Development of new copper-catalyzed cross-coupling reactions

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Simone, SG.

In memory of Flavia Roncalli

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Abbreviations

Abbreviation	Meaning
Ac	Acetyl
Alk	Alkyl
Ar	Aromatic
Ph	Phenyl
Cp	Cyclopentadienyl
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	Dimethyl sulfoxide
Dvtms	Divinyltetramethylsiloxane
E^+	Electrophile
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
equiv.	Equivalent
ESI	Electrospray Ionization
HRMS	High-Resolution Mass Spectrometry
ACN	Methyl cyanide
MO	Molecular Orbital
NHC	*N*-Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
OA	Oxidative Addition
ppm	Part per million
RE	Reductive Elimination
RT	Room temperature
SET	Single Electron Transfer
S_N2	Bimolecular nucleophilic substitution
TBAF	Tetrabutylammonium Fluoride
THF	Tetrahydrofuran
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TMSCl	Trimethylsilyl chloride
LA	Lewis acid
AIBN	2,2'-Azobis(2-methylpropionitrile)
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
HOBt	1-Hydroxybenzotriazole
IMes	1,3-*Bis*(2,4,6-trimethylphenyl)imidazolinium
IPr	1,3-*Bis*(2,6-diisopropylphenyl)imidazolium
HOAt	1-Hydroxy-7-azabenzotriazole
TMEDA	*N*,*N*,*N*',*N*'- Tetramethylethylenediamine
B_2Pin_2	*Bis*(pinacolato)diboron
Cbz	Benzyloxycarbonyl
dtbpy	Di-*tert*-butylpyridine
EWG	Electron withdrawing group
EDG	Electron donating group
Mes	Mesityl
TBAT	Tetrabutylammonium difluorotriphenylsilicate
PMHS	Poly(methylhydrosiloxane)

Abbreviation	Meaning
Nu	Nucleophile
DMAc	Dimethylacetamide
DTBP	Di-*tert*-butyl peroxide
NMP	*N*-Methyl-2-pyrrolidone
Cy	Cyclohexane
PEG-400	Polyethylene glycol 400
dcpp	1,3-*Bis*(dicyclohexylphosphino)propane
	bis(tetrafluoroborate)
TC	Thiophene-2-carboxylate
TMP	2,2,6,6-Tetramethylpiperidine
DMBP	4,4'-Dimethoxybenzophenone
DME	Dimethoxyethane
DPPP	1,3-*Bis*(diphenylphosphino)propane
TMHD	2,2,6,6-Tetramethyl-3,5-heptanedione
DEMS	Methyldiethoxysilane
Bpy	2,2′-Bipyridine
PMDETA	*N*,*N*,*N*′,*N*′′,*N*′′-Pentamethyldiethylenetriamine
DPPE	1,2-*Bis*(diphenylphosphino)ethane
cataCXium A	Di(1-adamantyl)-*n*-butylphosphine
DMPHEN	2,9-Dimethyl-1,10-phenanthroline
DCP	Dicumyl peroxide
MTBE	Methyl *tert*-butyl ether
dba	dibenzylideneacetone
dcypf	[1,1′-*Bis*(di-cyclohexylphosphino)ferrocene]
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIPEA	*N*,*N*-Diisopropylethylamine
dippp	1,3-*Bis*(di-i-propylphosphino)propane
DMEDA	1,2-Dimethylethylenediamine
BINAP	(±)-2,2′-*Bis*(diphenylphosphino)-1,1′-binaphthalene
DPEphos	*Bis*[(2-diphenylphosphino)phenyl] ether
Me_4Ph	3,4,7,8-Tetramethyl-1,10-phenanthroline
DMEA	Dimethylethanolamine
ICP-MS	Inductively coupled plasma mass spectrometry
NBS	*N*-bromosuccinimmide
NIS	*N*-Iodosuccinimide
Me-Dalphos	Di(1-adamantyl)-2-dimethylaminophenylphosphine
Phen	1,10-Phenanthroline
DavePhos	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
$TC^{+}DA$	Trifluoromethylation cation donation ability
***t*-BuXPhos**	2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl
$TMSCF_3$	Trifluoromethyltrimethylsilane
NaOAsc	Sodium ascorbate
Cp^*	1,2,3,4,5-Pentamethylcyclopentadiene
Triaz	Triazole
PTFE	Polytetrafluoroethylene
COware	Screwable two-chamber glass sytem
AcOEt	Ethyl Acetate

General introduction

General introduction

Since everything we know and around us is made of atoms and molecules, organic chemistry is intimately part of our daily life, to the point that we end up forgetting it, underestimating its indispensable contribution to most scientific disciplines. The importance of organic chemistry in our life is such that it is unthinkable to live without organic chemistry, and that our future, without the indispensable contribution of this experimental discipline, would be much worse.

Among all the different areas of study of organic chemistry, catalysis is an important area of chemistry and a research area in constant development. The definition of catalysis is related to a substance named “catalyst” that increases the rate of a reaction without modifying the overall standard Gibbs energy change in the reaction. In a reaction, the catalyst is both a reactant and a product. Catalysis can be classified as homogeneous catalysis, in which only one phase is involved, and heterogeneous catalysis, in which the reaction occurs at or near an interface between phases. Nowadays, catalysis is a well-established technology that continues to evolve. Catalysis is an extremely important area of chemistry for the development of new catalytic systems and new reactions. Indeed, for the advancement of society, it is crucial to be able to develop new catalytic systems that work more efficiently and have wider applications in a variety of scientific fields, including agrochemistry, polymer chemistry, medical chemistry, and materials science. In fact, chemical research enables the development of new, improved, selective, more general, and environmentally friendly processes to meet the growing demand for such processes. For these reasons, it is not surprising that organic chemists have had the desire to discover and develop new chemical reactions more and more unique able to satisfy the growing demand for new chemicals for more than 200 years.

Utilizing transition metals as catalysts for novel reactions led to a fundamentally significant advancement in organic synthesis by enabling the discovery of previously unheard of reactions and, most importantly, new methods for forming chemical bonds between atoms. Because metal-catalyzed reactions have fundamentally changed the logic by which disconnections are made and organic molecules are synthesized, they are widely used in both industry and academia.

The most important examples of these new metal-catalyzed reactions are olefin metathesis reactions and cross-couplings catalyzed by palladium, as evidenced by the attributions of the Nobel Prize for Chemistry in 2005 to Yves Chauvin, Robert Grubbs and Richard Schrock for their work on metathesis reactions and in 2010 to Richard Heck, Ei-Ichi Negishi and Akira Suzuki for their work on palladium catalysis.

More recently, copper catalysis has been extensively revisited, notably through the pioneering works of Buchwald, Ma and Taillefer which, through the introduction of chelating ligands for copper. Initiating a real renaissance of reactions initially discovered by Ullmann and Goldberg. In fact, in the last two decades, the development of modern copper catalysis has provided organic chemists with the tools necessary for the creation of carbon-heteroatom bonds such as carbon-nitrogen, carbon-oxygen, carbon-phosphorus, carbon-carbon and carbon-sulphur under relatively mild reaction conditions.

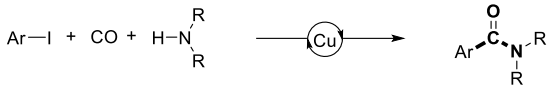
Recently, copper-catalyzed cross-coupling reactions have been extended to carbonylative ones. From a historical perspective, metal-catalyzed carbonylative reactions with carbon monoxide have been focused for decades on the use of noble metals such as palladium, which still remains one of the most widely used metals in academic and industrial laboratories. Some limitations met with this metal, mostly associated to the cost of palladium and its ligands, and to issues with its reactivity, have however stimulated research

on the use of metal catalysis based on other metals. Among the metals that had a deep impact in chemical synthesis and whose efficiency is now well established, copper is, as mentioned above, one of the most widely used ones.

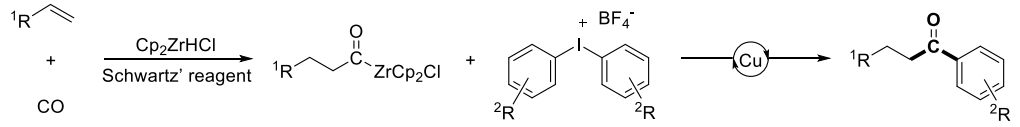
In this context, the research work carried out during the course of this thesis is devoted to the development of new copper-catalyzed carbonylative cross-coupling reactions for the preparation of carbonyl derivatives. In addition, still remaining in the domain of copper catalysis, a second independent subject dedicated to the development of a new synthetic strategy for the preparation of trifluoromethylated alkenes based on a broadly applicable copper-catalyzed trifluoromethylation of vinylsiloxanes was studied in our laboratory. Therefore, this manuscript will be, quite naturally, divided into two distinct parts which will focus on the development of new copper-catalyzed carbonylative cross-coupling reactions (part 1) and the development of a new copper-catalyzed cross-coupling for the trifluoromethylation of vinylsiloxanes (part 2). These two subjects will be discussed in detail in the four chapters of this manuscript.

The first chapter (p. 11-85) will consist of a bibliographical study which will aim to place the first part of this work in its context and which will be devoted to a literature overview of copper-catalyzed carbonylative cross-coupling reactions. A presentation of the most modern catalytic systems available for the formation of carbonyl derivatives will be presented with a detailed discussion of the selected articles.

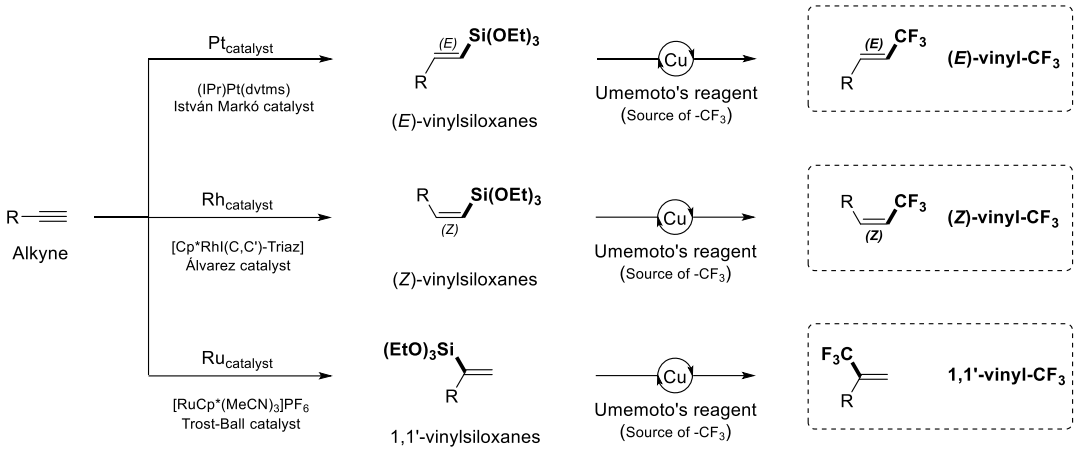
The second chapter (p. 86-119) will be devoted to the results obtained for the development of the first copper-catalyzed carbonylative cross-coupling reaction between aryl iodides and amines. Firstly, the optimization for the development of the copper-catalyzed carbonylative cross-coupling by a systematic variation of all crucial parameters will be presented. Then, with a methodical variation of the nature of both reaction partners the scope of this chemical transformation and its limitations will be described.



The third chapter (p. 120-153) will first provide a brief introduction on the formation and reactivity of acylzirconocene complexes. Then, the results obtained for the development of a novel approach for the synthesis of aryl-alkyl ketones via a copper-catalyzed carbonylative arylation using alkyl acylzirconocene chlorides, readily prepared from alkenes and carbon monoxide, will be discussed in detail.



Chapter 4 (p. 154-195) will start with a brief bibliographic introduction for the synthesis of trifluoromethylated alkenes, which will be followed by a discussion of the results obtained for the development of a new method for the preparation of trifluoromethylated olefins based on a broadly applicable copper-catalyzed trifluoromethylation of vinylsiloxanes, starting materials that are readily prepared, in a divergent manner, from alkynes.



Finally, a general conclusion (p. 194-196) and an experimental part (p. 197-238) will close this manuscript.

List of publications

This work will be the subject of the following publications:

1. "Copper-catalyzed carbonylative arylation coupling of alkenes with aryl iodonium salts: efficient synthesis of alkyl-aryl ketones", Grosso, S.; Mlynczak, M.; Riant, O.; Evano, G. *Manuscript under redaction.*

2. "Copper-catalyzed trifluoromethylation of vinylsiloxanes", Grosso, S.; Marchese, M.; Salamone, L.; Riant, O.; Evano, G. *Manuscript under redaction.*

First part: Carbonylative cross-coupling reactions

Chapter 1: Literature overview of copper-catalyzed carbonylative cross-coupling reactions

Chapter 1. Literature overview of copper-catalyzed carbonylative cross-coupling reactions

1.1. Introduction

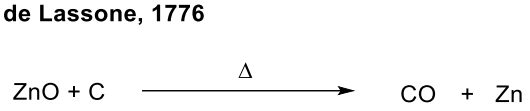
Built around the development of new copper-catalyzed carbonylative cross-coupling reactions, the first part of the bibliographical study included within this manuscript will aim to place this work in its context and will be devoted to the presentation of transition metal-catalyzed carbonylative cross-coupling reactions.

Then, this section will be followed by a more detailed and exhaustive discussion of a specialized area of copper catalysis dedicated to the development of new carbonylative cross-coupling reactions. A global overview of the state-of-the-art will be presented and all reactions and processes discussed have been classified accordingly to the nature of the product formed. For each catalytic system under consideration, the model reaction studied, the scope of the methodology and the catalytic cycle will be described and discussed.

1.2. General overview on carbonylative reactions

In this first section, we will focus on the keys concepts required to plan and develop new carbonylative cross-coupling reactions. Thus, we will first introduce the general concepts required to understand the physico-chemical properties of carbon monoxide, the mechanisms involved in its activation and the interactions of carbon monoxide with metals.

The earliest record of CO appeared in the 300s BC, when Aristotle recorded that burning coals produced toxic fumes. Since the discovery and identification of carbon monoxide by de Lassone and W.C. Cruikshank at the end of the 18th century by heating zinc oxide with coke (Scheme 1),[1] the exploration of the utilization of this small molecule in organic chemistry has become one of great interest, notably for the development of carbonylation reactions.



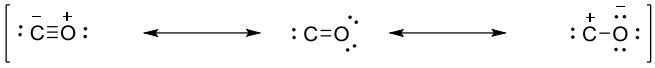
Scheme 1. First discovery of carbon monoxide in human history.

From a structural and chemical-physical point of view, it is important to highlight that carbon monoxide is the simplest oxocarbon, which is isoelectronic with other triply-bonded diatomic species with 10 valence electrons. These species include molecular nitrogen (N_2), the cyanide anion (CN^-) and the nitrosonium cation (NO^+). The carbon and oxygen atoms are connected together by a triple bond made up of a net two π bonds and one σ bond.

The distance separating the oxygen atom from the carbon atom is 112.8 pm.[2] The bond-dissociation energy of 1072 kJ/mol is higher than that of N_2 (942 kJ/mol), making it one of the strongest chemical bonds

[1] Cruickshank, W. *J. Nat. Philos. Chem*. **1801**, *5*, 201–211.
[2] (a) Gilliam, O. R.; Johnson, C. M.; Gordy, W. *Phys. Rev*. **1950**, *78*, 140–144. (b) Haynes, W. M. *Handb. Chem. Phys.* 95th ed.; Vol. 91; CRC Press, **2010**.

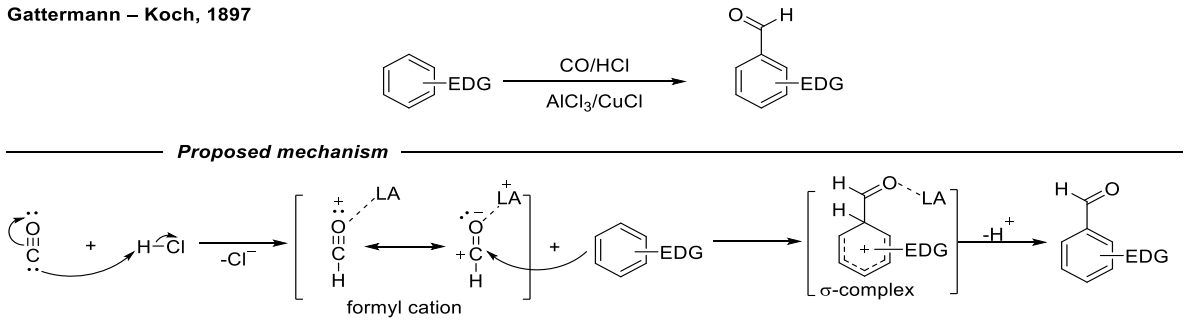
currently known within the category of bimolecular neutral molecules. A free molecule of carbon monoxide has a small dipole moment of 0.122 D with a net negative charge δ^- onto the carbon atom.[3] The molecule is therefore asymmetric and, despite the greater electronegativity of oxygen, the dipole moment points from the more-negative carbon to the more-positive oxygen. Carbon monoxide has three resonance structures (Scheme 2) and since the σ-symmetrical highest occupied molecular orbital of CO is more localized on the carbon atom, the resonance form with a partial negative charge on carbon and a partial positive charge on oxygen $^-C{\equiv}O^+$ is the most frequently used. Since its first discovery, carbon monoxide has been used to develop new carbonylation reactions.



Scheme 2. Resonance structures for carbon monoxide.

The term "carbonylation" was first coined by W. Reppe at BASF in the 1930s and usually refers to organic reactions that incorporate carbon monoxide into the parent compound.[4] In general, a molecule of carbon monoxide is incorporate into a substrate either by the insertion of CO into an existing bond, or by the addition of CO to unsaturated compounds, such as alkynes or alkenes. To perform carbonylative reactions, the activation of CO is crucial for the success of these transformations and from the point of view of the reaction intermediates, carbonylation reactions can be classified into four categories:

1) Strong acid-initiated cationic carbonylations: in this case the activation of carbon monoxide is carried out through the formation of a formyl cation intermediate, which is formed *in situ* by the reaction of CO and strong acid (Scheme 3). The most representative example is the Gattermann-Koch reaction discovered in 1897 where a formyl group (CHO) is introduced onto electron-rich arenes under Friedel-Crafts acylation conditions.[5] Stoichiometric amounts of the Lewis acid ($AlCl_3$ or $FeCl_3$) and activator (Cu_2Cl_2, $TiCl_4$, or $NiCl_2$) promote the reaction under atmospheric pressure of CO.



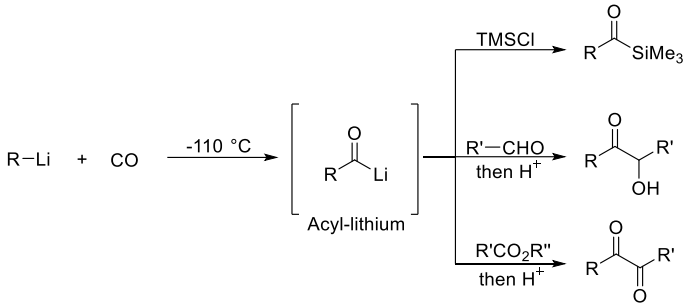
Scheme 3. Strong acid-initiated carbonylation: the Gattermann-Koch reaction.

[3] Scuseria, G. E.; Miller, M. D.; Jensen, F.; Geertsen, J. *J. Chem. Phys.* **1991**, *94*, 6660–6663.

[4] Falbe, J. *New Syntheses with Carbon Monoxide*, 1th ed.; Vol. 1; Springer, **1980**.

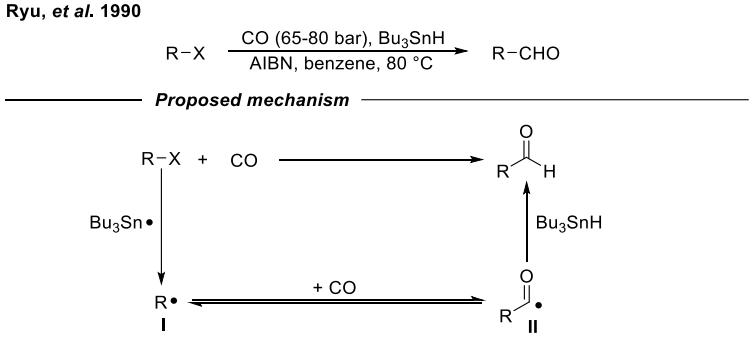
[5] (a) Gattermann, L.; Koch, J. A. *Chem. Ber.* **1897**, *30*, 1622–1624. (b) Gattermann, L. *Ann.* **1906**, *347*, 347–386. (c) Gattermann, L. *Ann.* **1908**, *357*, 313–383. (d) Crounse, N. N. *Org. React*. **1949**, *5*, 290–301.

2) Anionic carbonylations: in this case the activation of carbon monoxide is carried out through the formation of an acyl anion species formed upon addition of nucleophiles onto carbon monoxide and subsequent trapping by an electrophile (Scheme 4). These transformations are quite common with organometallic compounds such as organolithium and organomagnesium reagents. Representative examples of such carbonylations are the seminal reports of Seyferth group in which an acyl lithium was successfully trapped with electrophiles by careful control of the reaction conditions.[6] For instance, by reacting alkyl lithium reagents with CO in the presence of chlorotrimethylsilane, acyltrimethylsilanes were prepared in good yields. Moreover, the acyl lithium anion could be also trapped *in-situ* with ketones and esters to produce 1,2-diketones and α-hydroxy ketones, respectively. Unfortunately, the use of such acyl anions is hampered by their limited stability.



Scheme 4. Anionic carbonylation.

3) Radical carbonylation: in such reactions the activation of carbon monoxide is carried out through the formation of an acyl radical species, by addition of radical species to CO. This reaction is an equilibrium shifted to the formation of the acyl radical species **II** from alkyl radicals **I**, but disfavoured for aryl radical species. As an historical example, Ryu and co-workers reported in 1990 that the treatment of alkyl halides with AIBN/Bu_3SnH under CO pressure furnished the corresponding homologated aldehydes (Scheme 5).

