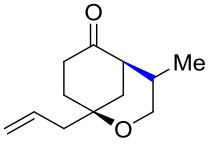
19f[d] (53%, dr = 1:1) n = 1
19g[d] (72%, dr = 3:2) n = 2



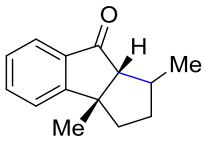
19h[c] (43%)



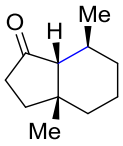
19i[c] (53%, dr 2.7:1)



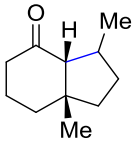
19j (41%)



19k[c] (76%, dr 1.2:1)



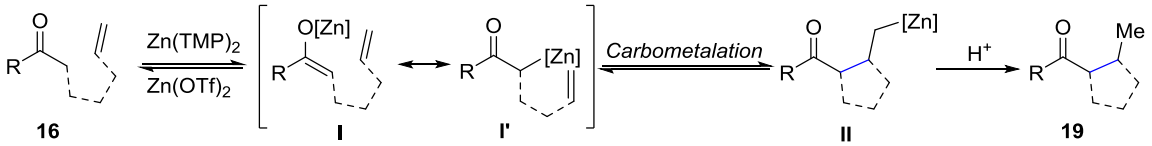
19l[c] (64%)



19m[c] (68%, dr 2:1)

[a] Reactions performed using **16** (0.2 mmol scale), 1.2 equiv. of $Zn(TMP)_2$ and 1.5 equiv. of $Zn(OTf)_2$, in 1,2-dimethoxyethane (0.1 M), at 80°C. After 4 h, the reactions were quenched using $NH_4Cl_{(aq)}$, affording compounds **19**. [b] Isolated yields after column chromatography. Unless otherwise indicated dr > 20:1. [c] Reaction time: 2 h. [d] Reaction time: 6 h. [e] Reaction time: 3 h.

Considering these results and those obtained in the alkene difunctionalization initiated by unstabilized ketones, a possible mechanism is reported in Scheme 81. The formation of zinc enolates **I** and **I'** is followed by a carbometalation reaction, leading to the alkyl zinc species **II**, which is than trapped with a proton source, forming products **19**.



Scheme 81 – Proposed pathway for the anionic cyclization reaction

6.3 Conclusion

In conclusion, starting from unstabilized ketones tethered to unactivated alkenes, an efficient zinc mediated anionic cyclization has been developed in order to access different cyclic and bicyclic architectures. Although this method has shown to be efficient for a wide range of different ketones, only the proton H^+ has been used for quenching the reaction. Therefore, more experiments, involving the use of different electrophiles, should be then conducted in order to investigate the generality of this new methodology for new types of difunctionalization reactions distinct from those mentioned in the *Chapter 5*.