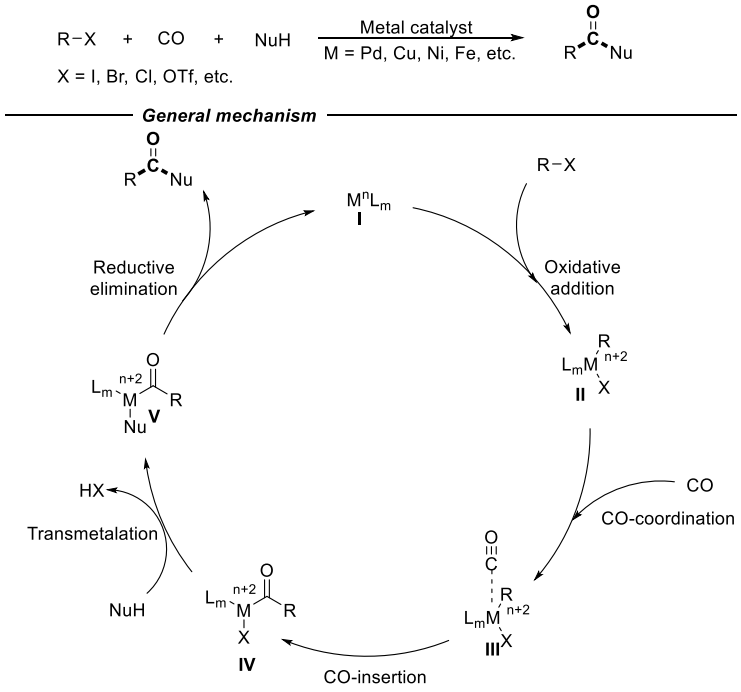


Scheme 5. Tin-hydride-induced carbonylation of alkyl halides.

4) Transition metal-catalyzed carbonylation: in this case, the activation of carbon monoxide involves the formation of metal carbonyl complexes. These transformations are based on catalytic cycles in which elementary reactions occur in sequence. Generally, the catalytic cycles involved in such metal catalyzed cross-coupling reactions start with the oxidative addition of R-X (aryl-, alkyl- and pseudo-halides) onto the metal catalyst M^nL_m **I** yielding a $RM^{n+2}XL_m$ complex **II** as depicted in Scheme 6. Subsequent coordination and insertion of carbon monoxide into the R-M^{n+2} bond yields a transient acylmetal intermediate $RCOM^{n+2}XL_m$ **IV** that evolves to the target product after coordination of the

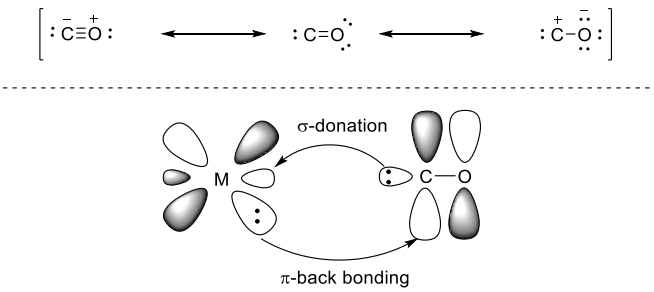
[6] (a) Seyferth, D.; Weinstein, R.M. *J. Am. Chem. Soc*. **1982**, *104*, 5534–5535. (b) Seyferth, D.; Weinstein, R.M.; Wang, W. *J. Org. Chem.* **1983**, *48*, 1144–1146.

nucleophile and a reductive elimination step. In the last years, transition metal-catalyzed carbonylation reactions have received significant attention due to their mild conditions, high yield with high selectivity, good tolerance of sensitive functional groups and broad substrate scope, especially when compared to the other strategies to activate carbon monoxide.[7]



Scheme 6. Transition-metal catalyzed carbonylation.

Before moving to the overview of transition metal-catalyzed carbonylative reactions, some considerations on metal carbonyl complexes must be discussed. Carbon monoxide can form complexes with a wide range of transition metals due to its strong σ-donating and π-accepting abilities. Indeed, CO has a C-centered lone pair (HOMO), a σ-bond generated from the p_z orbitals of C and O, and two orthogonal π-bonds, which together give the C-O triple bond. In addition, there are also two C-O antibonding π* orbitals, which could accept electron density form sufficiently high-lying orbitals such as the occupied 3d (or 4d, 5d) levels of transition metals. Therefore, it is this combination of σ, π and π* orbitals which is responsible for the reactivity of CO.[8] A simplified graphical representation of the orbital interactions in metal-carbonyl complexes is depicted in Scheme 7.

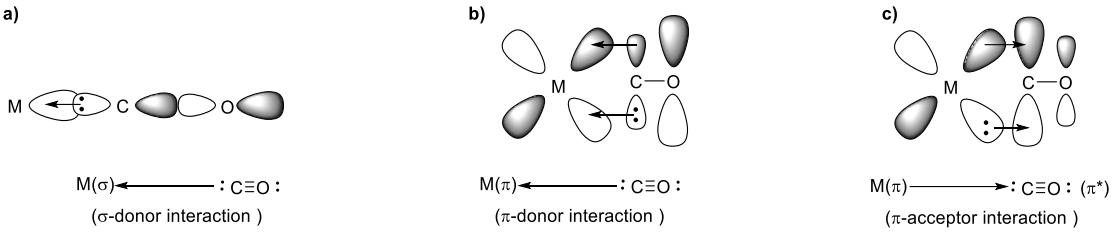


Scheme 7. σ-donation and π-backdonation in metal-carbonyl complexes.

[7] Zhao, S.; Mankad, N. *Catal. Sci. Technol*. **2019**, *9*, 3603–3613.

[8] Bochmann, M. *Organometallics and Catalysis: An Introduction*, 1st ed.; Vol. 1; Oxford University Press, **2015**.

CO can interact with a transition metal in three ways: as σ-donor, π-donor and π-acceptor, as depicted in the following Scheme 8. Of these, the σ-donor and π-acceptor contributions are the most important; in particular, the π-acceptor capacity of CO is responsible for its ability to bind electron-rich metal centers. The π-donor interaction is weak (and often neglected). The representations of these three ways of interactions of CO with a metal center are depicted in the following Scheme 8.



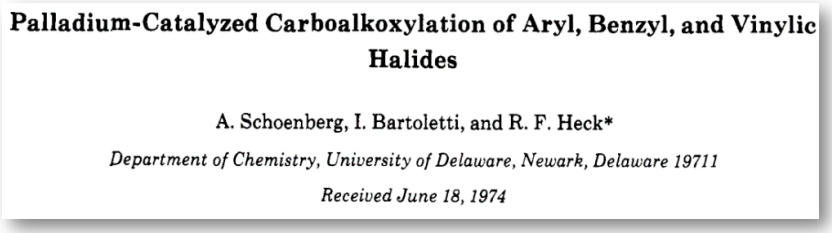
Scheme 8. Interactions between carbon monoxide molecular orbitals and metal d orbitals.

These interactions are responsible for a strengthening of the M–C bond. Although the donation of the 3σ lone par to the metal strengthens the C–O bond, this is often more than compensated by the back donation from the metal into the CO π* orbital, which weakens the C–O bond.

Following this brief introduction, we will now focus our attention to transition metal-catalyzed carbonylative cross-coupling reactions, which from a chronological point of view, were the first one to be investigated, starting with palladium catalysis.

1.3. Noble metal-catalyzed carbonylative cross-coupling reactions

Most research on transition metal catalyzed carbonylation reactions are based on catalysis by noble metals such as Pd, Ru, Rh and Ir. This field of catalysis was pioneered by Richard Heck who described in 1972 their first seminal work on palladium-catalyzed alkoxycarbonylation of aryl halides (Scheme 9).[9] Under the conditions reported by the Heck group, aryl, vinyl and benzyl halides react with carbon monoxide and an alcohol under a low pressure of carbon monoxide (1 atm) in the presence of a tertiary amine as base and a catalytic amount of a palladium-triphenylphosphine complex at high temperature (Scheme 10). The reactions need the addition of a base to neutralize the acid generated in the reaction and to promote the generation of the Pd(0) species, which is essential to initiate the catalytic cycle. Following these studies, a large number of palladium precursors, primarily Pd(II) salts but also a number of Pd(0) complexes have been reported to promote such carbonylative cross-coupling reactions.



Palladium-Catalyzed Carboalkoxylation of Aryl, Benzyl, and Vinylic Halides

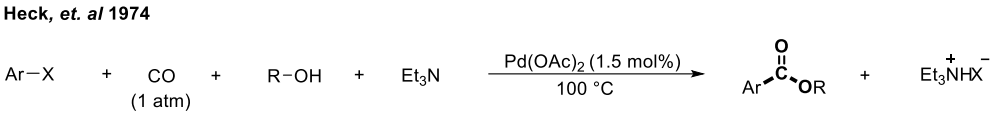
A. Schoenberg, I. Bartoletti, and R. F. Heck*

Department of Chemistry, University of Delaware, Newark, Delaware 19711

Received June 18, 1974

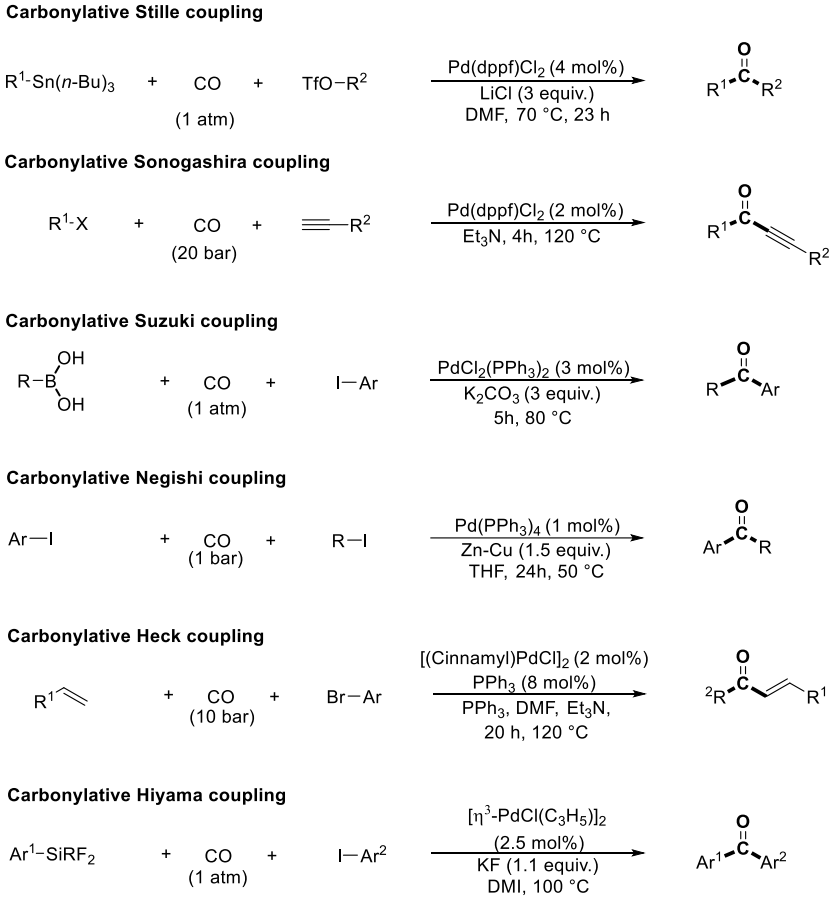
Scheme 9. First seminal work on palladium-catalyzed alkoxycarbonylation of aryl halides.

[9] (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318–3326. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327–3331.



Scheme 10. Seminal work of Heck on the first Pd-catalyzed carbonylative cross-coupling reaction.

The importance of Pd in carbonylative cross-coupling reactions is exemplified by the many named carbonylative reactions of this type reported in literature such as the Heck carbonylation,[10] Suzuki-Miyaura,[11] Sonogashira,[12] Hiyama,[13] Negishi[14] and Stille[15] (Scheme 11). As Pd-catalyzed carbonylative reactions have been extensively studied and frequently summarized,[16] those results will not be covered here again, but an overview of other noble metals used for the catalysis of carbonylative reactions will be provided instead.



Scheme 11. Representative examples of palladium-catalyzed carbonylative cross-coupling reactions.

[10] Wu, X. F.; Haijun, J.; Neumann, H.; Beller, M. *ChemCatChem* **2011**, *3*, 726 –733.

[11] (a) Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. *J. Org. Chem.* **1998**, *63*, 4726–4731. (b) Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett*. **1993**, *34*, 7595–7598.

[12] Kobayashi, T.; Tanaka, M. *J. Chem. Commun*. **1981**, 333–334.

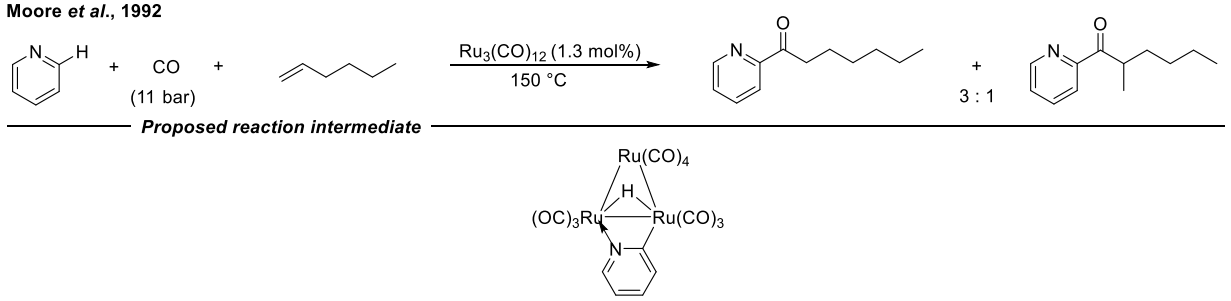
[13] (a) Natanaka, Y.; Hiyama, T. *Chem. Lett.* **1989**, *18*, 2049–2052. (b) Hatanaka, Y.; Fukushima, S.; Hiyama, T. *Tetrahedron* **1992**, *48*, 2113–2126.

[14] (a) Tamaru, Y.; Ochiai, H.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett*. **1983**, *24*, 3869–3872. (b) Yasui, K.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem*. **1995**, *60*, 1365–1380.

[15] (a) Tanaka, M. *Tetrahedron Lett*. **1979**, *28*, 2601–2602. (b) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557–1565.

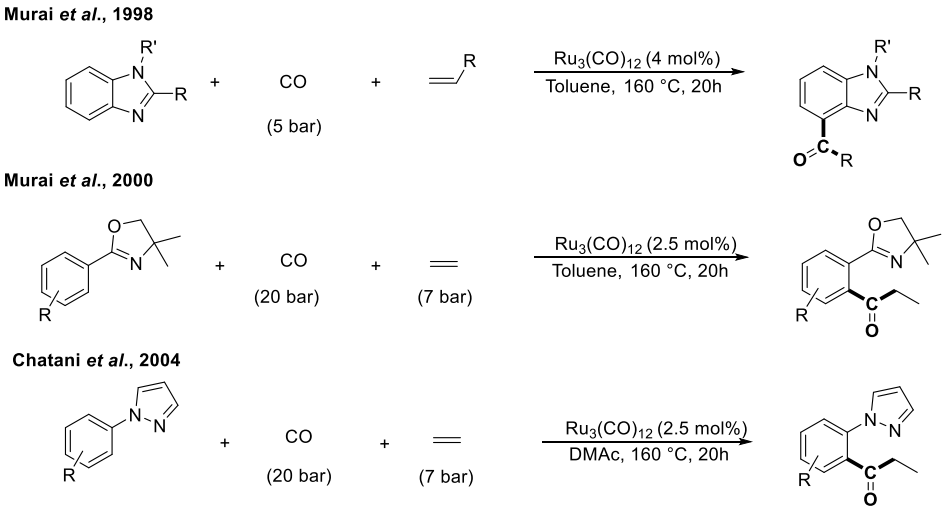
[16] Johansson S., C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed*. **2012**, *51*, 5062–5085.

In 1992, the Moore group indeed reported for the first time a ruthenium-catalyzed carbonylative C–H activation reaction, in which pyridine and other nitrogen-containing aromatic compounds have been smoothly *ortho*-acylated with a combination of alkenes and CO using 1.3 mol% of $Ru_3(CO)_{12}$ as catalyst.[17] Notably, internal olefins like *cis*- and *trans*-2-hexene yield the same proportion of linear/branched carbonyl compounds as terminal olefins. According to the experiments carried out to investigate the reaction mechanism, the authors suggested that the coordinatively unsaturated metal center of the trinuclear cluster coordinates to pyridine and then an *ortho*-metalation gives the key intermediate shown below (Scheme 12).



Scheme 12. $Ru_3(CO)_{12}$ catalyzed carbonylation of pyridine.

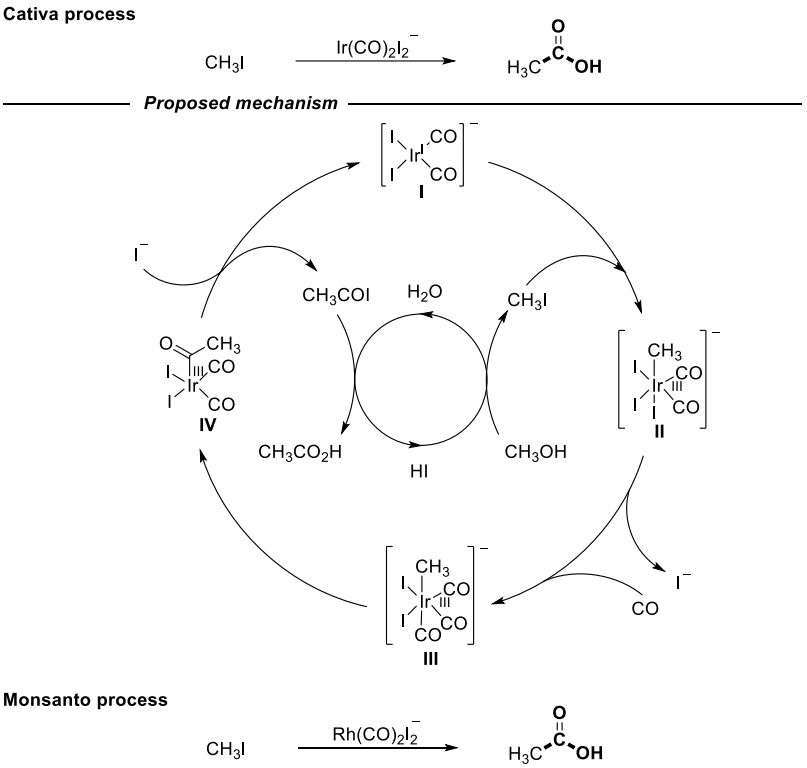
After the seminal work described by Moore and co-workers, the Murai and Chatani's group developed new other ruthenium-catalyzed carbonylation reactions of arenes and hetero-arenes. For example, aza-heterocycle,[18] 2-phenyloxazolines,[19] and *N*-arylpyrazoles,[20] were all carbonylated into the corresponding carbonyl derivatives using $Ru_3(CO)_{12}$ as the catalyst under relatively low pressure of carbon monoxide (Scheme 13). Through these strategies, a direct carbonylation at a C–H bond adjacent to the nitrogen heterocycles, which acts as a directing group, can be easily achieved.



Scheme 13. Representative examples of $Ru_3(CO)_{12}$ catalyzed carbonylative C–H activation reactions.

[17] Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; La Bounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc*. **1992**, *114*, 5888–5890.
[18] Fukuyama, T.; Chatani, N.; Tatsumi, J.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc*. **1998**, *120*, 11522–11523.
[19] Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D. R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem*. **2000**, *65*, 1475–1488.
[20] (a) Asaumi, T.; Chatani, N.; Matsuo, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem*. **2003**, *68*, 7538–7540. (b) Asaumi, T.; Matsuo, T.; Fukuyama, T.; Ie, Y.; Kakiuchi, F.; Chatani, N. *J. Org. Chem*. **2004**, *69*, 4433–4440.

Among all the other noble metals, also iridium showed to be a useful catalyst used in organic synthesis to promote carbonylative cross-coupling reactions.[21] The most representative example is certainly the industrial carbonylation of methanol to acetic acid, which is nowadays known as the Cativa process (Scheme 14). In 1996, BP chemicals reported a novel industrial process for the methanol carbonylation which represents an advancement over conventional rhodium-based technology.[22] Indeed, the Cativa process offers a significant improved catalyst stability, which enables low water concentrations, high reaction rates, reduced by-product formation and improved yields. Specifically, the process relies on an iridium-based catalyst. The catalytic cycle of the Cativa process starts with the oxidative addition of the methyl iodide with active catalyst **I** to furnish intermediate **II**. After a ligand exchange step, in which iodide is replaced with carbon monoxide, the intermediate **III** is formed following a migratory insertion of carbon monoxide into the iridium-carbon bond generating an acyl-iridium intermediate **IV**. Finally, the active catalyst **I** is regenerated with a reductive elimination step releasing the highly electrophilic acetyl iodide which is spontaneously hydrolysed to form acetic acid. During this process, hydroiodic acid is generated and transforms methanol into methyl iodide.



Scheme 14. Iridium and rhodium-catalyzed carbonylation of methanol to acetic acid (Cativa and Monsanto process).

The last noble metal frequently employed to perform carbonylative reactions is rhodium. Despite the excellent activities in non-carbonylation transformations, Rh has been much less studied in comparison to palladium in carbonylative transformations. There are however several interesting applications to mention as the Monsanto process that is the rhodium version of the Cativa process. Indeed, rhodium is known to be largely employed for the industrial preparation of acetic acid by carbonylation of methanol, a process which has been developed by BASF in 1960 and further improved by Monsanto in 1966 (Scheme 14). This procedure operates at a pressure of 30-60 atm and a temperature of 150-200 °C.

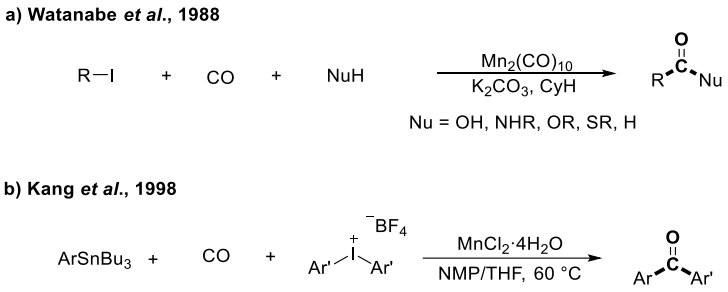
[21] Kezuka, S.; Takeuchi, R. *Synthesis*, **2006**, *20*, 3349–3366.
[22] (a) Sunley, G. J.; Watson, D. J. *Catal. Today* **2000**, *58*, 293–307. (b) Jones, J. H. *Platinum Met. Rev*. **2000**, *44*, 94–105.

After presenting a broad overview and illustrating the most significant carbonylation reactions catalyzed by noble metals, we will focus in the next section of this chapter on non-noble metal catalyzed carbonylative cross-coupling.

1.4. Non-noble metal catalyzed carbonylative cross-coupling reactions

Although catalytic systems based on noble metals for carbonylation reactions have advantages in reactivity and efficiency, their high costs and toxicity represent a strong limitation for their applications on large scales. The use of non-noble catalysts is therefore fully relevant in this perspective and also in terms of reactivity. Carbonylative cross-coupling reactions catalyzed by early transition metals with half-occupied or less than half-occupied 3d shells (Sc, Ti, V, Cr and Mn) are rare and unusual, which might be due to the oxidative addition onto alkyl, aryl and pseudo-halides being not favored.

Indeed, only few examples of manganese-catalyzed carbonylations have been reported.[23] In 1988, the Watanabe group described the use of manganese catalysts in the carbonylative coupling of various nucleophiles and alkyl iodides (Scheme 15a).[24] Alcohols and amines can be used as reaction partners to prepare alkyl esters and amides. Additionally, also thiols, azides as well as hydrides can also be used as nucleophiles. Few years later, the Kang group reported a novel carbonylative cross-coupling of organostannanes with hypervalent iodonium salts catalyzed by $MnCl_2 \cdot 4H_2O$ (5 mol%).[25] Good yields of the desired biaryl ketones have been obtained under a CO atmosphere of 1 bar (Scheme 15b).



Scheme 15. Mn-Catalysed carbonylative cross-coupling of iodides.

Other non-noble catalysts utilized in transition metal-catalyzed carbonylative reactions are based on Fe, Co and Ni. All these metals are located in the late part of the periodic table and therefore are rich in electrons in the valence orbitals, which implies that the oxidative addition on alkyl, aryl and pseudo-halides is easily favored. Due to their high availability, affordability and biological compatibility, iron salts have been utilized in carbonylation chemistry since the middle of the 20th century. The Collman reagent, also known as $Na_2Fe(CO)_4$, has indeed been widely used as a stoichiometric carbonylation reagent.[26] Although there are

[23] (a) Calderazzo, F. *Inorg. Chem.* **1965**, *4*, 293–296. (b) Li, Y.; Zhu, F.; Wang, Z.; Rabeah, J.; Brückner, A.; Wu, X. F. *ChemCatChem*. **2017**, *9*, 915–919.

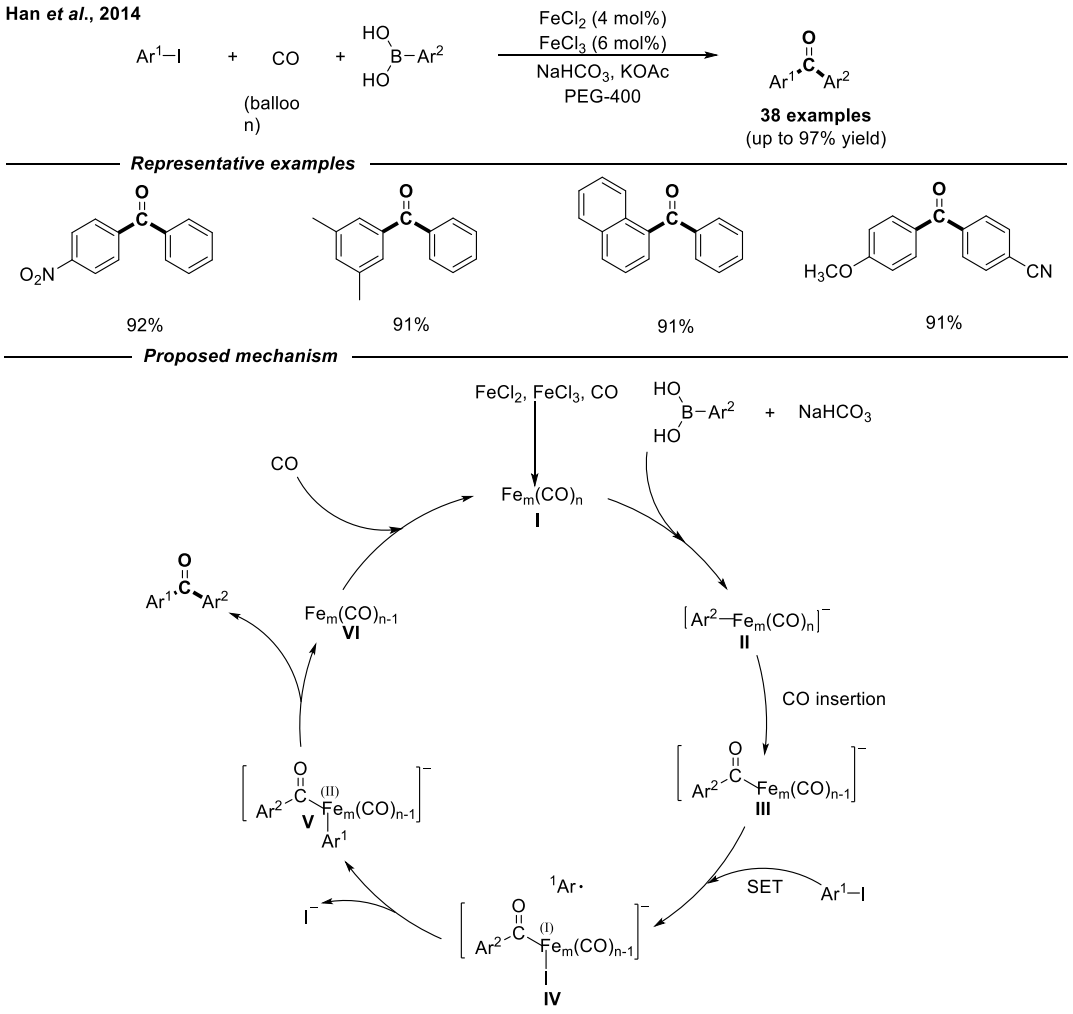
[24] (a) Kondo, T.; Tsuji, Y.; Watanabe, Y.; *Tetrahedron Lett*. **1988**, *29*, 3833–3836. (b) Kondo, T.; Sone, Y.; Tsuji, Y.; Watanabe, Y. *J. Organomet. Chem.* **1994**, *473*, 163–173.

[25] Kang, S. K.; Kim, W. Y.; Lee, Y. T.; Ahn, S. K.; Kim, J. C. *Tetrahedron Lett*. **1998**, *39*, 2131–2132.

[26] (a) Collman, J. P. *Acc. Chem. Res.* **1975**, *8*, 342–347. (b) Collman, J. P.; Winter, S. R.; Komoto, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 249–250. (c) Collman, J. P.; Winter, S. R.; Clark, D. R. *J. Am. Chem. Soc.* **1972**, *94*, 1788–1789. (d) Collman, J. P.; Hoffman, N. W. *J. Am. Chem. Soc.* **1973**, *95*, 2689–2691.

several examples of stoichiometric iron-mediated carbonylation reactions,[27] iron-based catalytic processes are however still underdeveloped and typically require high pressures of carbon monoxide.[28]

In 2014, the Han group described the first iron-catalysed carbonylative Suzuki reaction performed with 4 mol% of $FeCl_2$ and 6 mol% $FeCl_3$ in combination with a large excess of $NaHCO_3$ in PEG-400 as solvent. The reaction is carried out under an atmospheric pressure of carbon monoxide with various aryl iodides and arylboronic acids to furnish the corresponding diaryl ketones in good yields (Scheme 16).[29]



Scheme 16. Iron-catalysed carbonylative Suzuki reaction.

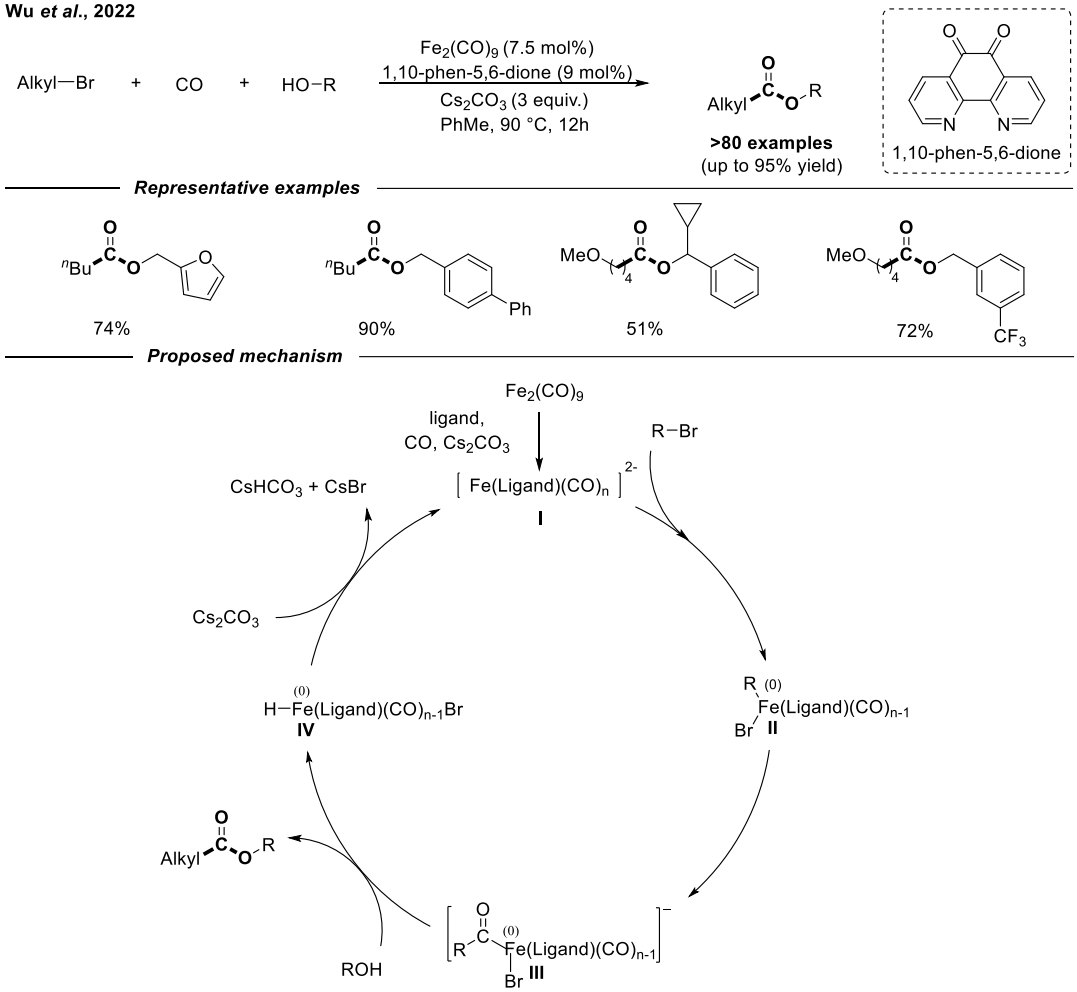
In their mechanistic studies, the authors found that an iron carbonyl species was formed and acted as the active catalyst. The authors proposed that the catalytic cycle starts with the generation *in situ* of $Fe_m(CO)_n$ **I** from $FeCl_3$ and $FeCl_2$ under a pressure of carbon monoxide. Then, the arylboronic acid, with the assistance of the base, undergoes a transmetallation to form highly nucleophilic organoiron complex **II**, which further gives an acyl organoiron complex **III** by intramolecular carbon monoxide migratory insertion.

[27] Periasamy, M.; Rameshkumar, C.; Radhakrishnan, U.; Devasagayaraj, A. *Curr. Sci*. **2000**, *78*, 1307–1313.
[28] (a) Driller, K. M.; Prateeptongkum, S.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed*. **2011**, *50*, 537–541. (b) Driller, K. M.; Klein, H.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed*. **2009**, *48*, 6041–6044.
[29] Han, W.; Zhong, Y. *Chem. Commun.* **2014**, *50*, 3874–3877.

At this point, the aryl iodide and the acyl-iron complex reacts together to generate a transient species of iron(II) **V**.[30] Finally, reductive elimination furnishes the desired carbonylated product and restores the catalytically active species **I** upon coordination of carbon monoxide.

Recently, the Wu group reported an innovative protocol for the iron-catalyzed alkoxycarbonylation of unactivated alkyl bromides, which are quite challenging substrate due to the high bond dissociation energy of the C−Br bond (Scheme 17).[31] The optimized reaction conditions allowed the preparation of esters using 7.5 mol% of $Fe_2(CO)_9$, 9 mol% of 1,10-phenanthroline-5,6-dione and 3.0 equiv. of Cs_2CO_3 in toluene under at 90 °C. The substrate scope is broad and the methodology showed to be robust.

Considering the results obtained during the mechanism investigation, the authors proposed a plausible pathway in which the active catalytic species **I** is generated using $Fe_2(CO)_9$ with the assistance of the base and CO. Following the *in situ* formation of a stabilized iron-catalyst, an alkyl-iron complex **II** is formed by a two-electron transfer reaction with alkyl bromide. Then, a CO-migratory insertion occurs and the resulting acyl-iron complex **III** provides the ester product after the nucleophilic attack of the alcohol. Subsequently, in the presence of a base, a reductive elimination of hydrobromic acid occurs, and the Fe^{2+} complex **I** is regenerated.

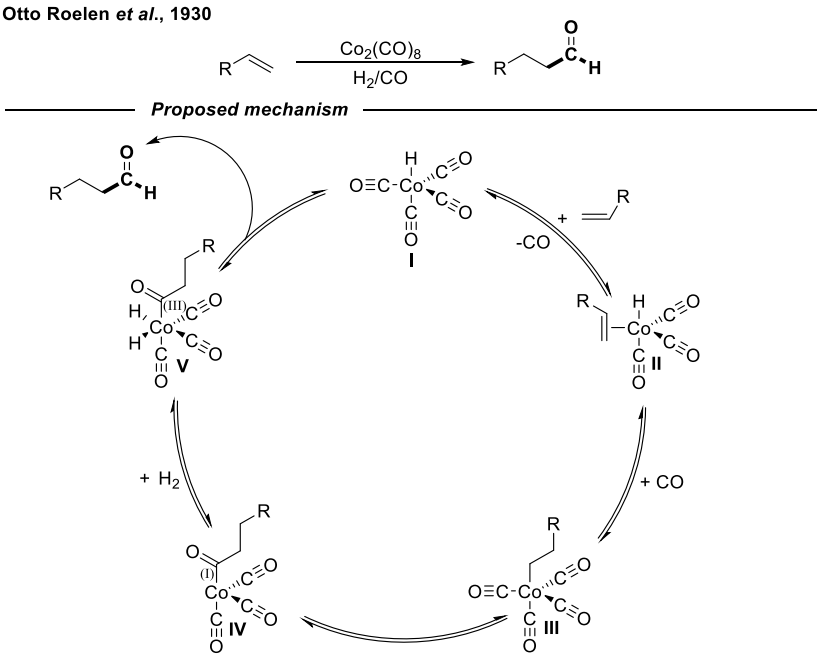


Scheme 17. Iron-catalyzed alkoxycarbonylation of alkyl bromides.

[30] (a) Brunet, J. J.; El Zaizi, A. *J. Organomet. Chem*. **1995**, *486*, 275–277. (b) Brunet, J. J.; Taillefer, M. *J. Organomet. Chem.* **1990**, *384*, 193–197. Brunet, J. J.; de Montauzon, D.; Taillefer, M. *Organometallics*, **1991**, *10*, 341–346.

[31] Ai, H. J.; Leidecker, B. N.; Dam, P.; Kubis, C.; Rabeah, J.; Wu, X. F. *Angew. Chem. Int. Ed.* **2022**, *61*, e202211939.

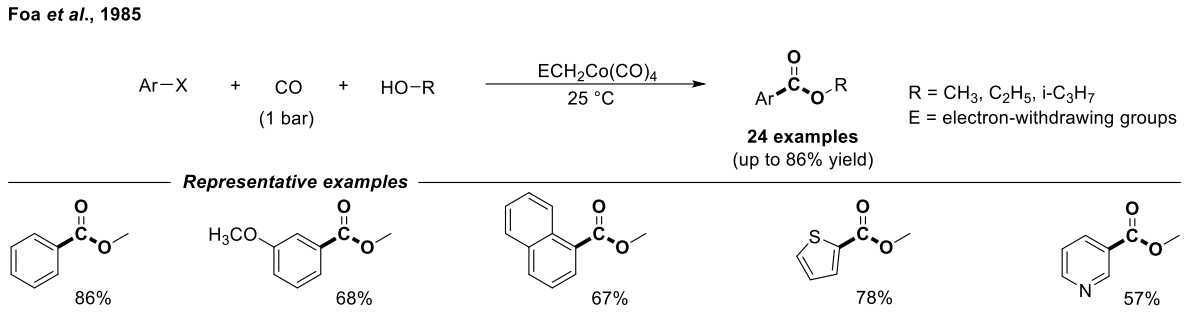
The use of cobalt to catalyze the carbonylation reaction appeared in the early twentieth century when in 1938 Otto Roelen was studying the Fischer-Tropsch reaction, which converts H_2/CO into alkanes and alkenes when using a cobalt catalyst deposited on a ThO_2/SiO_2 support, traces of propanal were observed and Roelen discovered that cobalt was able to catalyze specifically the hydrocarbonylation of ethylene.[32] In this way, an alkene can be converted to the homologous aldehyde by the addition of H_2 and CO, catalyzed by $CO_2(CO)_8$ (Scheme 18). Nowadays, using this well-established reaction, more than 4 million tons of aldehydes are made annually in this way. The reaction mechanism of the hydroformylation starts with the reaction between $Co_2(CO)_8$ and H_2 to give $HCo(CO)_4$ **I**, which is the active catalyst. The process begins with the dissociation of CO from cobalt tetracarbonyl hydride. Then, after the binding of the alkene onto the cobalt catalyst **II**, the olefin inserts to give an alkyl tetracarbonyl cobal complex **III**. At this point, the migratory insertion of carbon monoxide gives an acyl-cobalt species **IV**, which following an oxidative addition of hydrogen evolves to a dihydrido complex **V**. Finally, the homologated aldehyde is released by reductive elimination.[33]



Scheme 18. Alkene hydroformylation using cobalt catalyst.

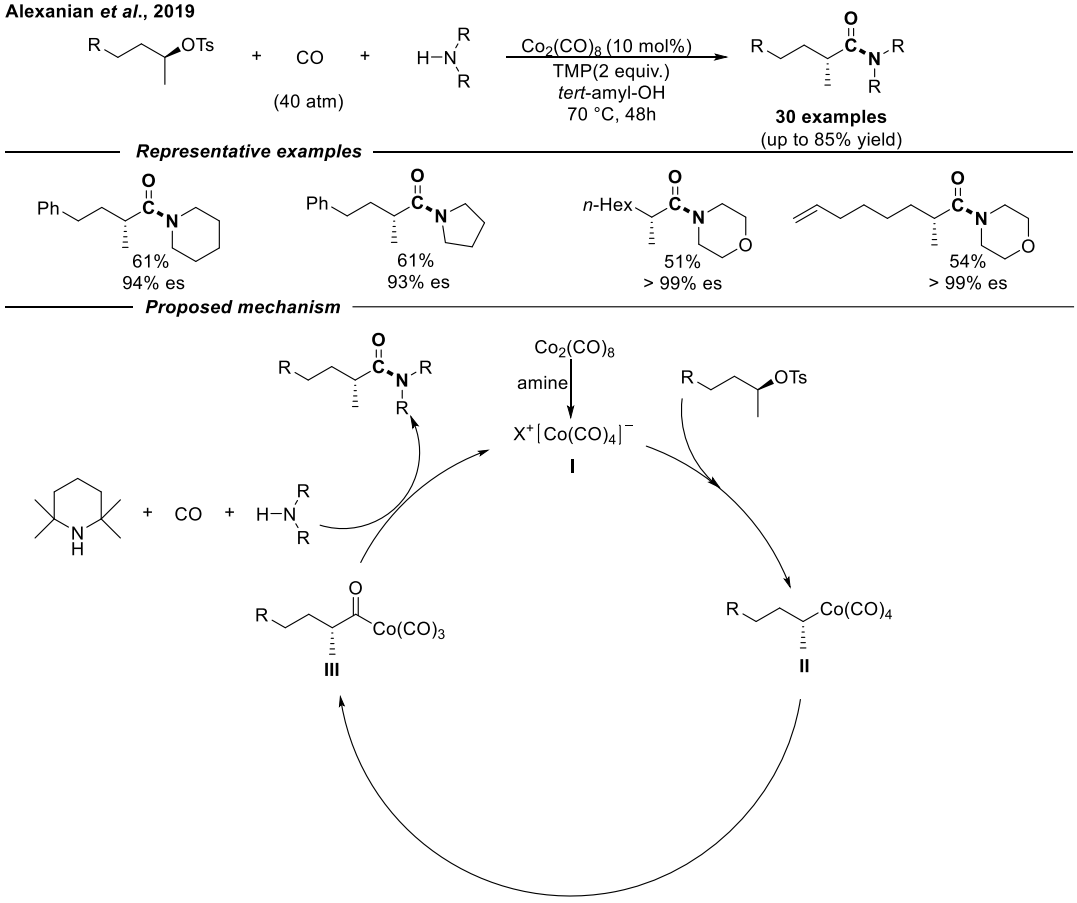
In 1985, the Foa group reported a novel protocol for the preparation of ester through a cobalt-catalyzed carbonylative cross-coupling of aromatic and heteroaromatic halides (Scheme 19).[34] Using this protocol, the alkoxycarbonylation of aryl halides has been conveniently catalyzed in alcoholic solution by alkylcobalt carbonyl complexes. The presence of an electron-withdrawing group in the alkyl chain of the alkylcobalt carbonyl complexes provides an increased stability, in this way they can be handled easily under an inert atmosphere at 0 °C.