6.4 Experimental Section

6.4.1 List of ketones 16

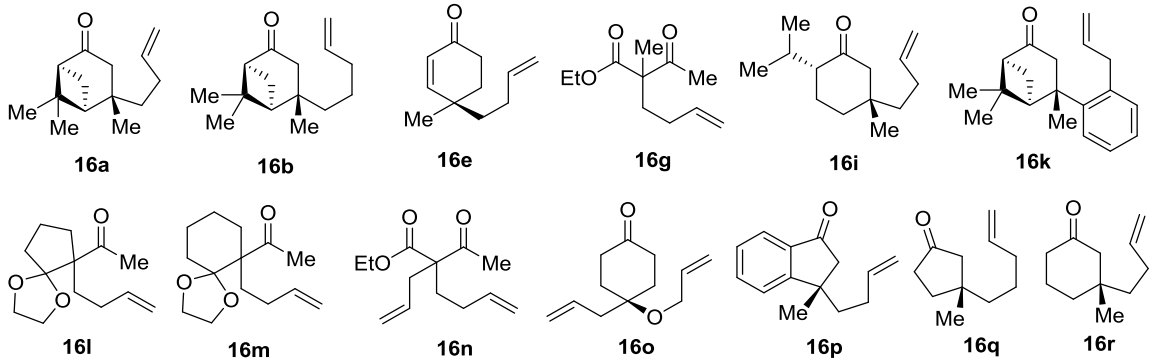


Figure 14 – Olefins utilized in the anionic cyclization reaction

6.4.2 General Information

All reactions were carried out under an inert nitrogen atmosphere with dry solvents under anhydrous conditions unless otherwise stated. All reactions were capped with a rubber septum, or Teflon-coated silicon microwave cap unless otherwise stated. Stainless steel cannula or syringe was used to transfer solvent, and air- and moisture sensitive liquid reagents. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as the visualizing agent and potassium permanganate, an acidic solution of *p*-anisaldehyde, phosphomolybdic acid, or I2 on SiO2 as developing agents. Flash column chromatography employed SiliaFlash® P60 (40-60 μm, 230-400 mesh) silica gel purchased from SiliCycle, Inc. All reaction solvents were purified using a Seca solvent purification system by Glass contour. *N*,*N*-diisopropylamine, and TMSCl were distilled over CaH_2. $CuBr{\cdot}SMe_2$ was prepared and purified according to the literature procedure.[255] $Zn(TMP)_2$ (0.5 M in toluene) and *n*-BuLi (2.5 M in hexanes) were purchased from Sigma-Aldrich. 4-bromo-1-butene was purchased from Oakwood Products, Inc and purified via neat filtration through a 2 cm pad of dry silica in a 5.75 inch pipette prior to use. All other reagents were used as received without further purification, unless otherwise stated. All new compounds were characterized by means of ^{1}H-NMR, ^{13}C-NMR, FT-IR (thin film), and GCMS. NMR spectra were recorded using a Varian 400 MHz NMR spectrometer, Varian 500 MHz NMR spectrometer, or a Varian 600 MHz NMR spectrometer. All ^{1}H-NMR data are reported in δ units, parts per million (ppm), and were calibrated relative to the signals for residual chloroform (7.26 ppm) in deuterochloroform ($CDCl_3$). All ^{13}C-NMR data are

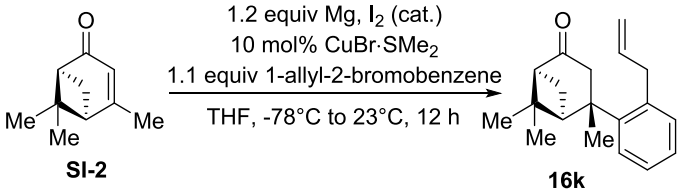
reported in ppm relative to $CDCl_3$ (77.16 ppm) and were obtained with ^1H decoupling unless otherwise stated. The following abbreviations or combinations thereof were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, abq = ab quartet, br = broad, m = multiplet, and a = apparent. All IR spectra were taken on an FT-IR/Raman Thermo Nicolet 6700. Gas chromatography mass spectra (GCMS) were recorded on an Agilent Technologies 6890N Network Gas Chromatograph System with an Agilent Technologies 5973N Mass Selective Detector. High resolution mass spectra (HRMS) were recorded on a Waters Xevo high resolution mass spectrometer using QTOF (quadrupole-time of flight).

Compounds **16a**, **16e**, **16g**, **16i**, **16l**, **16m**, **16n, 16o** and **16p** were prepared according to the literature procedure.[245]

Compound **16b** were prepared as reported in *Chapter 5.4.4* of this dissertation.

Compounds **16q**[273] and **16r**[274] were prepared according to the literature procedure.

6.4.3 Synthesis of (1S,4S,5R)-4-(2-allylphenyl)-4,6,6-trimethylbicyclo[3.1.1]heptan-2-one (16k)



To a flame-dried 20 mL microwave vial was added magnesium turnings (52.8 mg, 2.2 mmol, 1.2 equiv) and a catalytic amount of I_2 (*ca.* 5 mg). The reaction vessel was capped, evacuated, and backfilled with N_2 and THF (4.0 mL, 0.5 M) was added to the reaction vessel. The reaction vessel was then moved to a 70 °C pre-heated oil bath and stirred for 10 minutes. The reaction vessel was then removed from the oil bath and to the reaction mixture was added 1-allyl-2-bromobenzene (0.3 mL, 2.0 mmol, 1.1 equiv) dropwise over 15 minutes as to maintain a gentle reflux. The reaction vessel was then moved back to a 70 °C oil bath and stirred for 30 minutes. The reaction vessel was then removed from the oil bath and cooled to ambient temperature.

In a separate flame-dried 20 mL microwave vial equipped with a magnetic stir bar was added CuBr•SMe_2 (41.3 mg, 0.2 mmol, 10 mol %). The reaction vessel was evacuated and backfilled with N_2 before THF (4 mL, 0.45 M) was added to the reaction vessel. The

reaction mixture was then cooled to −40 °C in a dry ice-acetonitrile bath and the previously prepared Grignard solution was added dropwise over 15 minutes. The reaction mixture was stirred at −40 °C for 30 minutes before it was cooled to −78 °C in a dry ice-acetone bath and **SI-2** (0.28 mL, 1.8 mmol, 1.0 equiv) was added dropwise. The reaction mixture was stirred for 12 hours and slowly warmed to ambient temperature.

To the reaction mixture was added sat. aq. NH_4Cl (10 mL) and Et_2O (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (10% Et_2O/hexanes) afforded **16k** (270.3 g, 56%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, J = 7.6, 1.6 Hz, 1H), 7.19–7.10 (m, 2H), 7.00 (d, J = 7.2 Hz, 1H), 5.99 (ddt, J = 16.4, 10.0, 6.0 Hz, 1H), 5.14–5.05 (m, 2H), 3.51 (d, J = 6.0 Hz, 2H), 2.99 (s, 2H), 2.75–2.70 (m, 2H), 2.55 (at, J = 4.8 Hz, 1H), 1.54 (s, 3H), 1.50 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.4, 149.6, 138.1, 137.8, 132.9, 126.0, 125.9, 124.9, 116.5, 55.9, 52.8, 50.6, 40.1, 39.7, 38.5, 30.2, 27.9, 27.0, 25.9

IR (cm^{-1}): 2925, 1711, 1637, 1483, 1255, 1202, 987, 914, 760, 503, 467

GCMS (m/z): calc'd for $C_{19}H_{24}O$: 268.2; found: 268.1

Rf: 0.36 (10% Et_2O/hexanes)

6.4.4 General Procedure for the Anionic Cyclization

To a flame-dried 10 mL microwave vial equipped with a magnetic stir bar was added $Zn(OTf)_2$ (109 mg,0.3 mmol, 1.5 equiv). The vial was capped, evacuated, and backfilled with N_2 before anhydrous 1,2-dimethoxyethane (2.0 mL, 0.10 M) was added. To the reaction mixture was then added the ketone **16** (0.20 mmol, 1.0 equiv) and $Zn(TMP)_2$ (0.48 mL, 0.50 M in toluene, 0.24 mmol, 1.2 equiv). The reaction vessel was sealed with parafilm and placed into a pre-heated 80 °C oil bath and stirred until complete conversion of the starting ketone, monitored by TLC, or for a maximum of 6 hours. The reaction mixture was removed from the oil bath and cooled to ambient temperature before sat. aq. NH_4Cl was added. The mixture was diluted with Et_2O (2 mL) and the organic phase was separated. The aqueous phase was extracted with Et_2O (2 x 2 mL) and the combined organic extracts were filtered through a pad of dry silica in a glass pipette before being concentrated under reduced pressure by rotary evaporation with a low bath temperature,

in order to avoid the evaporation of the product. The crude mixture was purified by flash column chromatography on silica gel.