[32] Cornils, B.; Herrmann, W. A.; Rasch, M. *Angew. Chem. Int. Ed*. **1994**, *33*, 2144–2163.
[33] Heck, R. F.; Breslow, D. S. *J. Am. Chem. Soc.* **1961**, *83*, 4023–4027.
[34] Foa, M.; Francalanci, F.; Bencini, E.; Gardano, A. *J. Organomet. Chem.* **1985**, *285*, 293–303.



Scheme 19. Co-catalysed carbonylation of aryl halides.

Recently, a novel stereospecific aminocarbonylative cross-coupling of alkyl tosylates with amines using a commercially available cobalt catalyst was reported by the Alexanian group (Scheme 20).[35] Under pressure of 40 atm CO in *tert*-amyl alcohol, 10 mol% of $Co_2(CO)_8$ and two equivalents of 2,2,6,6-tetramethylpiperidine (TMP), chiral amides were obtained in good yield and with high stereocontrol from the corresponding tosylate. For this transformation, the authors proposed that the $Co_2(CO)_8$ first disproportionates yielding the cobaltate anion **I** by addition of the amine/TMP. Then, a S_N2 displacement of the tosylate by the anionic cobaltate carbonyl takes place to generate an alkylcobalt species **II** which undergoes CO migratory insertion with retention of configuration to finally afford an acylcobalt intermediate **III**. Finally, the nucleophilic displacement of the acylcobalt complex **III** with the amine furnishes the chiral target amide regenerating the catalyst.

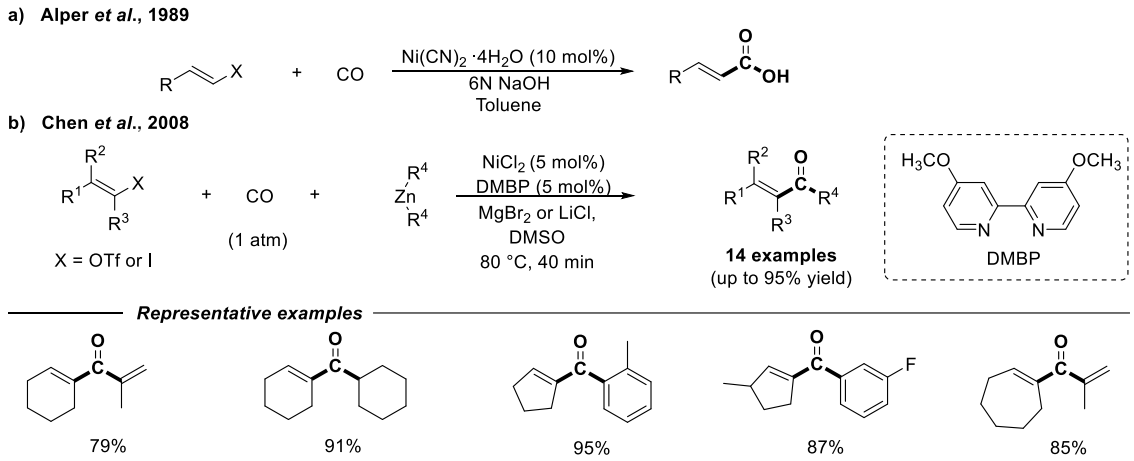


Scheme 20. Cobalt-catalyzed aminocarbonylation of alkyl tosylates.

[35] Sargent, B.; Alexanian, E. J. *Angew. Chem. Int. Ed*. **2019**, *28*, 9533–9536.

A last non-noble metal used to carry out carbonylation reactions is nickel but there are only limited examples of carbonylative cross-coupling reactions catalyzed by nickel. One of the first example appeared in 1989 when the Alper group described the first nickel-catalysed carbonylative transformation of vinyl halides to the corresponding acrylic acids (Scheme 21a).[36]

Nickel cyanide was found to be the best catalyst to promote the carbonylation of vinyl halides under phase transfer conditions. This protocol resulted to be simple both in execution and work-up exhibiting excellent stereochemical control of the configuration of the double bond. However, the main disadvantage of this transformation is the use of a highly concentrated sodium hydroxide. Another representative example of the use of nickel catalysis for carbonylative cross-coupling reaction was reported in 2008 by the Chen group who developed the first nickel-catalyzed carbonylative Negishi cross-coupling from enol triflates and diorganozinc reagents (Scheme 21b).[37] Using catalytic amounts of 4,4'-dimethoxy-2,2'-bipyridine (DMBP, 5 mol%) and nickel (II) chloride (5 mol%), this reaction allows the preparation of enones in good yields under mild reaction conditions and low carbon monoxide pressure.



Scheme 21. Nickel-catalyzed carbonylative cross-coupling reactions.

In summary, the major developments in non-noble metal catalyzed carbonylative transformations have been outlined and discussed in this section. Cheap metals including manganese, iron, cobalt and nickel have been described in order to furnish a general overview of the state of the art. Unfortunately, compared with noble metal catalysts such as Pd, Rh and Ir, non-noble catalysts have been much less studied and the number of reactions are still limited. Furthermore, the catalyst loadings are still relatively high. In the future, more systematic studies should be performed to understand the underlying chemistry. Based on the understanding of reaction mechanisms, the catalyst efficiency can be enhanced and new reactivity can be further discovered.

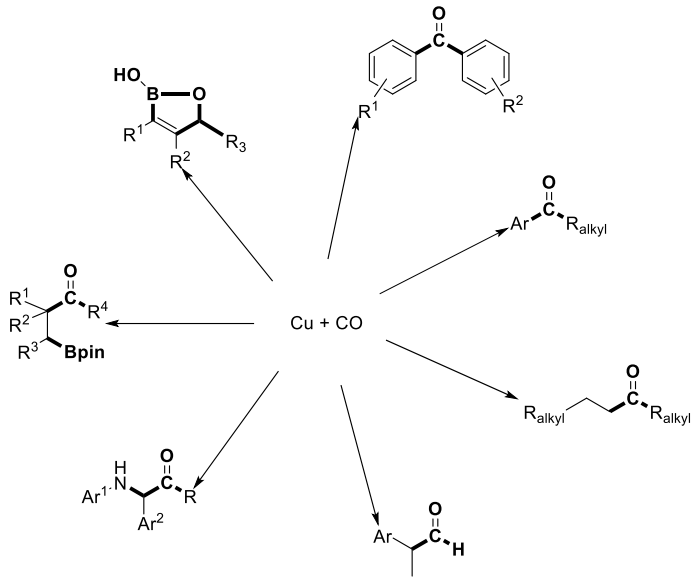
[36] Alper, H.; Amer, I.; Vasapollo, G. *Tetrahedron Lett*. **1989**, *30*, 2615–2616.
[37] Wang, Q.; Chen, C. *Tetrahedron Lett*. **2008**, *49*, 2916–2921.

1.5. Copper-catalyzed carbonylative cross-coupling reactions

In this section, we will overview and discuss the state-of-the-art in copper-catalyzed carbonylative cross-coupling reactions. These reactions will be discussed considering the structure of the products. Each section will be discussed by presenting the catalytic system utilized, the standard reaction conditions, some representative examples of the scope and, of course, the catalytic cycle involved. The discussion will start with an overview of copper-catalyzed carbonylative cross-coupling reactions yielding to ketones and aldehydes.

1.5.1 Copper-catalyzed carbonylative cross-coupling reactions for the synthesis of ketones and aldehydes

Ketones and aldehydes represent a vast family of compounds that are widely employed in pharmaceutical industry, agrochemistry and material industries.[38] Ketones and aldehydes are also common functional groups utilized in numerous transformations as result various procedures have been established over the years for their synthesis. In addition to the classical synthetic routes to ketones, carbonylative cross-coupling reactions have emerged as an attractive alternative and great progress has been made in the last 20 years, notably based on copper catalysis (Scheme 22).

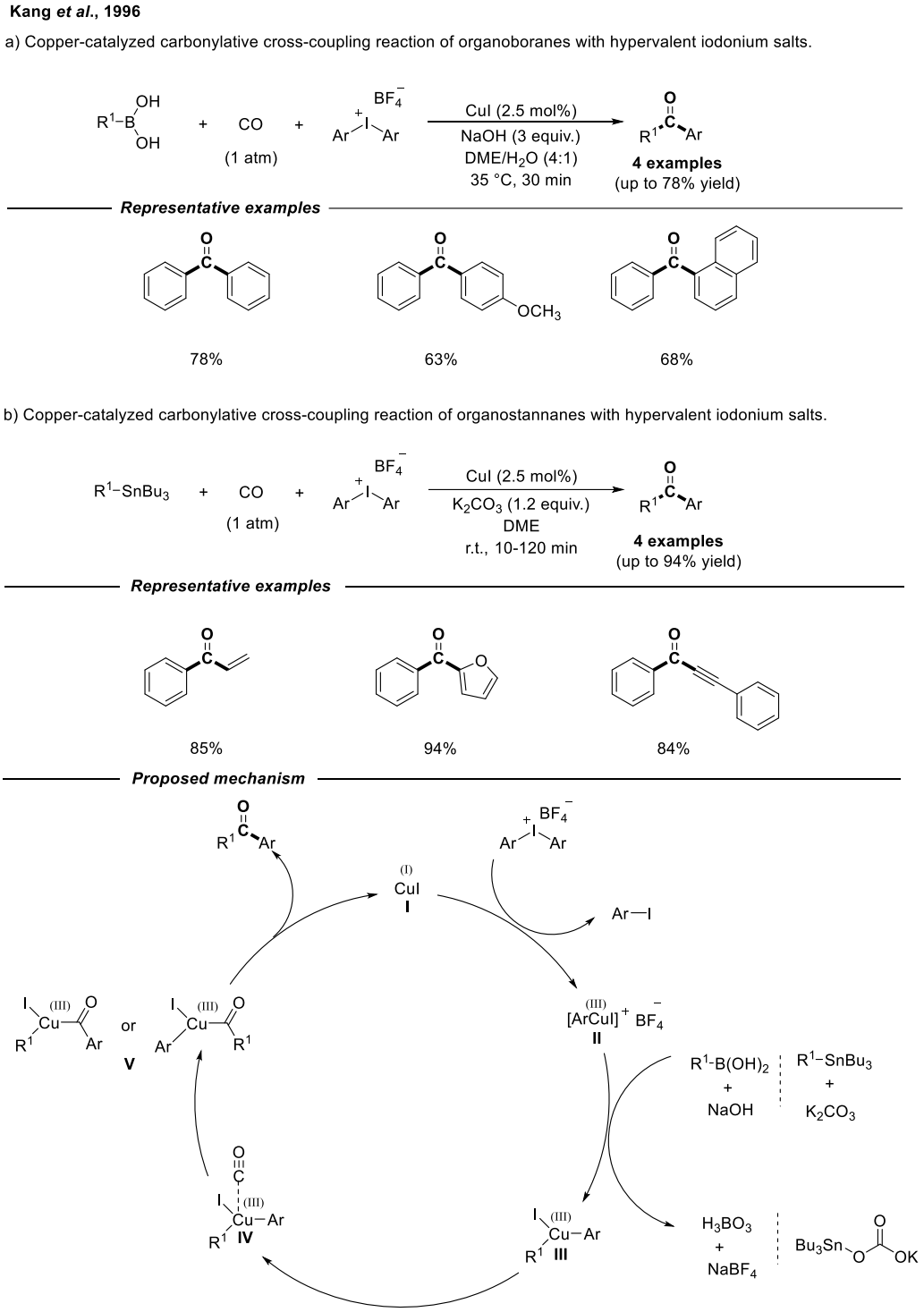


Scheme 22. Examples of ketones obtained by copper-catalyzed carbonylative cross-coupling.

The first report on a copper catalyzed carbonylative cross-coupling reaction was described by the Kang group in 1996 using aryl boronic acids (Scheme 23a) or aryl stannanes (Scheme 23b) with diaryliodonium salts.[39] These reactions can be carried out under very mild reaction conditions (at room temperature for 10-120 min with only 2.0 mol% of CuI) under 1 atm of carbon monoxide. These reactions represent valuable alternatives for the preparation of aromatic ketones to carbonylative Stille and Suzuki cross-coupling using an inexpensive copper catalyst. With respect to the reaction mechanism, it is presumed that the oxidative addition of Cu(I) salt **I** to the starting iodonium salt results in the formation of a transient Cu(III)Ar species **II**, thereafter follow the transmetallation with organostannanes or organoboranes to furnish

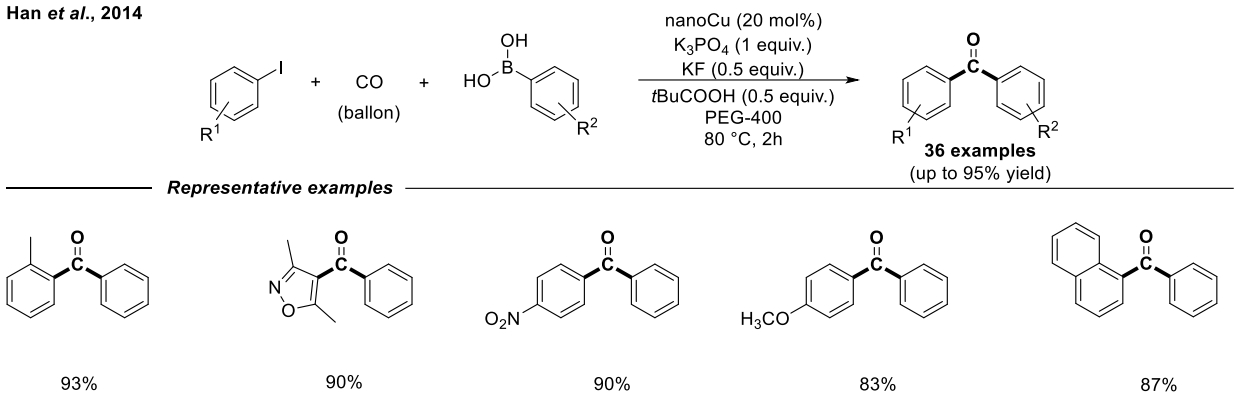
[38] a) Franck, G. H.; Stadelhofer, J. W.; *Industrial Aromatic Chemistry*; 1st ed.; Vol. 1; Springer-Verlag: Berlin, **1988**. b) Surburg, H.; Panten, J. *Common Fragrance and Flavor Materials*, 5th ed.; Vol. 1; Wiley-VCH: Weinheim, **2006**.
[39] Kang, S.; Yamaguchi, T.; Kim, T. *J. Org. Chem*. **1996**, *61*, 9082–9083.

a Cu(III) R^1Ar **III**. Then, the Cu(III)-complex after coordination **IV** and CO-insertion yields a transient acylcopper(III) intermediate **V** that evolve to the target product after reductive elimination. The desired aromatic ketones are formed with good to excellent yields although only limited examples were described and both the reaction partners did not contain electron-withdrawing substituents.



Scheme 23. Copper-catalyzed carbonylative cross-coupling reaction of organostannanes and organoboranes with hypervalent iodonium salts.

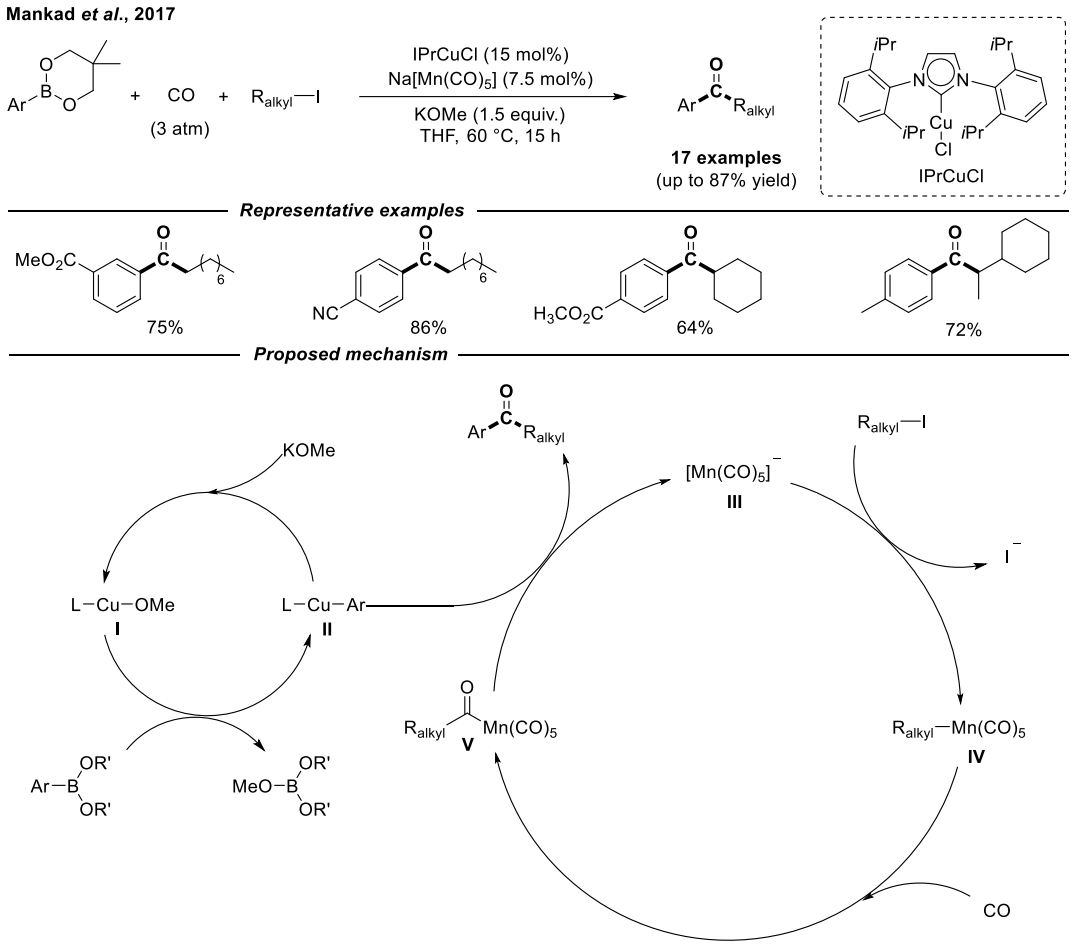
Few years later, the Han group reported an effective nanocopper-catalyzed carbonylative cross-coupling of aryl iodides with arylboronic acids at atmospheric pressure of carbon monoxide (Scheme 24). They managed to perform the first copper-catalyzed carbonylative Suzuki reactions using only 20 mol% of nanocopper in the absence of ligands.[40] This practical protocol affords good to excellent yields of the desired ketones in poly(ethyleneglycol) at 80 °C. The use of commercially available aryl iodides, rather than more reactive electrophiles like aryl iodonium salts, is the main benefit of this protocol.



Scheme 24. Nanocopper-catalyzed carbonylative cross-coupling of aryl iodides with arylboronic acids.

Following these studies, the Mankad group reported in 2017 a Cu/Mn bimetallic system for the carbonylative cross-coupling of arylboronic esters with commercially available alkyl iodides allowing for the synthesis of aryl-alkyl ketones (Scheme 25).[41] The main advantage of this protocol is the use of C(sp^3)-hybridized electrophiles, since most of the protocols reported previously were limited to substrates lacking β-hydrogens for which β-hydride elimination cannot take place. The reaction is carried out with 15 mol% of IPrCuCl and 7.5 mol% of Na[$Mn(CO)_5$] under a low pressure of carbon monoxide (3 atm) with mild reactions conditions (60°C in THF) for 15h. This procedure is compatible with a wide range of aryl boronic esters and proceeds smoothly for both primary and secondary alkyl iodides, resulting in an effective alternative to the Pd-catalyzed carbonylative Suzuki-Miyaura reaction. A preliminary mechanism has been proposed by the authors consisting of two dependent catalytic cycles. Firstly, the Cu-carbene **I** engages in transmetallation with arylboronic acid to generate an arylcopper nucleophile **II**. In the meantime, the Mn-carbonyl co-catalyst **III** activates the alkyl iodide by a single-electron transfer mechanism to form an alkyl-$Mn(CO)_5$ species **IV**. At this point, under carbon monoxide atmosphere a molecule of CO inserts into the Mn-alkyl bond via migratory insertion to afford the acylmanganese intermediate **V**. Thereafter, the two catalytic cycles intersect each other and, through transmetallation of the nucleophilic arylcopper(I) **II** onto the electrophilic acylmanganese intermediate **V**, form the desired carbonylated coupling product.

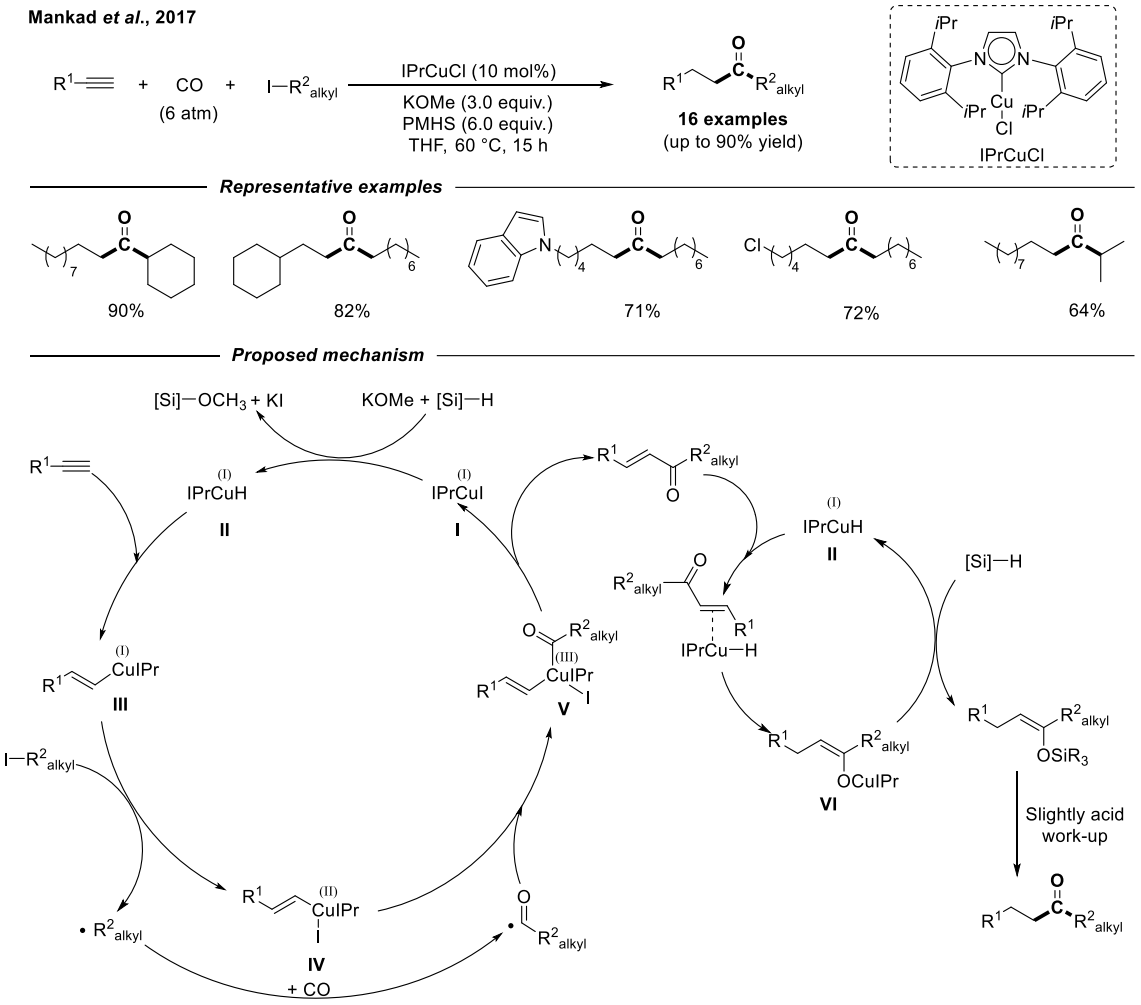
[40] Cheng, L.; Zhong, Y.; Ni, Z.; Du, H.; Jin, F.; Rong, Q.; Han, W. *RSC Adv.* **2014**, *4*, 44312–44316.
[41] Pye, D. R.; Cheng, L. J.; Mankad, N. P. *Chem. Sci.* **2017**, *8*, 4750–4755.