(1*S*,3*aR*,4*R*,6*S*,7*aR*)-1,3a,5,5-tetramethyloctahydro-*7H*-4,6-methanoinden-7-one (19a): Following the general procedure using ketone **16a** (41.3 mg), compound **19a** has been purified by chromatography column (2% Et_2O/hexane), obtaining a pale yellow oil; yield 96 % (39.7 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (at, J = 5.2 Hz, 1H), 2.42 (adt, J = 10.8, 6.4 Hz, 1H), 2.00 (at, J = 6.0 Hz, 1H), 1.95–1.89 (m, 1H), 1.84 (d, J = 10.0 Hz, 1H), 1.84–1.78 (m, 1H), 1.71–1.61 (m, 2H), 1.44–1.39 (m, 1H), 1.35 (s, 3H), 1.25 (d, J = 6.4 Hz, 3H), 1.21 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.4, 62.9, 58.4, 52.3, 44.6, 44.5, 42.9, 41.1, 34.5, 29.3, 27.4, 25.8, 25.2, 21.4.

IR (cm^{-1}): 2947, 2871, 1700, 1462, 1376, 1269, 1201, 1041, 1006, 828, 751, 524.

GCMS (m/z): calc'd for $C_{14}H_{22}O$: 206.2; found: 206.2

Rf: 0.43 (10% Et_2O/hexanes).

(1*R*,3*S*,4*aR*,5*S*,8*aR*)-2,2,5,8a-tetramethyloctahydro-1,3-methanonaphthalen-4(*1H*)-one (19b): Following the general procedure using ketone **16b** (44.1 mg), compound **19b** has purified by chromatography column (3% Et_2O/hexane), obtaining a colorless oil; yield 92 % (40.6 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (at, J = 5.2 Hz, 1H), 2.44 (adt, J = 10.8, 6.4 Hz, 1H), 1.89–1.82 (m, 1H), 1.80 (at, J = 6.0 Hz, 1H), 1.75–1.54 (m, 7H), 1.37 (s, 3H), 1.27–1.21 (m, 1H), 1.19 (s, 3H), 1.11 (d, J = 6.4 Hz, 3H), 1.04 (s, 3H), 0.99–0.95 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.7, 59.3, 58.8, 55.0, 40.6, 35.9, 32.2, 31.5, 30.5, 28.0, 27.7, 25.8, 25.2, 22.4, 16.7.

IR (cm^{-1}): 2946, 2870, 1463, 1378, 1259, 1203, 1097, 1033, 804, 517.

GCMS (m/z): calc'd for $C_{15}H_{24}O$: 220.2; found: 220.2

Rf: 0.45 (10% Et_2O/hexanes).

(2*S*,4*R*,4a*R*,10*S*,10*aR*)-3,3,4a,10-tetramethyl-3,4,4a,9,10,10a-hexahydro-2,4-methanophenanthren-1(*2H*)-one (19c): Following the general procedure using ketone **16k** (53.7 mg), compound **19c** has been purified by chromatography column (3% Et_2O/hexanes), obtaining a white solid; yield 53 % (28.2 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.17 (m, 2H), 7.10 (atd, J = 6.8, 1.2 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 2.97–2.89 (m, 1H), 2.67–2.60 (m, 2H), 2.51–2.41 (m, 3H), 2.25 (adt, J = 11.2, 6.0 Hz, 1H), 1.59 (s, 3H), 1.39 (s, 3H), 1.20 (s, 3H), 1.09 (d, J = 7.2 Hz, 3H), 0.94 (d, J = 10.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.3, 144.5, 135.5, 129.4, 126.8, 126.3, 125.8, 58.2, 58.1, 56.0, 40.4, 39.3, 35.0, 31.0, 28.9, 27.7, 26.0, 25.2, 20.9.
IR (cm^{-1}): 2944, 2843, 1702, 1447 1381, 1254, 1181, 973, 760, 729, 520, 487.
GCMS (m/z): calc'd for $C_{19}H_{24}O$: 268.2; found: 268.1
Rf: 0.42 (10% Et_2O/hexanes).

(3*R*,5*R*,7*aR*)-5-isopropyl-3,7a-dimethyloctahydro-*4H*-inden-4-one (19d): Following the general procedure using ketone **16i** (41.7 mg), compound **19d** has been purified by chromatography column (2% Et_2O/hexanes), obtaining a colorless oil; yield 66 % (27.7 mg, 2:1 dr).
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45–2.33 (m, 0.33H), 2.26–2.13 (m, 2H), 2.13–2.09 (m, 0.33H), 1.97–1.75 (m, 3.67H), 1.73–1.60 (m, 1.67H), 1.57–1.52 (m, 1H), 1.50–1.43 (m, 1H), 1.41–1.20 (m, 2H), 1.10 (s, 2H), 1.04 (s, 1H), 1.03 (d, J = 6.4 Hz, 2H), 0.96 (d, J = 6.4 Hz, 1H), 0.92 (d, J = 6.8 Hz, 2H), 0.90 (d, J = 6.4 Hz, 1H), 0.85–0.83 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.7, 215.3, 70.0, 68.0, 55.5, 52.1, 48.3, 45.0, 40.7, 40.4, 38.9, 38.7, 36.0, 34.7, 33.7, 32.7, 30.9, 28.5, 26.5, 26.3, 24.7, 21.6, 21.3, 21.3, 20.4, 20.3, 19.4, 18.6.
IR (cm^{-1}): 2952, 2868, 1694, 1458, 1377, 1368, 1169, 986, 659, 563.
GCMS (m/z): calc'd for $C_{14}H_{24}O$: 208.2; found: 208.2
Rf: 0.50 (10% Et_2O/hexanes)

(1*R*,5*R*,8*R*)-5,8-dimethylbicyclo[3.3.1]non-3-en-2-one (19e): Following the general procedure using ketone **16e** (32.9 mg), compound **19e** has been purified by chromatography column (10% Et_2O/hexanes), obtaining a pale yellow oil; yield 43 % (14.3 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (dd, J = 10.0, 2.0 Hz, 1H), 6.05 (d, J = 10.0 Hz, 1H), 2.36–2.32 (m, 1H), 2.08 (dd, J = 12.8, 2.8 Hz, 1H), 1.71–1.53 (m, 3H), 1.45–1.42 (m, 2H), 1.27–1.13 (m, 1H), 1.11 (s, 3H), 0.89 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7, 157.0, 131.2, 49.5, 42.6, 34.8, 33.6, 28.7, 28.1, 19.7.
IR (cm^{-1}): 2956, 2923, 2869, 1670, 1455, 1374, 1218, 1103, 1076, 825, 730, 502.
GCMS (m/z): calc'd for $C_{11}H_{16}O$:164.1; found:164.2

Rf: 0.32 (10% Et_2O/hexanes)

9-methyl-1,4-dioxadispiro[*4.0.5*^{6}*.3*^{5}]tetradecan-7-one (19f): Compound **19f** was prepared from **16l** (44.9 mg) according to the general procedure. Purification by flash column chromatography on silica gel (10% Et_2O/hexanes) afforded two separable diastereoisomers **19f$_1$** (12.1 mg, 27%) and **19f$_2$** (11.6 mg, 26%) as colorless oils.

19f$_1$ - *Rf:* 0.35 (20% Et_2O/hexanes) - ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99–3.85 (m, 4H), 2.47–2.27 (m, 4H), 1.84–1.63 (m, 4H), 1.62–1.50 (m, 3H), 1.40 (atd, *J* = 12.8, 5.2 Hz, 1H), 1.27–1.20 (m, 1H), 0.98 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.4, 118.1, 65.5, 64.3, 58.1, 50.2, 35.0, 34.5, 34.4, 33.7, 31.2, 22.7, 19.2.