Scheme 25. Cu/Mn bimetallic catalysis enables carbonylative Suzuki–Miyaura coupling.

In the same year, the Mankad group pushed the process a step further by developing a novel protocol using alkynes as starting material which are appealing coupling partner in cross-coupling reactions. The utility of this method was demonstrated by the preparation of a library of unsymmetrical dialkyl ketones using alkynes, alkyl iodides and CO (6 atm) via copper-catalyzed hydrocarbonylative coupling and reduction tandem sequence with high chemo- and regioselectivity (Scheme 26).[42] Using IPrCuCl (10 mol%) as the catalyst, various alkyl-substituted terminal alkynes could be coupled with alkyl iodides under a low pressure of carbon monoxide (6 atm) with polymethylhydrosiloxane (PHMS) as the reducing reagent. This reaction tolerates a variety of functional groups, affording corresponding unsymmetrical dialkyl ketones in good yield. The authors proposed a catalytic cycle in which the IPrCuCl is converted *in-situ* with PMHS to form the active IPrCuH catalyst. Then, a copper-catalyzed *anti*-Markovnikov hydrocupration of the alkyne takes place, affording an *E*-alkenylcopper(I) intermediate **III** through a *syn*-addition on the triple bond.[43] Subsequently, the alkenylcopper(I) species **III** undergoes a single electron transfer with the alkyl iodide to generate an alkyl radical and an alkenylcopper (II) species **IV**. Thereafter, the radical R· undergoes carbonylation to generate an acyl radical species that combines with the alkenylcopper (II) species to yield an acyl alkenyl copper(III) intermediate **V**. A reductive elimination finally takes place to afford the α,β-unsaturated ketone. In the second part of the tandem sequence, the newly formed enone undergoes to a 1,4-reduction by IPrCuH to afford the saturated ketone. Here, the regioselectivity of the reduction is due to the carbophilic nature of the copper hydride complex (NHC-CuH) which furnish the 1,4-addition product exclusively.

[42] Cheng, L. J.; Mankad, N. P. *J. Am. Chem. Soc.* **2017**, *30*, 10200–10203.
[43] Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916–2927.



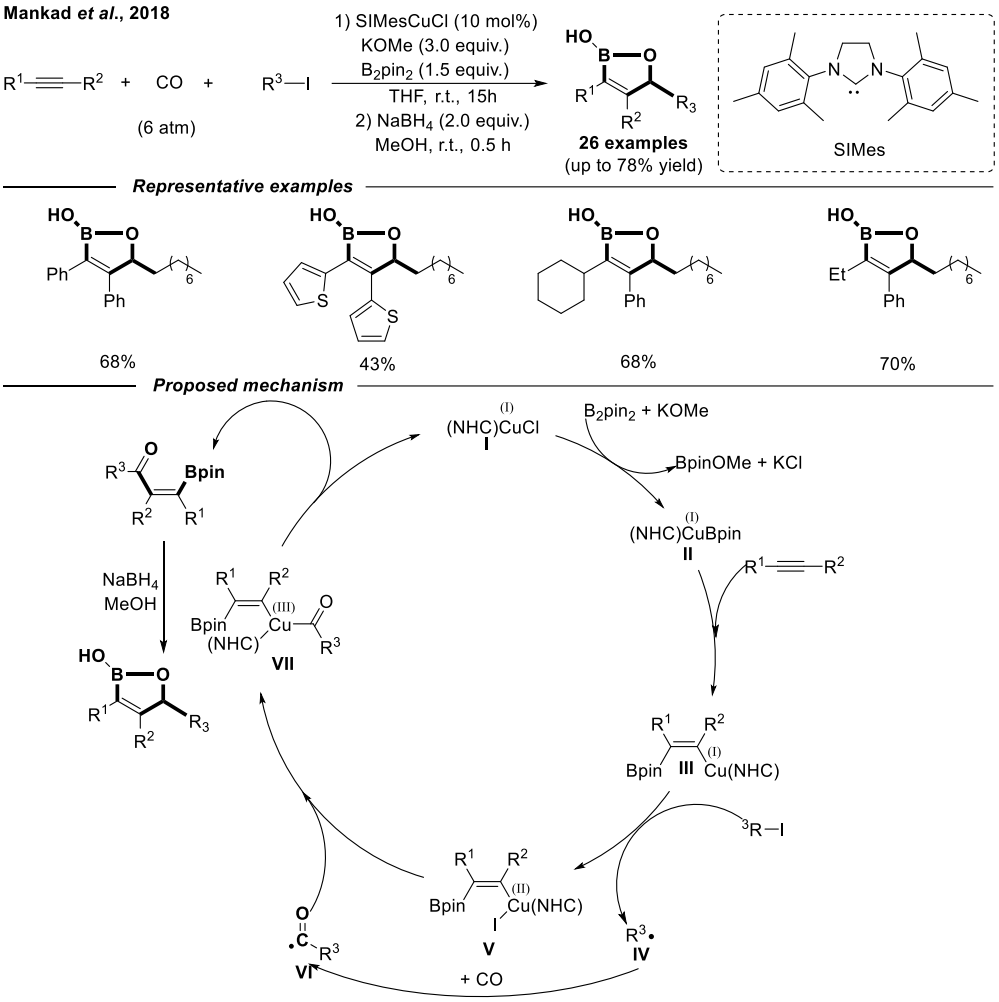
Scheme 26. Cu-catalyzed hydrocarbonylative coupling of terminal alkynes with alkyl iodides.

In continuation of their studies, the Mankad group reported in 2018 a novel copper-catalyzed carbonylative cross-coupling reactions yielding tetrasubstituted oxaboroles from internal alkynes, alkyl halides, bis(pinacolato)diboron (B_2Pin_2) and CO (Scheme 27).[44] The catalytic system consists of 10 mol% of SIMesCuCl, which is sufficient to catalyze the reaction in good yields under a low pressure of carbon monoxide. The utility of this method was demonstrated by the various transformations of the corresponding reduced oxaborole, including halogenation, oxidation, and protodeboration to provide densely substituted allylic alcohol and ketone derivatives. Moreover, the Suzuki-Miyaura coupling of β-boryl-tetrasubstituted enones with an aryl halide enabled the synthesis of an all carbon tetrasubstituted enone, compounds that are difficult to synthetize using current techniques. As for the mechanism, in the presence of KOMe and B_2pin_2, the active copper complexes LCu-Bpin **I** reacts with the internal alkyne to afford the β-boroalkenylcopper(I) complex **II**. The *syn*-addition of the pinacolborylcopper species LCu-Bpin **I** tend to occur with terminal selectivity (*anti*-Markovnikov), where the Lewis acidic boron center is attached to the less substituted carbon via preferential formation of a more stable alkenyl cationic transition state.[45]

[44] Cheng, L. J.; Mankad, N. P. *Angew. Chem. Int. Ed.* **2018**, *57*, 10328–10332.

[45] (a) Tsushima, T.; Tanaka, H.; Nakanishi, K.; Nakamoto, M.; Yoshida, H. *ACS Catal.* **2021**, *11*, 14381–14387. (b) Moon, J.; Jung, H.; Lee, Y.; Lee, S.; Yun, J.; Lee, J. *Organometallics* **2015**, *11*, 2151–2159.

At this point, an alkyl radical **III** is generated from the reaction of the copper(I) complex and the alkyl halide to provide a copper(II) complex **IV** with a single electron transfer process. Then, the radical species undergoes carbonylation to give the acyl radical species **V**, which reacts with the copper(II) complex to form the copper (III) intermediate **VI**. As last step of the mechanism, a reductive elimination takes place to afford the desired β-borylated tetrasubstituted enone.

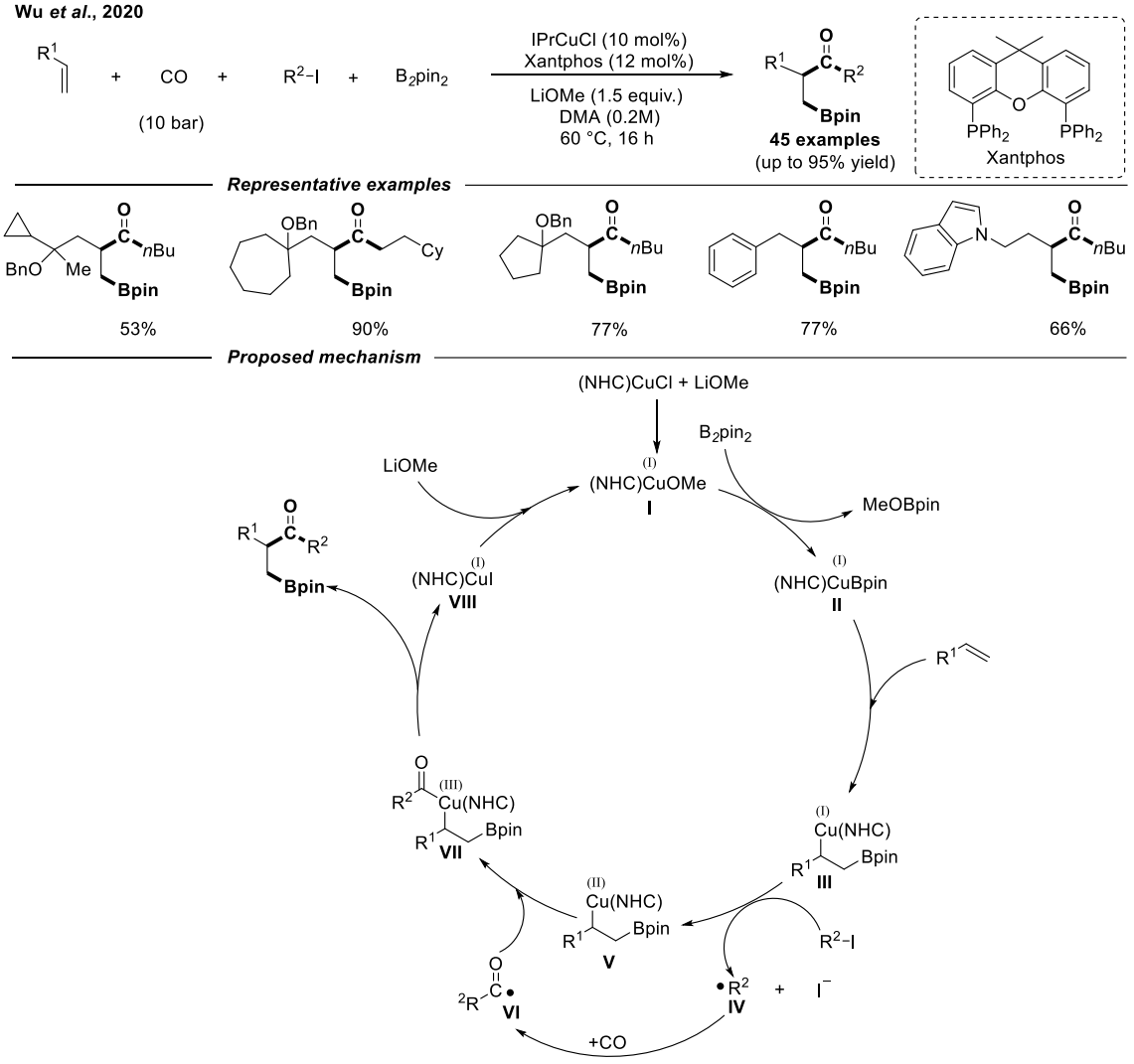


Scheme 27. Copper-catalyzed borocarbonylative coupling of internal alkynes with unactivated alkyl halides.

In a related approach, the Wu group in 2020 reported a Cu-catalyzed borocarbonylative four component cross-coupling of alkenes with alkyl halides for the synthesis of β-boryl ketones (Scheme 28).[46] The reaction is performed with a catalytic system based on 10 mol% of IPrCuCl and 12 mol% of Xantphos under 10 atm of carbon monoxide and using an excess of B_2pin_2 (2.0 equiv.). With the optimized reaction conditions, the authors obtained a broad range of β-boryl ketones in moderate to excellent yields with excellent functional group tolerance and complete regioselectivity. A plausible catalytic cycle has been proposed in which (NHC)CuOMe reacts with B_2pin_2 to afford a borylcopper species (NHC)CuBpin **II**. Thus, the (NHC)CuBpin species **II** is involved in a borylcupration of the olefin to obtain a boryl cuprated intermediate **III**. The reaction of borylcupration occurs with *syn*-addition of the pinacolborylcopper species (NHC)CuBpin onto the alkene with terminal selectivity (*anti*-Markovnikov), where the Lewis acidic boron center is attached to the less substituted carbon. At this point, an alkyl radical **IV** is generated from the reaction of the copper(I) complex **III** and the alkyl iodide to provide a copper(II) complex **V** with a single electron transfer process.

[46] Wu, F. P.; Yuan, Y.; Schünemann, C.; Kamer, P. C. J.; Wu, X.F. *Angew. Chem. Int. Ed.* **2020**, *59*, 10451–10455.

Then, the radical species **IV** undergoes carbonylation to furnish the acyl radical species **VI**, which reacts with the copper(II) complex **V** to form the copper (III) intermediate **VII**. Finally, this species highly reactive **VIII** regenerates the Cu(I) catalyst through a reductive elimination which furnish the desired β-boryl ketone.

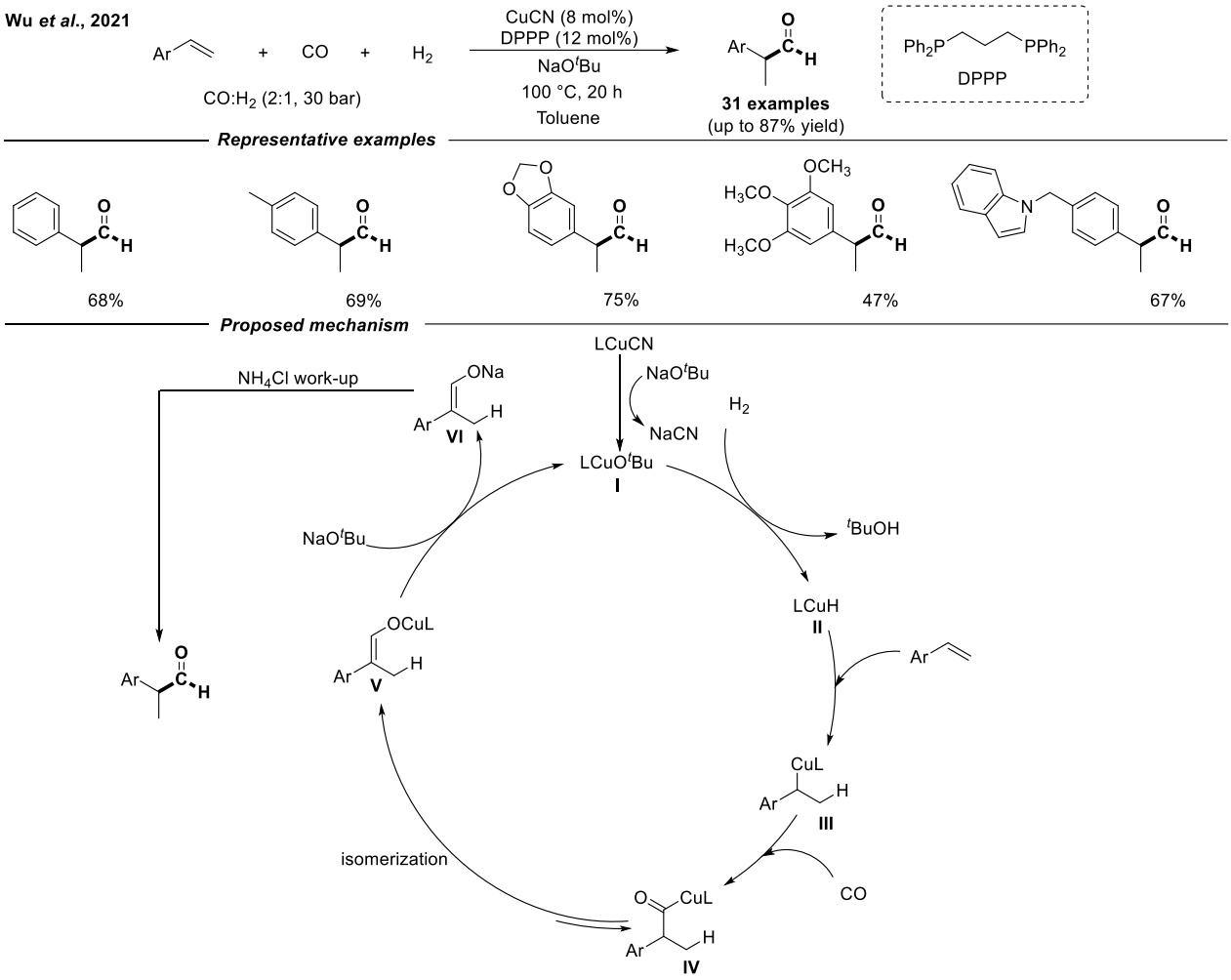


Scheme 28. Copper-catalyzed borocarbonylative cross-coupling of olefins with alkyl halides for the synthesis of β-boryl ketones.

In addition to the functionalization of alkenes and alkynes to prepare ketones or enones, copper-catalyzed carbonylative cross-coupling reactions have also been employed to synthesize aldehydes through hydroformylation, a reaction which is one of the most significant homogeneously catalyzed reactions in industrial organic chemistry. Considering the importance of this transformation, the Wu group reported in 2021 the first copper-catalyzed hydroformylation of alkenes to generate branched aldehydes (Scheme 29).[47] The catalytic system consists of a combination of CuCN and DPPP in the presence of NaO^{t}Bu as the base and under a mixture of CO and H_2 (2:1, 30 bar). With this protocol, various olefins were tested, affording the desired branched aldehydes in good yields. Based on some mechanistic studies, the authors proposed that the reaction pathways start with the generation of a LCuO^{t}Bu complex **I**, which will afford the corresponding copper hydride LCuH **II** after reaction with H_2. Afterwards, a hydrocupration takes place onto the double bond of the alkene to give an alkylcopper intermediate **III** which will react with carbon monoxide to produce an

[47] Geng, H. Q.; Meyer, T.; Frankec, R.; Wu, X. F. *Chem. Sci*. **2021**, *12*, 14937–14943.

acylcopper complex **IV**. At this point, the acyl-copper **IV** tautomerizes to the vinyl alkoxide copper species **V**. Concomitantly, in the presence of NaO^{t}Bu, a cation exchange takes place to form a sodium vinyl alkoxide species, which will give the key intermediate **VI**. Finally, the sodium vinyl alkoxide species will evolve to the desired products in function of the reaction conditions leading to the formation of the corresponding branched aldehydes.