19f$_2$ - *Rf:* 0.22 (20% Et_2O/hexanes) - ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97–3.88 (m, 4H), 2.51 (ddd, *J* = 14.0, 4.8, 0.4 Hz, 1H), 2.22–2.13 (m, 2H), 2.09–1.93 (m, 3H), 1.90–1.72 (m, 3H), 1.66–1.51 (m, 3H), 1.36–1.27 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.1, 118.3, 65.4, 64.1, 59.9, 47.9, 34.4, 34.1, 32.8, 30.5, 29.9, 21.1, 18.9.

IR (cm^{-1}): 2952, 2874, 1698, 1456, 1442, 1309, 1213, 1152, 1126, 1063, 1016, 945, 931, 584, 528, 473.

GCMS (m/z): calc'd for $C_{13}H_{20}O_3$: 224.1; found: 224.2

9-methyl-1,4-dioxadispiro[*4.0.5*^{6}*.4*^{5}]pentadecan-7-one (19g): Compound **19g** was prepared from **16m** (47.7 mg) according to the general procedure. Purification by flash column chromatography on silica gel (20% Et_2O/hexanes) afforded two separable diastereoisomers **19g$_1$** (13.7 mg, 29%) and **19g$_2$** (20.5 mg, 43%) as colorless oils.

19g$_1$ - *Rf:* 0.32 (20% Et_2O/hexanes) - ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97–3.86 (m, 4H), 2.43 (dd, *J* = 13.2, 4.8 Hz, 1H), 2.36–2.29 (m, 2H), 2.18–2.11 (m, 1H), 2.00–1.88 (m, 1H), 1.76–1.63 (m, 4H), 1.56–1.47 (m, 3H), 1.44–1.31 (m, 3H), 0.98 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.8, 111.5, 64.4, 64.3, 55.0, 49.7, 34.0, 33.9, 32.7, 31.5, 29.5, 23.2, 21.7, 20.9.

19g$_2$ - *Rf:* 0.21 (20% Et_2O/hexanes) - ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03–3.78 (m, 4H), 2.27–2.18 (m, 4H), 1.91–1.79 (m, 3H), 1.72–1.61 (m, 3H), 1.59–1.38 (m, 4H), 1.12–1.01 (m, 1H), 0.98 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.6, 110.9, 65.6, 64.3, 56.8, 48.0, 34.8, 33.4, 32.1, 31.0, 29.0, 23.5, 22.3, 21.5.

IR (cm^{-1}): 2929, 2869, 1707, 1450, 1298, 1182, 1102, 1085, 1032, 954, 859, 565.

GCMS (m/z): calc'd for $C_{14}H_{22}O_3$: 238.2; found: 238.2

Ethyl-1,4-dimethyl-2-oxocyclohexane-1-carboxylate (19h): Following the general procedure using ketone **16g** (39.7 mg), compound **19h** has been purified by chromatography column (10 Et_2O/hexanes), obtaining a colorless oil; yield 43 % (17 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, J = 7.0 Hz, 2H), 2.57–2.51 (m, 1H), 2.39 (ddd, J = 13.6, 7.2, 4.0 Hz, 1H), 2.25–2.15 (m, 3H), 1.92–1.84 (m, 1H), 1.73 (ddd, J = 13.6, 9.2, 4.0 Hz, 1H), 1.52–1.43 (m, 1H), 1.34 (s, 3H), 1.26 (at, J = 7.2 Hz, 4H), 0.98 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9, 173.3, 61.4, 57.0, 46.8, 33.8, 32.8, 28.9, 20.9, 20.2, 14.2.

IR (cm^{-1}): 2935, 2871, 1735, 1712, 1456, 1377, 1258, 1090, 1026, 860.

GCMS (m/z): calc'd for $C_{11}H_{18}O_3$: 198.1; found: 198.2

Rf: 0.41 (20% Et_2O/hexanes).