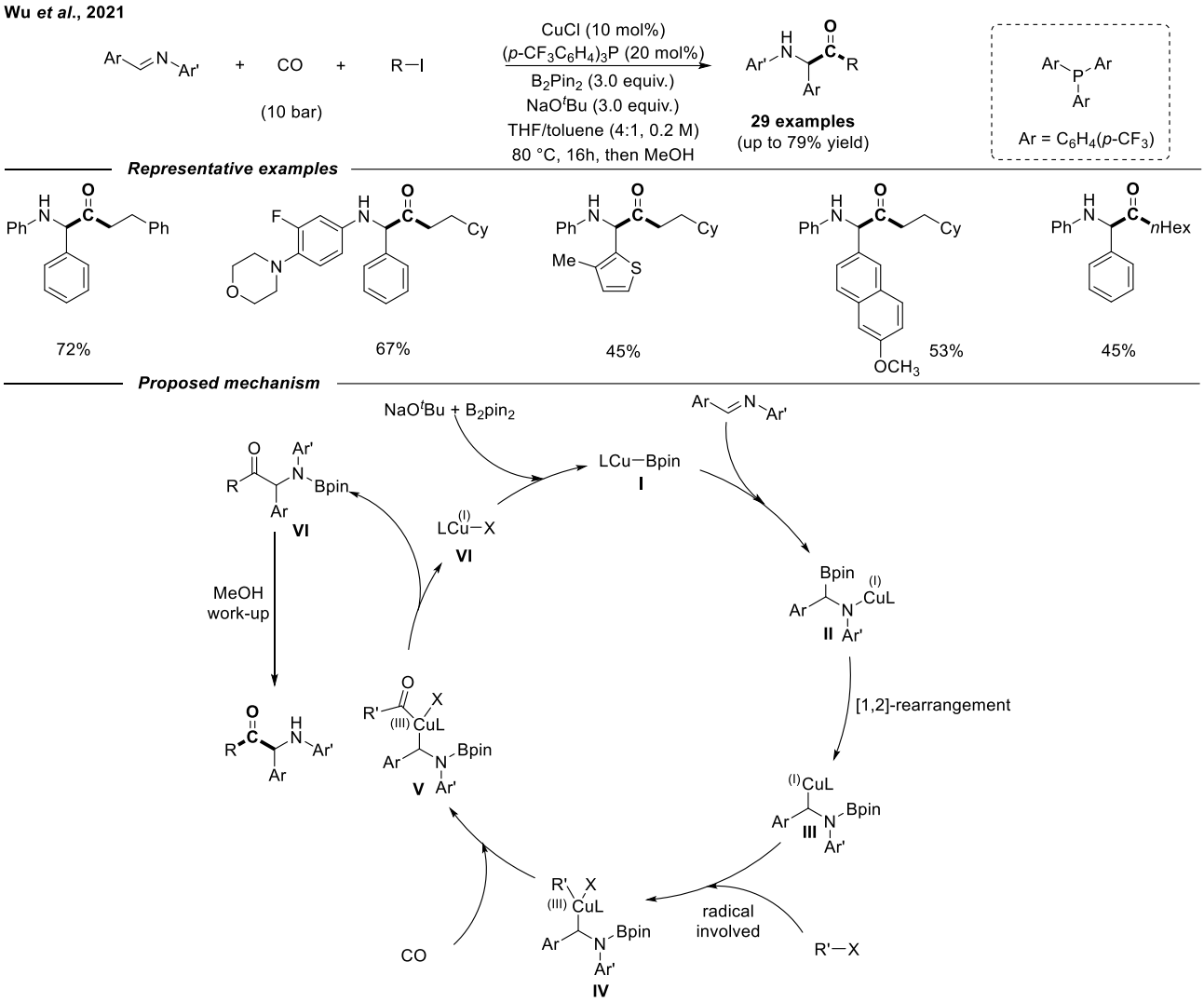


Scheme 29. Copper-catalyzed hydroformylation of styrenes.

One year later, the Wu group has exploited the knowledge they gained for the preparation of ketones via copper-catalyzed carbonylative cross-coupling to prepare α-amino ketones.[48] The α-amino ketones have been prepared in good yields through a copper-catalyzed borocarbonylation from imines and alkyl iodides under a low pressure of carbon monoxide (10 bar). The catalytic system consists of 10 mol% of CuCl and 20 mol% of (*p*-$CF_3C_6H_4$)$_3$P as the ligand in the presence of B_2pin_2 (3.0 equiv.) and NaO^{t}Bu (3.0 equiv.) (Scheme 30). The possible reaction pathway proposed by the authors starts with the generation of a LCu-Bpin complex **I** generated from CuCl, B_2pin_2 and NaO^{t}Bu which inserts into the C=N bond of imine to furnish an α-boryl amido-copper complex **II**. At this point, the N–Cu bond is weaker and the copper intermediate undergoes to an intramolecular 1,2-rearrangement to afford an α-amino alkyl copper complex **III**. This alkylcopper species reacts with the starting alkyl iodide to generate a copper (III) complex **IV**. Afterwards, carbon monoxide coordinates onto the copper metal center to afford an alkyl acyl-copper(III) intermediate **V** after a step of

[48] Wu, F. P.; Wu, X. F. *Angew. Chem. Int. Ed.* **2021**, *60*, 695–700.

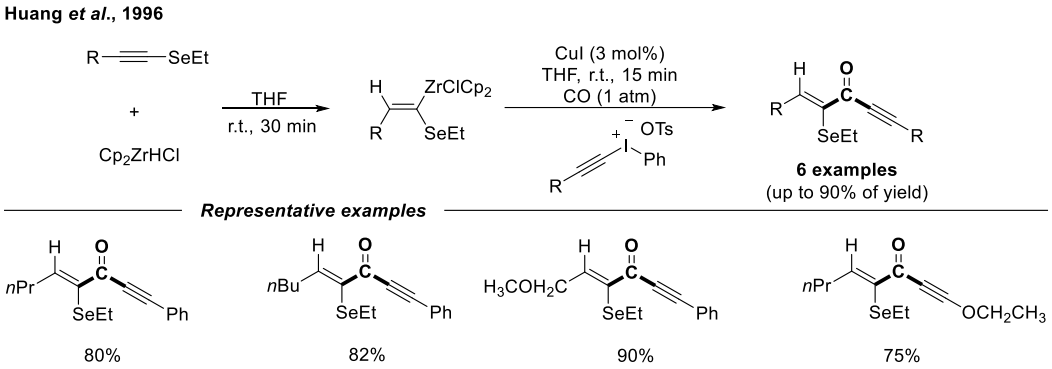
CO-insertion of a molecule of carbon monoxide. The final step is a reductive elimination followed with a work-up with methanol, which release the final product.



Scheme 30. Copper-catalyzed carbonylative synthesis of α-amino ketones from imines and alkyl iodides.

Copper-catalyzed carbonylative cross-coupling reactions can be also be used for the preparation of ynones, a versatile class of carbonyl derivatives. In order to install the carbonyl group and synthetize ynones, more and more frequently the attention is turned to copper-catalyzed carbonylation reactions. In 1996, the Huang group indeed described a novel copper-catalyzed carbonylative cross-coupling of (*E*)-α-selanylvinylzircononiums with alkynyliodonium tosylates under extremely mild conditions (Scheme 31).[49] This protocol starts with the hydrozirconation of alkynyl selenides followed with the insertion of carbon monoxide to generate a (*E*)-α-selanylenoylzirconium complex which reacts with alkynyliodonium salts in the presence of 3 mol% of CuI. With this method was possible to prepare a small library of six unsymmetrical vinyl alkynyl ketones in good yields.

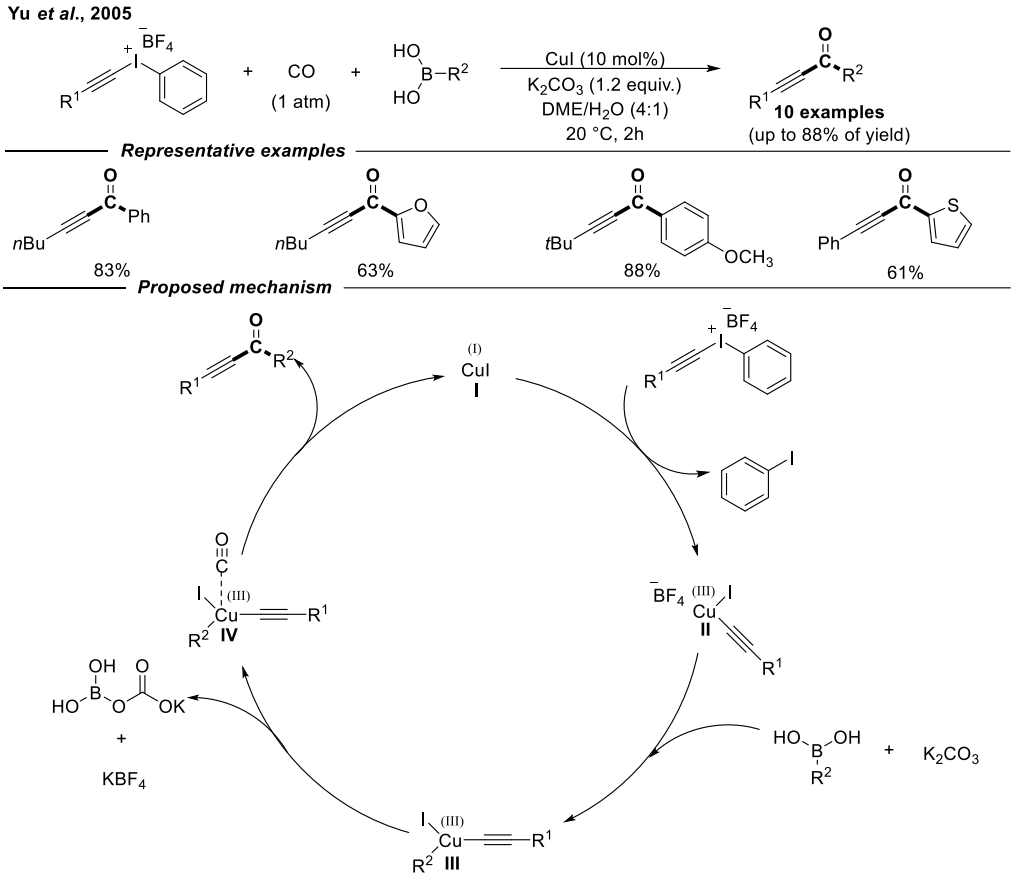
[49] Sun, A. M.; Huang, X. *Tetrahedron,* **1999**, *55*, 13201–13204.



Scheme 31. Copper-catalyzed carbonylative cross-coupling of (*E*)-α-selanylvinylzirconiums with alkynyliodonium tosylates.

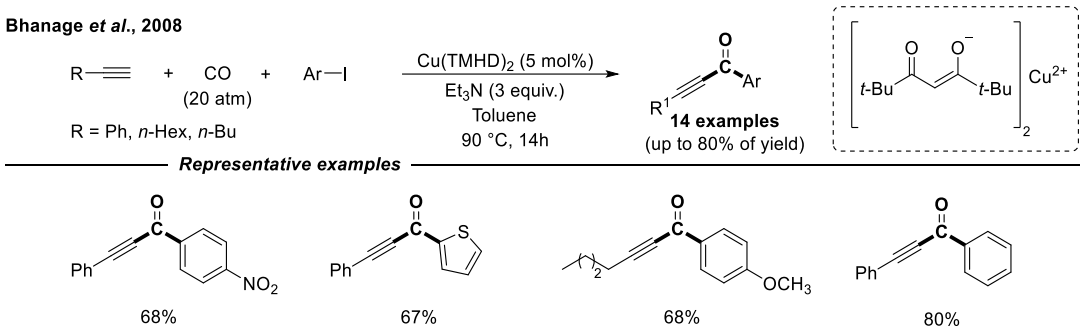
Subsequently, the Yu group then expanded the use of alkynyliodonium salts for the synthesis of ynones using boronic acids, which have the advantage of being commercially and readily available starting material.[50] With this copper-catalyzed carbonylative cross-coupling, a variety of alkynyliodonium salts are coupled with aryl boronic acids, as well as organostannanes, under mild reaction conditions (Scheme 32). Under optimal conditions, the reaction was performed by the addition of the alkynyl iodonium salt to a solution of phenylboronic acid with 10 mol% of CuI and K_2CO_3 in DME-H_2O (4:1) at 20 °C for two hours. The carbonylative cross-coupling reaction was achieved under a low pressure of carbon monoxide atmosphere. Although the exact mechanistic aspects of this transformation have not been elucidated, the authors proposed that the alkynyl iodonium salt reacts with CuI **I** via an oxidative addition to form a transient alkynyl copper (III) intermediate **II** which will react first with the boronic acid via a transmetallation step to furnish the R^2-alkynyl-Cu(III) intermediate **III**. Under carbon monoxide atmosphere, carbon monoxide will be coordinated onto the copper metal center of the intermediate **IV** and will follow a migratory CO insertion in the Cu–R bond before the reductive elimination will take place to form the α,β-ynone. Alkynyl iodonium salts must however be prepared before use, typically using oxidizing agents like 3-chloroperoxybenzoic acid (mCPBA), which is clearly the biggest drawback of this procedure.

[50] Yu, C.; Kweon, J.; Ho, P. *Synlett*. **2005**, *37*, 2631–2634.



Scheme 32. Copper-catalyzed carbonylative coupling reaction of alkynyliodonium salts with organoboronic acids.

In 2008, an interestingly alternative that uses more attractive alkynes as starting materials has been proposed by the Bhanage group with a copper *bis*(2,2,6,6-tetramethyl-3,5-heptanedionate)-catalyzed carbonylative Sonogashira coupling reactions of aliphatic and aromatic alkynes with aryl iodides (Scheme 33).[51] Using $Cu(TMHD)_2$ as the optimal catalyst, toluene as the solvent, and triethylamine as the base, the carbonylative Sonogashira coupling of alkynes with various aryl iodides was possible. This method is extremely effective for the ynones synthesis as it works under mild reaction conditions with a cheap copper catalyst and commercially available starting material. No significant variations due to electronic and steric effect was observed, the carbonylative Sonogashira coupling works well with a wide variety of aryl iodides containing electron withdrawing and electron donating groups.



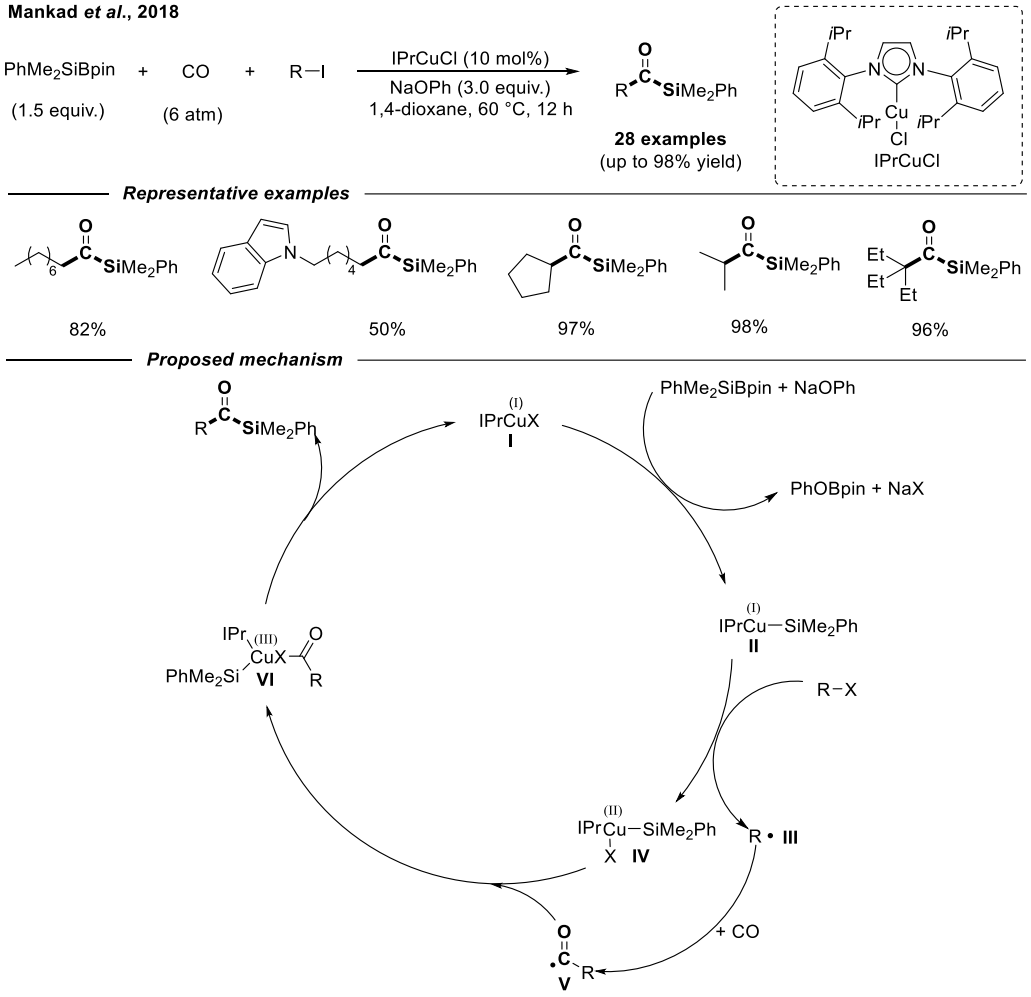
Scheme 33. Copper-catalyzed carbonylative Sonogashira coupling reaction of alkynes with aryl iodides.

[51] Tambade, P.J.; Patil, Y.P.; Nandurkar, N.S.; Bhanage, B. M. *Synlett*. **2008**, *6*, 886–888.

After discussing the most advanced techniques for producing aldehydes and ketones via copper-catalyzed carbonylative cross-couplings, the next section will focus on cutting-edge synthetic procedures for the preparation of boron- and silicon-containing compounds. These compounds are highly important and widely used in organic synthesis and materials science. In particular, acylsilanes and acylboranes, are versatile synthetic building blocks that have been used in various intriguing transformations with increasing frequency.

1.5.2 Copper-catalyzed carbonylative cross-coupling reactions for the synthesis of boron- and silicon-containing compounds

A further step forward in the preparation of carbonyl compounds using new copper-catalyzed carbonylative cross-coupling has been achieved with the work of the Mankad group which reported in 2020 a copper(I)-catalyzed carbonylative silylation of unactivated alkyl halides enabling an efficient synthesis of alkyl-substituted acylsilanes in good yields (Scheme 34).[52] Given the utility of acylsilanes in organic chemistry, the development of an efficient access to acylsilanes using carbon monoxide as cheap C1 source is important. The catalytic system developed by Mankad is based on a combination of 10 mol% of IPrCuCl with 1.5 equiv. of $PhMe_2SiBpin$ under a low pressure of carbon monoxide (6 atm) at 60 °C.



Scheme 34. Copper-catalyzed carbonylative silylation of alkyl halides.

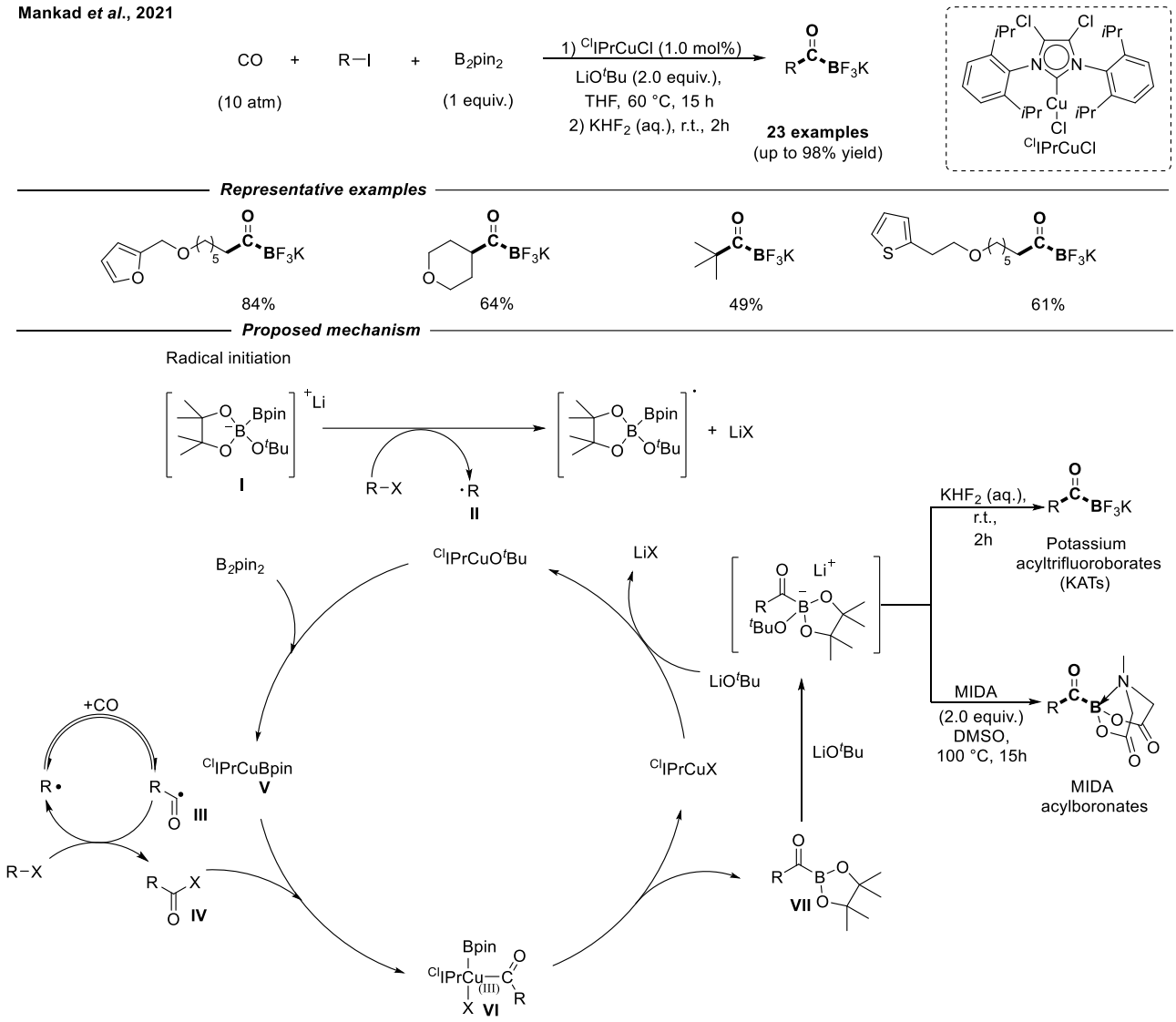
[52] Cheng, L. J.; Mankad, N. P. *J. Am. Chem. Soc*. **2020**, *142*, 80–84.

Due to the mild reaction conditions, a variety of functional groups are tolerated, and primary, secondary and tertiary alkyl halides are all applicable. Based on several mechanistic experiments, the authors proposed a mechanism where, firstly, a silylcopper(I) complex **II** is generated by the reaction of $PhMe_2Si$-Bpin with IPrCuOPh, which is formed from IPrCuCl **I** and NaOPh. Then, the IPrCu(I)$SiMe_2Ph$ **II** reacts with a single electron transfer (SET) with the alkyl halide to generate an alkyl radical R· **III** and a silylcopper(II) complex **IV**. The radical species R· **III**, then undergoes carbonylation to give an acyl radical species **V**, which is more reactive than the alkyl radical species and thus collapses with copper (II) complex **IV** to form *in-situ* a highly reactive copper(III) intermediate **VI**. Finally, reductive elimination affords the acylsilane as desired product and regenerates the copper(I) catalyst **I**. In 2021, as continuation of their research on the development of new reactions of carbonylation, the Mankad group developed a new protocol for the copper-catalyzed carbonylative borylation of unactivated alkyl halides in order to synthetize acylboron derivatives from a commercially available diboron reagent (B_2pin_2) (Scheme 35). Acylborons compounds are described as unstable intermediates because boron has an electron-deficient nature that induces interaction of nucleophiles with the boron atom through its empty p-orbital, leading to the instability of acylboranes by making them inclined to oxidation or 1,2-Brook-type rearrangements.

To circumvent this problem, the Mankad group transformed the tricoordinate acylborons *in-situ* to the corresponding potassium acyltrifluoroborates with an aqueous work up with KHF_2.[53] The catalytic system developed consists of 1.0 mol% of ^{Cl}IPrCuCl, B_2pin_2 and LiO^tBu under a low pressure of carbon monoxide (10 atm), enabling the use of a variety of alkyl iodides with different functional groups. Under the same reaction conditions, the alkyl electrophile scope could be extended from primary alkyl iodides to secondary and tertiary alkyl iodides as well as acyclic and cyclic secondary alkyl iodides. The formation of tetracoordinated acylboron intermediates has also been exploited for the conversion of B(pin) into B(MIDA) by heating the crude reaction mixture with *N*-methyliminodiacetic acid (MIDA).

The reaction mechanism proposed by the authors starts with the reaction between LiO^tBu and B_2pin_2 to produce a tetra-alkoxy diboron compound **I**. This activated $B(sp^2)$–$B(sp^3)$ complex reduces the alkyl halide through a single-electron transfer (SET) process, affording an alkyl radical **II** intermediate which undergoes carbonylation under a pressure of carbon monoxide to give an acyl radical **III**, which reacts with the alkyl halide to afford an acyl halide **IV**. Thereafter, the active catalyst **V**, a boryl copper intermediate follows an oxidative addition step with the acyl halide **IV** to form an acyl boryl copper(III) complex **VI**. Finally, reductive elimination affords the tricoordinated acylboron **VII** and regenerate the copper(I) catalyst. Then, the acylboron reacts with LiO^tBu to form a more stable tetracoordinated boron complex which can be easily converted in the corresponding potassium acyltrifluoroborates and *N*-methyliminodiacetyl acylboronates.

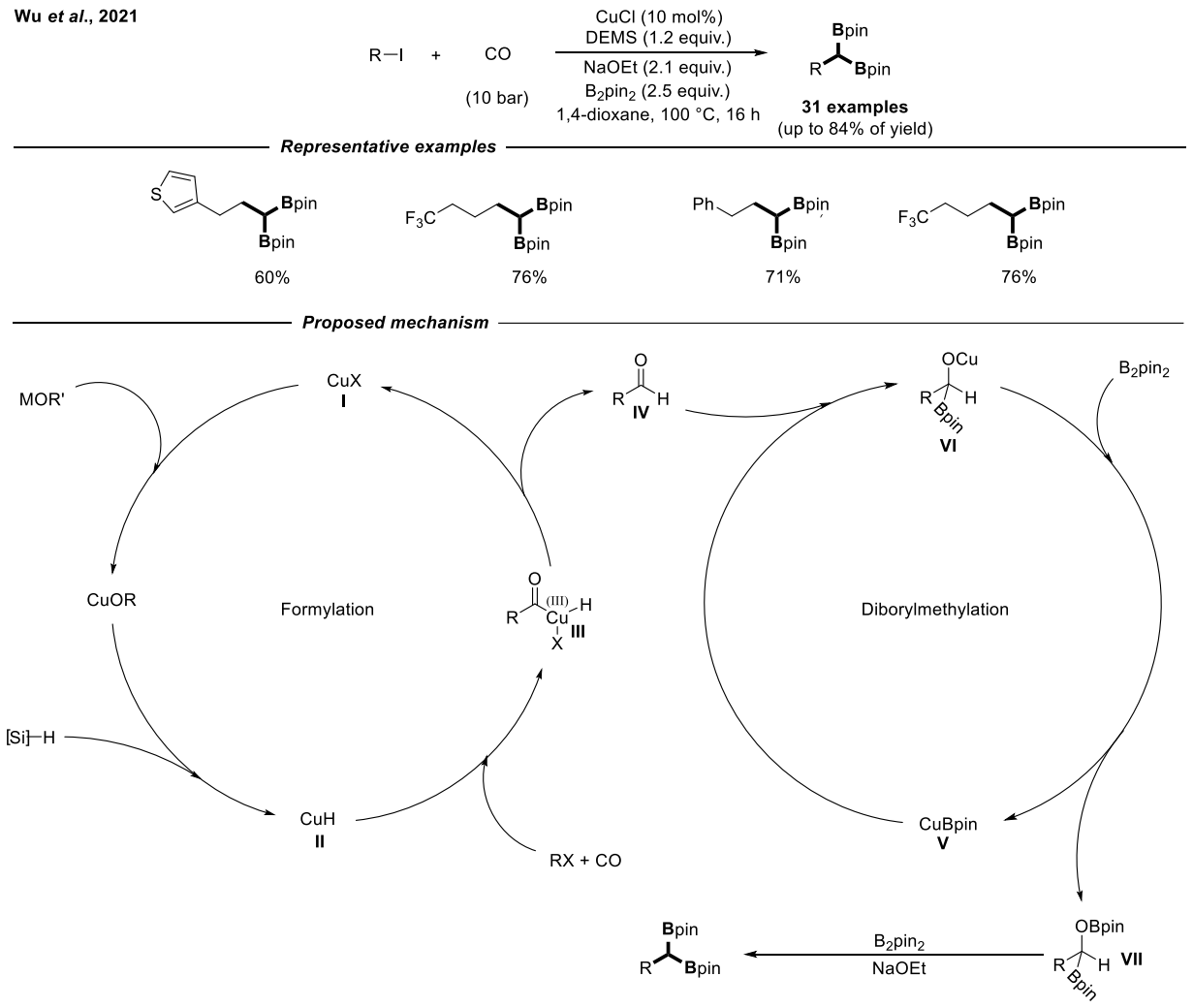
[53] Cheng, L. J.; Zhao, S.; Mankad, N. P. *Angew. Chem. Int. Ed*. **2021**, *60*, 2094–2098.



Scheme 35. Synthesis of acylboron compounds via Cu-catalyzed carbonylative borylation of alkyl halides.

In line with previous studies, the Wu group reported a novel copper-catalyzed diborylmethylation of alkyl iodides with carbon monoxide as C1 source (Scheme 36).[54] With this protocol, various alkyl iodides can be transformed into the desired diborane compounds in good yields since the catalytic system enables a borylative methylation by trapping the alkyl radical using both Cu-H and Cu-Bpin species under an atmosphere of carbon monoxide. The reagents for the borylative methylation consists of iodoalkane, bis(pinacolato)diboron (B_2pin_2) and methyldiethoxysilane (DEMS) under a low pressure of carbon monoxide with 10 mol% of CuCl. The catalytic cycle starts with the reaction between the copper catalyst **I**, the metal alkyl oxide MOR' and silane to generate the copper hydride complex **II**. Afterwards, the copper hydride **II** reacts with the alkyl iodide via a radical intermediate to produce an acyl-copper hydride complex **III**, after the coordination of carbon monoxide and an insertion step. Then, the aldehyde is formed with a reductive elimination step **IV**. Subsequently, a boryl-copper complex **V**, Cu–Bpin, is generated from the reaction between B_2pin_2 and CuOEt. Then, the Cu–Bpin **V** attacks the carbonyl of the aldehyde to furnish an α-boryl-oxido-copper complex **VI**. Subsequently, the α-boryl-oxido-copper complex **VI** reacts for two times in row with the B_2pin_2 and is transformed into the targeted diborylmethylated product under the assistance of NaOEt as base.

[54] Wu, F. P.; Wu, X. F. *Angew. Chem. Int. Ed*. **2021**, *60*, 11730–11734.

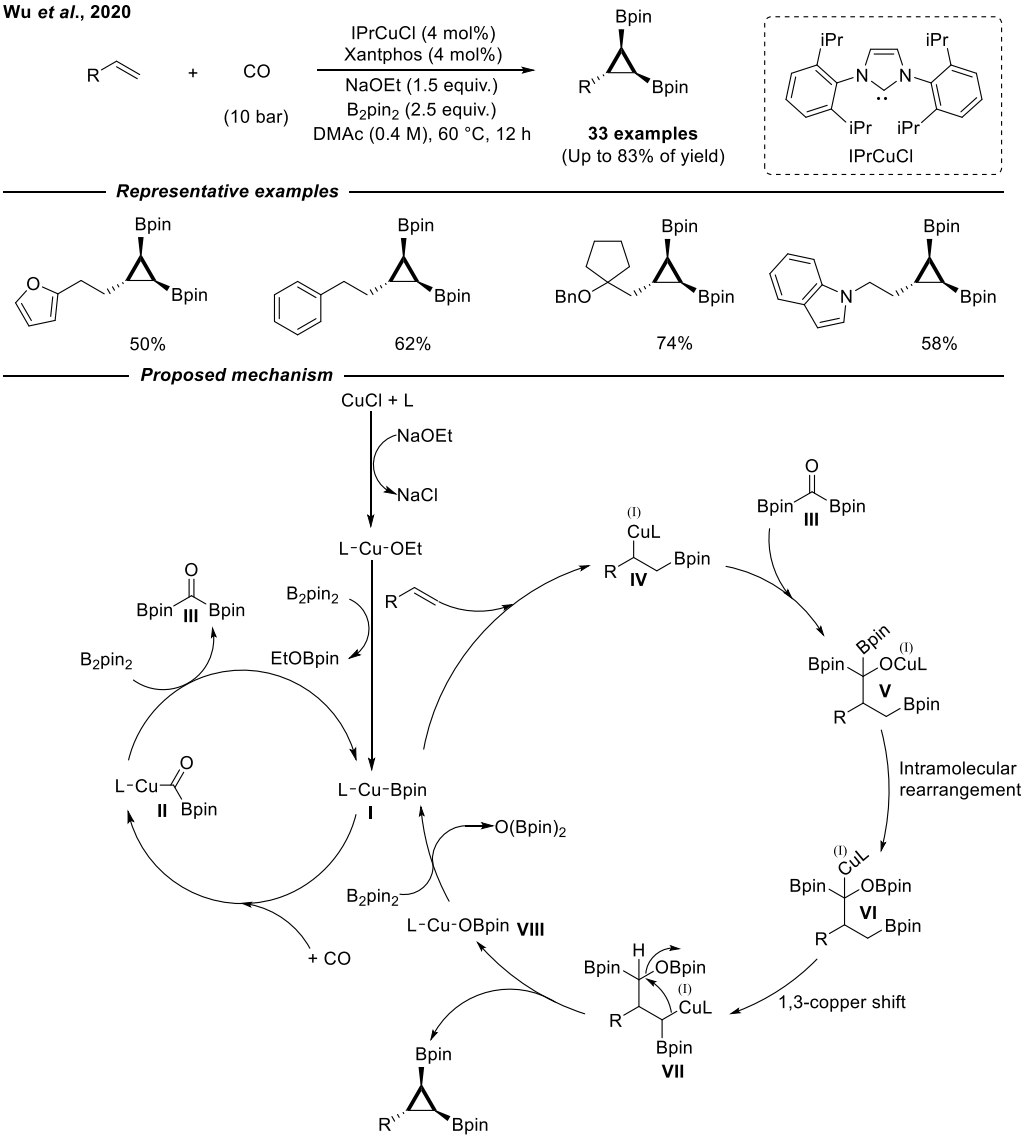


Scheme 36. Copper-catalyzed borylative methylation and diborylmethylation of alkyl iodides with carbon monoxide.

In 2020, Wu group reported a copper(I)-catalyzed synthesis of stereodefined cyclopropyl bis(boronates) from alkenes using CO as the C1 source (Scheme 37).[55] In this transformation, various alkenes were transformed into the desired bis(boronate ester)-substituted cyclopropanes in good yields and excellent stereoselectivity. The catalytic system consists of 4 mol% of IPr·CuCl and Xantphos at 60 °C under a low pressure of carbon monoxide with 1.5 equiv. of NaOEt and 2.5 equiv. of B_2pin_2. Moderate to good yields were achieved with the aliphatic alkenes tested showing good functional group compatibility towards ethers, esters, silane, thioether and amines. The authors have proposed a possible reaction pathway where the active copper complex LCu(I)Bpin **I** is formed with the reaction between NaOEt, B_2pin_2 and IPrCuCl. Then, two interconnected catalytic cycles based on this LCu(I)Bpin **I** complex begin. In the left catalytic cycle, CO reacts with the copper complex LCu(I)Bpin through an insertion step, producing LCuCOBpin intermediate **II**. Then, the *bis*(boryl) ketone intermediate **III** is eliminated after reaction with B_2pin_2. In the right catalytic cycle, an alkene substrate coordinates and inserts into the Cu–B bond of the complex **I** to give an alkyl copper intermediate **IV**. Then, the *in-situ* produced *bis*(boryl) ketone intermediate reacts with the alkylcopper intermediate **IV** and follow a spontaneous intramolecular rearrangement and a 1,3-copper shift, which

[55] Wu, F. P.; Luo, X.; Radius, U.; Marder, T.B.; Wu, X. F. *J. Am. Chem. Soc.* **2020**, *142*, 14074–14079.

eliminates cyclopropyl boronate as the final product and generates the LCu(I)OBpin complex **VIII**. Finally, the LCuOBpin complex reacts with B_2pin_2 to regenerate the LCu–Bpin to close the catalytic cycle.



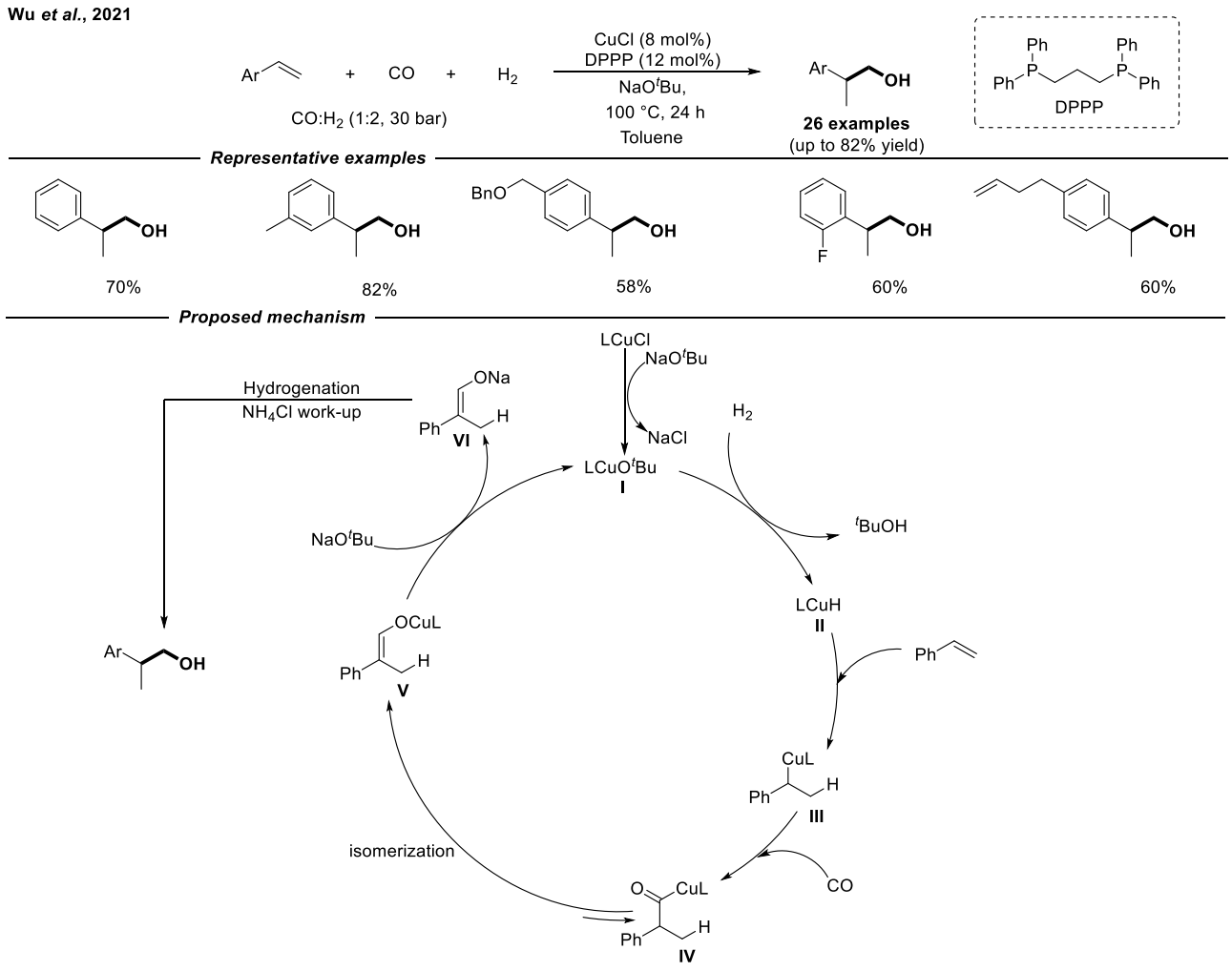
Scheme 37. Copper-catalyzed synthesis of cyclopropyl bis(boronates) from alkenes with carbon monoxide.

After discussing the most advanced techniques for producing aldehydes and ketones via copper-catalyzed carbonylative cross-couplings, the next section will focus on cutting-edge synthetic procedures for producing alcohols, another very important class of compounds widely used in organic chemistry.

1.5.3 Copper-catalyzed carbonylative cross coupling reactions for the synthesis of alcohols

Alcohols are common structural motifs in organic molecules and, moreover, are versatile synthetic building blocks. In the past decades, numerous approaches have been developed for the preparation of alcohols and among them the direct carbonylation of organic halides with carbon monoxide an interestingly possibility. Here, we summarized some examples of copper-catalyzed carbonylation reactions for the synthesis of alcohols.

In continuation of their studies on copper catalyzed carbonylation reactions, the Wu group reported in 2021 a copper-catalyzed method for the hydromethylation of alkenes to generate alcohols (Scheme 38). The catalytic system consists of CuCl (8 mol%) and DPPP (12 mol%) in the presence of NaO^{t}Bu as the base under a mixture of CO and H_2 (1:2, 30 bar).[56] With this protocol, various olefins were tested, affording the desired alcohols in good yields. Under this conditions is firstly generated an aldehyde and is then hydrogenated by the excess of H_2 to give the corresponding target alcohol. Based on the experimental results collected, the authors proposed that the reaction pathways starts with the generation of a LCuO^{t}Bu complex **I**, which affords the corresponding copper hydride LCuH **II** after reaction with H_2.

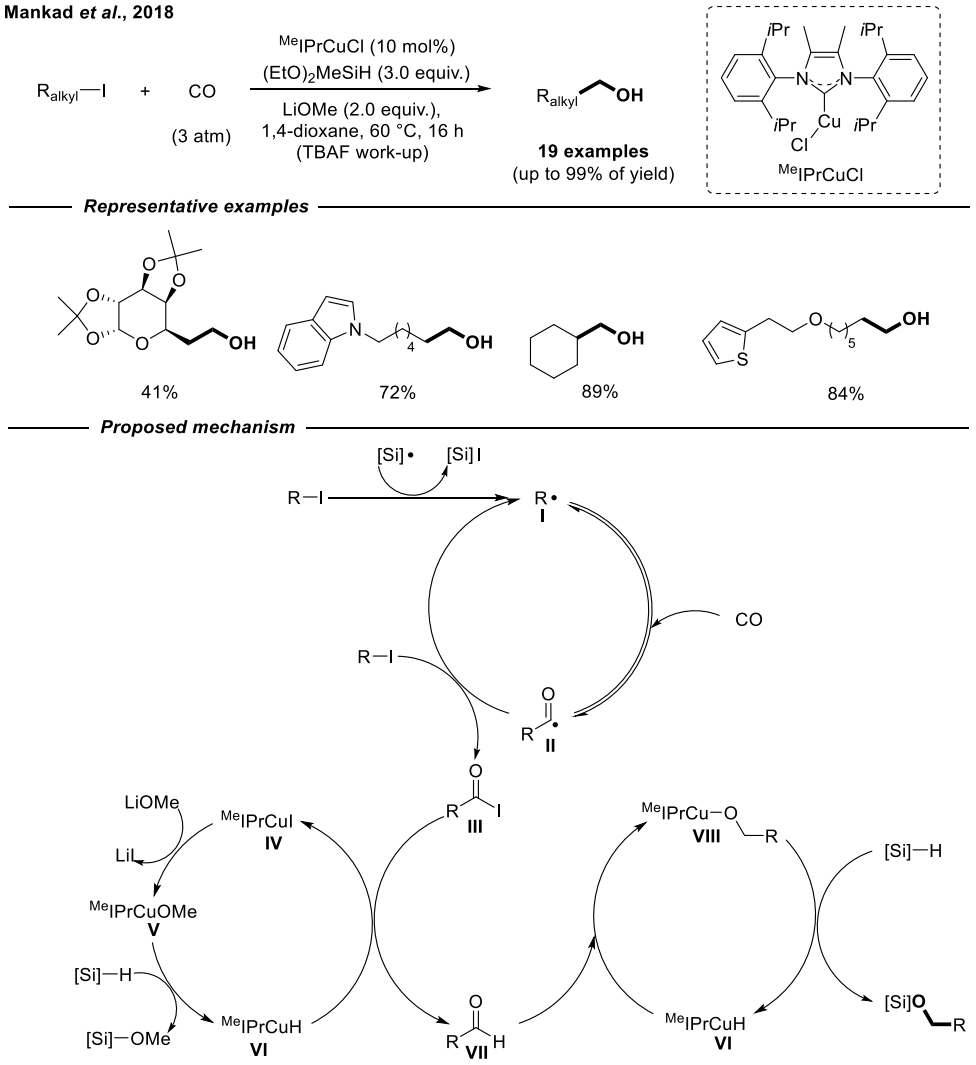


Scheme 38. Copper-catalyzed hydroxymethylation of alkenes.

[56] Geng, H. Q.; Meyer, T.; Frankec, R.; Wu, X. F. *Chem. Sci*. **2021**, *12*, 14937–14943.

Afterwards, hydrocupration takes place onto the double bond of the alkene to give an alkylcopper intermediate **III** which reacts with carbon monoxide to produce an acyl-copper complex **IV**. At this point, the acyl-copper tautomerizes to the vinyl alkoxide copper species **V**. Concomitantly, in presence of NaO^tBu a cation exchange takes place to form a sodium vinyl alkoxide species, which will give the key intermediate **VI**. Finally, the sodium vinyl alkoxide species **VI** will evolve to the desired alcohols after hydrogenation by the excess of H_2 and the work-up with NH_4Cl.