Ethyl 1-allyl-4-methyl-2-oxocyclohexane-1-carboxylate (19i): Compound **19i** was prepared from **16n** (44.9 mg) according to the general procedure. Purification by flash column chromatography on silica gel (4% Et_2O/hexanes) afforded two separable diastereoisomers **19i$_1$** (6.5 mg, 14%) and **19i$_2$** (17.5 mg, 39%) as colorless oils.

19i$_1$ - *Rf:* 0.51 (20% Et_2O/hexanes) - ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79–5.68 (m, 1H), 5.12–4.95 (m, 2H), 4.17 (q, J = 7.2 Hz, 2H), 2.60 (dd, J = 14.0, 7.2 Hz, 1H), 2.49–2.39 (m, 2H), 2.29 (dd, J = 14.0, 8.0 Hz, 1H), 2.18–2.11 (m, 1H), 1.85–1.70 (m, 2H), 1.45–1.34 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H), 0.99 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.1, 171.5, 133.5, 118.4, 61.4, 59.9, 49.5, 39.4, 35.4, 34.9, 31.4, 22.4, 14.3.

19i$_2$ - *Rf:* 0.61 (20% Et_2O/hexanes) - ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78–5.67 (m, 1H), 5.08–5.04 (m, 2H), 4.18 (q, J = 7.2 Hz, 2H), 2.62 (dd, J = 14.0, 6.8 Hz, 1H), 2.55 (dd, J = 13.6, 4.4 Hz, 1H), 2.40 (dd, J = 14.0, 7.6 Hz, 1H), 2.31 (ddd, J = 13.6, 6.4, 4.0 Hz, 1H), 2.26 – 2.13 (m, 2H), 1.93–1.85 (m, 1H), 1.77 (ddd, J = 13.6, 10.0, 4.0 Hz, 1H), 1.52–1.44 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.8, 171.7, 133.3, 118.6, 61.3, 60.7, 47.4, 38.5, 32.6, 30.7, 28.5, 19.9, 14.3.

IR (cm^{-1}): 2956, 2929, 1713, 1439, 1222, 1196, 1143, 1093, 1027, 918, 608

GCMS (m/z): calc'd for $C_{13}H_{20}O_3$: 224.1; found: 224.2

(1*R*,4*S*,5*R*)-1-allyl-4-methyl-2-oxabicyclo[3.3.1]nonan-6-one (19j): Following the general procedure using ketone **16o** (38.9 mg), compound **19j** has been purified by chromatography column (8% Et_2O/hexanes), obtaining a colorless oil; yield 41 % (15.9 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (ddt, J = 17.5, 10.5, 7.5 Hz, 1H), 5.13–5.07 (m, 2H), 3.81 (dd, J = 12.5, 5.5 Hz, 1H), 3.55 (at, J = 12.5 Hz, 1H), 2.57–2.51 (m, 2H), 2.46–2.38 (m, 1H), 2.26 (d, J = 7.5 Hz, 2H), 2.14–2.03 (m, 2H), 2.00–1.93 (m, 1H), 1.91–1.87 (m, 2H), 0.81 (d, J = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 213.3, 133.6, 118.4, 70.9, 68.0, 49.2, 47.1, 39.1, 36.2, 33.5, 32.1, 14.9.

IR (cm^{-1}): 2926, 1703, 1440, 1104, 1078, 990, 963, 915, 853, 640, 413.

GCMS (m/z): calc'd for $C_{12}H_{18}O_2$: 194.1; found: 194.2

Rf: 0.52 (40% Et_2O/hexanes)

(3*aS*,8*aR*)-1,3a-dimethyl-2,3,3a,8a-tetrahydrocyclopenta[*a*]inden-8(*1H*)-one (19k): Following the general procedure using ketone **16p** (40 mg), compound **19k** has been purified by chromatography column (4% Et_2O/hexanes), obtaining an orange oil; yield 76 % (30.3 mg, 1.2:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, J = 7.5, 3.5 Hz, 1H), 7.63–7.59 (m, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.36–7.33 (m, 1H), 2.55 (d, J = 10.0 Hz, 0.45H), 2.45–2.35 (m, 0.45H), 2.30–2.27 (m, 0.55 H), 2.06–1.98 (m, 1H), 1.86 (ddd, J = 12.5, 6.5, 5.5 Hz, 0.45H), 1.77 (atd, J = 13.0, 6.0 Hz, 0.55H), 1.69 (adt, J = 12.0, 6.0 Hz, 0.55H), 1.61–1.57 (m, 0.45H), 1.53 (s, 1.35H), 1.47 (s, 1.65H), 1.22 (d, J = 7.0 Hz, 1.35H), 1.09 (d, J = 7.0 Hz, 1.65H), 0.93 (ddd, J = 24.5, 12.0, 5.5 Hz, 0.55H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 209.1, 208.0, 163.1, 163.0, 137.8, 135.7, 135.5, 135.2, 127.5, 127.5, 124.3, 124.0, 123.5, 122.7, 68.0, 62.9, 51.8, 51.1, 40.7, 39.6, 39.1, 38.7, 34.6, 34.6, 28.5, 27.8, 21.1, 16.1.

IR (cm^{-1}): 2954, 2925, 2857, 1709, 1603, 1462, 1285, 764.

GCMS (m/z): calc'd for $C_{14}H_{16}O$: 200.1; found: 200.1

Rf: 0.35 (10%Et_2O/hexanes).

(3*aR*,7*S*,7*aR*)-3a,7-dimethyloctahydro-*1H*-inden-1-one (19l): Following the general procedure using ketone **16q** (33.3 mg), compound **19l** has been purified by chromatography column (3% Et_2O/hexanes), obtaining a pale yellow oil; yield 64 % (21.4 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36–2.21 (m, 2H), 2.09–2.01 (m, 1H), 1.63–1.29 (m, 8H), 1.00 (s, 3H), 0.98 (d, J = 8.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.5, 63.1, 38.7, 34.9, 34.7, 32.8, 30.5, 29.3, 29.3, 20.7, 19.9.
IR (cm^{-1}): 2323, 2870, 1736, 1455, 1379, 1152, 1113, 993, 507.
GCMS (m/z): calc'd for $C_{11}H_{18}O$: 166.1; found: 166.2
Rf: 0.41 (10% Et_2O/hexanes)

(3*aR*,7*aS*)-3,7a-dimethyloctahydro-*4H*-inden-4-one (19m): Following the general procedure using ketone **16r** (33.3 mg), compound **19m** has been purified by chromatography column (5% Et_2O/hexanes), obtaining a colorless oil; yield 68 % (22.6 mg, dr 2:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45–2.37 (m, 0.33H), 2.36–2.28 (m, 0.33H), 2.25–2.17 (m, 1.67H), 2.09–2.02 (m, 1H), 1.95–1.86 (m, 1.67H), 1.85–1.75 (m, 1.33H), 1.73–1.66 (m, 1.67H), 1.64–1.59 (m, 1H), 1.57–1.56 (m, 0.67H), 1.53–1.52 (m, 0.33H), 1.43–1.28 (m, 1H), 1.15–1.08 (m, 1H), 1.07 (s, 0.67H), 1.00–0.96 (m, 5.33H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.6, 215.2, 69.5, 53.8, 50.2, 47.6, 40.5, 40.5, 39.2, 38.1, 37.9, 34.3, 33.9, 33.2, 32.9, 32.3, 30.9, 26.9, 25.3, 22.6, 22.3, 20.2.
IR (cm^{-1}): 2952, 2925, 2868, 1710, 1459, 1379, 1233, 1098, 804, 503.
GCMS (m/z): calc'd for $C_{11}H_{18}O$:166.1; found:166.2
Rf: 0.55 (20% Et_2O/hexanes).

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