In continuation of their studies on copper catalyzed carbonylation reactions, the Mankad group reported in 2018 a copper-catalyzed method for the reductive carbonylation by which unactivated alkyl iodides can be hydroxymethylated to provide one-carbon-extended alcohol as products (Scheme 39).[57] Indeed, the starting alkyl iodide is first homologated to the corresponding aldehyde, which is then reduced to the corresponding alcohol. The reaction is carried out with 10 mol% of ^{Me}IPrCuCl in the presence of $(EtO)_2MeSiH$ as a hydride source under a pressure of carbon monoxide of 3.0 atm and mild reaction conditions (60 °C for 16h). Esters, nitriles, and heterocycles, among other sensible functional groups, were found to be well compatible with this method. Additionally, starting materials such as primary, secondary, and tertiary alkyl iodides can all be used with this protocol.

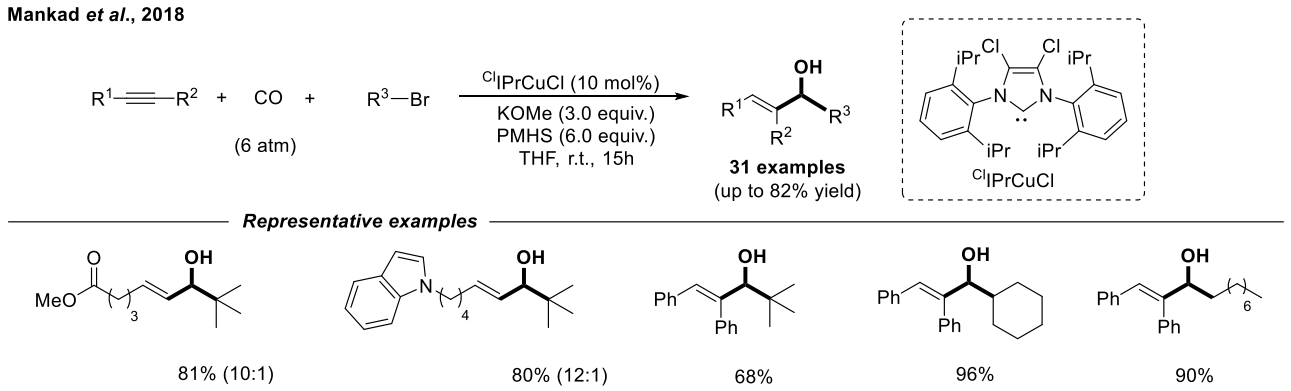


Scheme 39. Copper-catalyzed hydroxymethylation reaction of alkyl iodides for the synthesis of alcohols.

[57] Siling, Z.; Mankad, N. P. *Angew. Chem. Int. Ed.* **2018**, *57*, 5867–5870.

The reaction mechanism proposed by the authors start with the formation of an alkyl radical **I** through the reaction between the alkyl iodide and diethoxymethylsilane. Then, the alkyl radical **I** reacts with carbon monoxide to generate an acyl radical intermediate **II** which evolve to the corresponding acyl-iodide via an atom-iodide transfer **III**. Thus, a nucleophilic substitution takes place between the acyl iodide **III** and copper hydride **VI** to yield the homologated aldehyde **VII**. Finally, the aldehyde formed **VII** is subjected to a second reduction CuH-mediated to furnish the final silyl-protected alcohol, which is deprotected upon work-up.

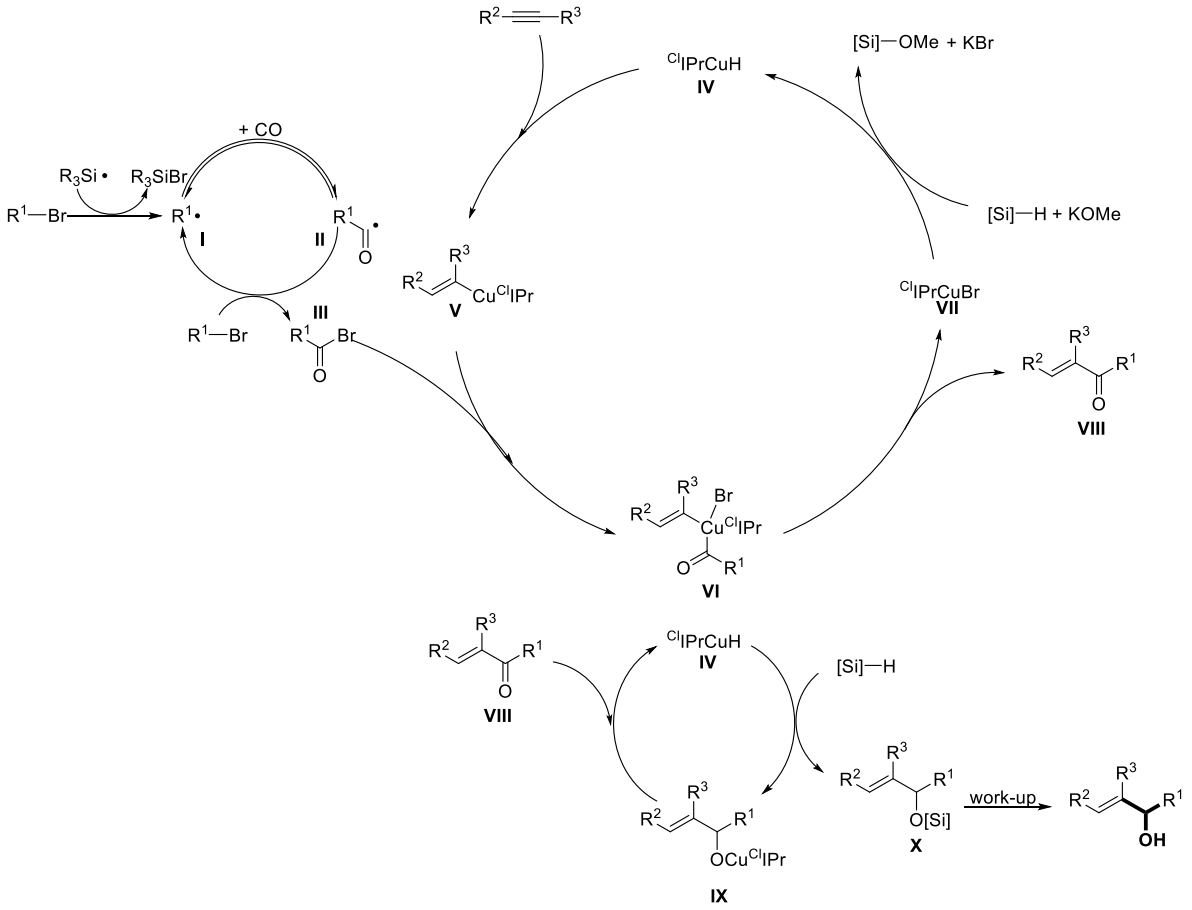
Recently, the Mankad group reported an additional attractive catalytic system for the synthesis of allylic alcohols from alkyl halides and alkynes via a copper-catalyzed hydrocarbonylative coupling and a selective 1,2-reduction of the intermediate enone (Scheme 40).[58] The reaction is performed with 10 mol% of ^{Cl}IPrCuCl in the presence of 6.0 equiv. of poly(methylhydrosiloxane) (PMHS) as the reducing agent under a pressure of carbon monoxide of 6 atm, at room temperature in THF for 15 hours. The mild reaction conditions allow the use of a variety of alkynes containing different functional groups, such as a benzyl ether, a chloroalkyl, a terminal alkene, as well as esters and nitriles.



Scheme 40. Synthesis of allylic alcohols from alkyl halides and alkynes via a Cu-catalyzed hydrocarbonylative coupling and a selective 1,2-reduction.

The hypothesized mechanism relies upon the generation of the corresponding alkyl radical **I** after the reaction of PMHS with the alkyl bromide. Thereafter, the alkyl radical **I** reacts with carbon monoxide to undergoes carbonylation and furnish the corresponding acyl radical **II**, which reacts with the alkyl halide to afford acyl halide **III** via a bromine-atom-transfer. Subsequently, an hydrocupration reaction onto the alkyne takes place to furnish the alkenylcopper intermediate **V**, whom after oxidative addition with the acyl halide **III** forms the copper(III) complex. Finally, the desired enone **VIII** is generated through a reductive elimination step to then undergoes to a selective 1,2-reduction Cu-catalyzed to furnish the allylic alcohol product after workup (Scheme 41).

[58] Cheng, L. J.; Islam, S. M; Mankad, N. P. *J. Am. Chem. Soc*. **2018**, *140*, 1159–1164.

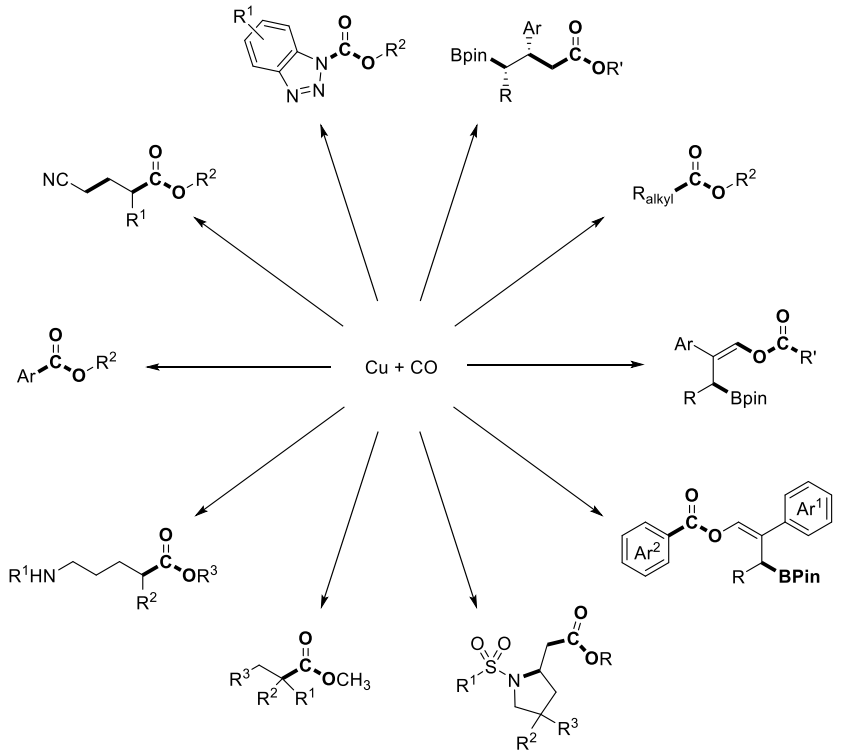


Scheme 41. Synthesis of allylic alcohols from alkyl halides and alkynes via a Cu-catalyzed hydrocarbonylative coupling and a selective 1,2-reduction.

Clearly, since the preparation of alcohols through copper-catalyzed carbonylative cross-coupling consists of a small number of representative examples, this area of study is still under development. Opportunity remains for the development of new protocols with higher efficiencies and with expanded reaction scope. In the next section, our attention will be devoted to the preparation of esters, an important class of compounds broadly used in organic chemistry.

1.5.4 Copper-catalyzed carbonylative cross-coupling reactions for the synthesis of esters

In addition to the synthesis of ketones and alcohols, the use of copper catalysis has been also applied to the preparation of esters, major chemicals widely used in various areas of chemistry. Considering the importance of esters in this section, we will devote our attention to the preparation of esters through copper-catalyzed carbonylative cross-coupling reactions. Alkoxycarbonylation is a straightforward process for the synthesis of esters, examination of the literature reveals that the majority of the carbonylation reactions reported are based on palladium catalysis. Copper-catalyzed alkoxycarbonylation reactions have emerged as an attractive area of research and progress have been made in the last 20 years in the field. All products that can be synthesized through the use of copper-catalyzed carbonylative cross-coupling reactions to prepare esters and derivatives are depicted in Scheme 42 below which serves as a general overview of progresses achieved.

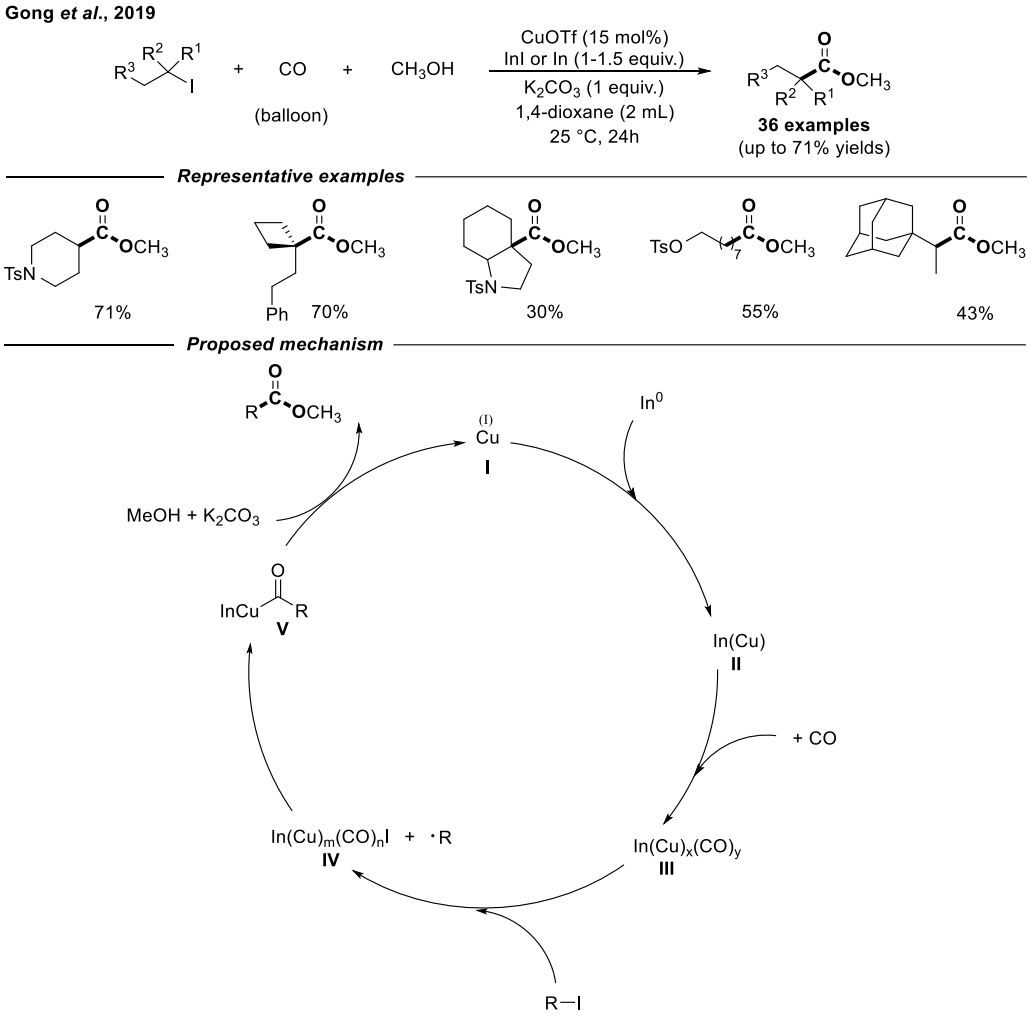


Scheme 42. Esters obtained by copper-catalyzed alkoxycarbonylation.

The Gong group reported a copper-catalyzed indium-mediated methoxycarbonylation of unactivated alkyl iodides (Scheme 43) under mild conditions and a low pressure of carbon monoxide (1 atm, CO balloon).[59] This transformation could efficiently furnish primary, secondary and tertiary alkyl esters in good yields. The main advantage of this synthetic method is the extremely mild reaction conditions, since the reaction takes place at room temperature and it is tolerant towards a wide range of functional groups such as Boc, Ts, acetal, OTs and silyl ether. Based on a preliminary mechanistic investigation, the authors proposed that indium is indispensable for the reaction to occur due to it may act as a mediator to facilitate the coordination between copper and carbon monoxide. The catalytic cycle starts with the generation of a bimetallic intermediate **II** after the reaction between the copper salt and indium, then the coordination of carbon monoxide generates an active species $InCu_x(CO)_y$ **III** with carbon monoxide coordinated onto the metal center. At this point, the active bimetallic species reacts with the alkyl iodide by single electron transfer (SET), which generates an alkyl radical and under a pressure of carbon monoxide evolve to intermediate **V**. Finally, the bimetallic acyl-In-Cu

[59] Chen, Y.; Su, L.; Gong, H. *Org. Lett.* **2019**, *21*, 4689–4693.

with methanolysis evolves to the desired final ester and regenerate the copper(I) catalyst **I**. Although a reaction mechanism has been proposed in the original manuscript, it is important to highlight that the catalytic cycle is not clear and the real nature of the reaction intermediates has not really been demonstrated.

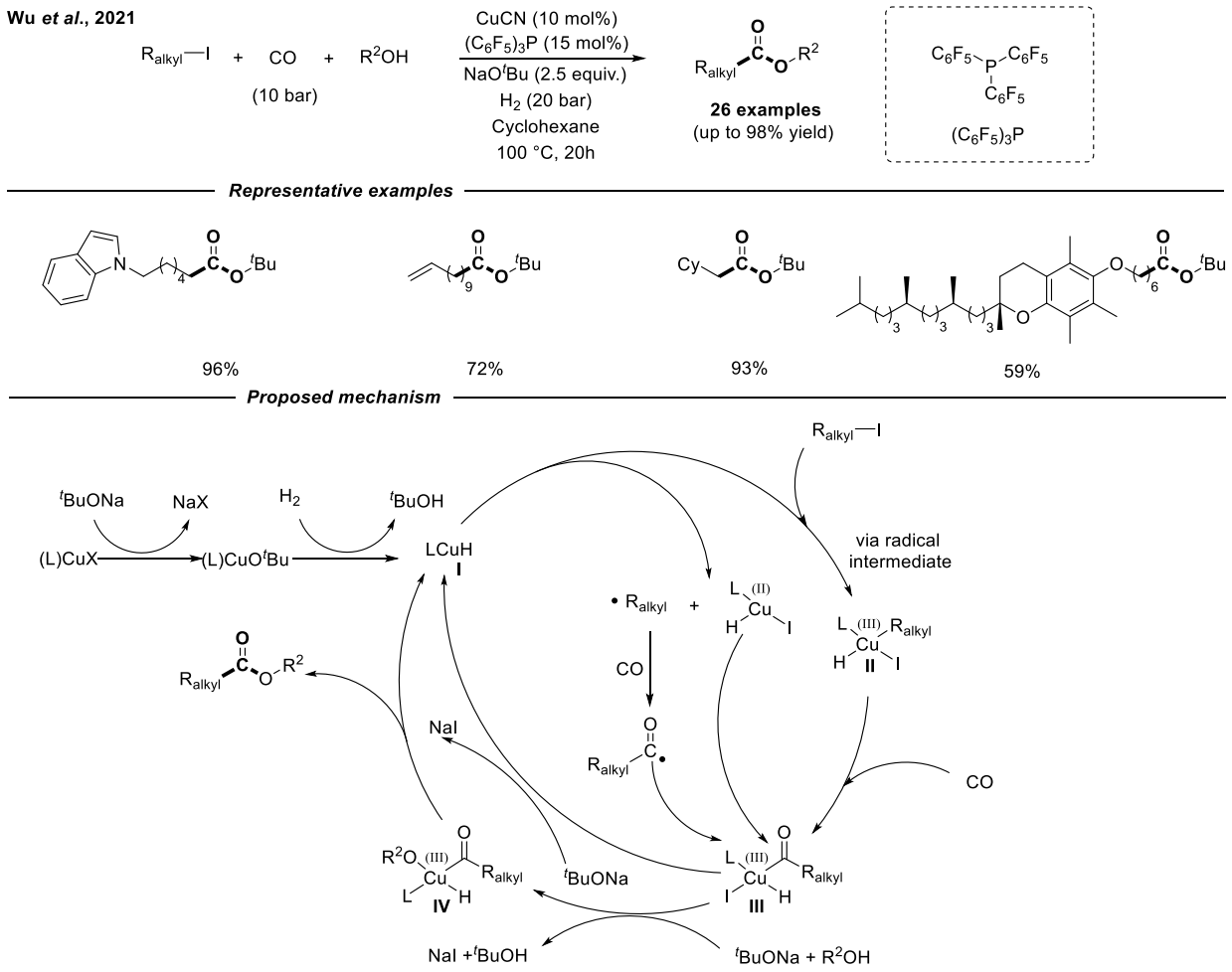


Scheme 43. Copper-catalyzed and indium-mediated methoxycarbonylation of alkyl iodides.

Recently, the Wu group discovered a new copper-catalyzed alkoxycarbonylation reaction of alkyl iodides with alcohols, where various alkyl iodides can be converted into the corresponding esters.[60] The challenges in the carbonylation of alkyl halides are raised from the slow rate of oxidative addition of the substrate with the metal center and the fast β-hydride elimination from the alkyl-metal intermediates. These difficulties were completely overcome through an innovative catalytic system relying on a combination of copper cyanide and tris(pentafluorophenyl)phosphine as ligand under a mixture of CO (10 bar) and H_2 (20 bar), namely syngas (CO + H_2), at 100°C for 20h (Scheme 44). Various functional groups such as –Cl, –Br, –I and –CN could be tolerated and afforded the desired products in good yield without hydrodehalogenation or reduction. Additionally, besides *tert*-butyl esters, other types of aliphatic esters could also be obtained by simply adding the desired alcohols to the reaction. For what concerns the reaction mechanism, the active catalytic species is the copper hydride **I** generated under a H_2 atmosphere. Under these conditions, no β-hydride elimination onto the alkyl-copper intermediate **II** occurs. The alkyl iodide reacts with the copper hydride **I** to generate an alkyl-Cu(III) intermediate **II**. Thereafter, carbon monoxide is coordinated onto the

[60] Geng, H. Q.; Wu, X. F. *Org. Lett.* **2021**, *23*, 8062–8066.

alkyl-metal species **II** and inserted in the C–Cu bond to generate an acyl-Cu(III) species **III** which can be generated as well by Cu(II) capturing an acyl radical. Finally, after an anion exchange on the acyl-metal species **IV**, the desired ester can be formed by reductive elimination.

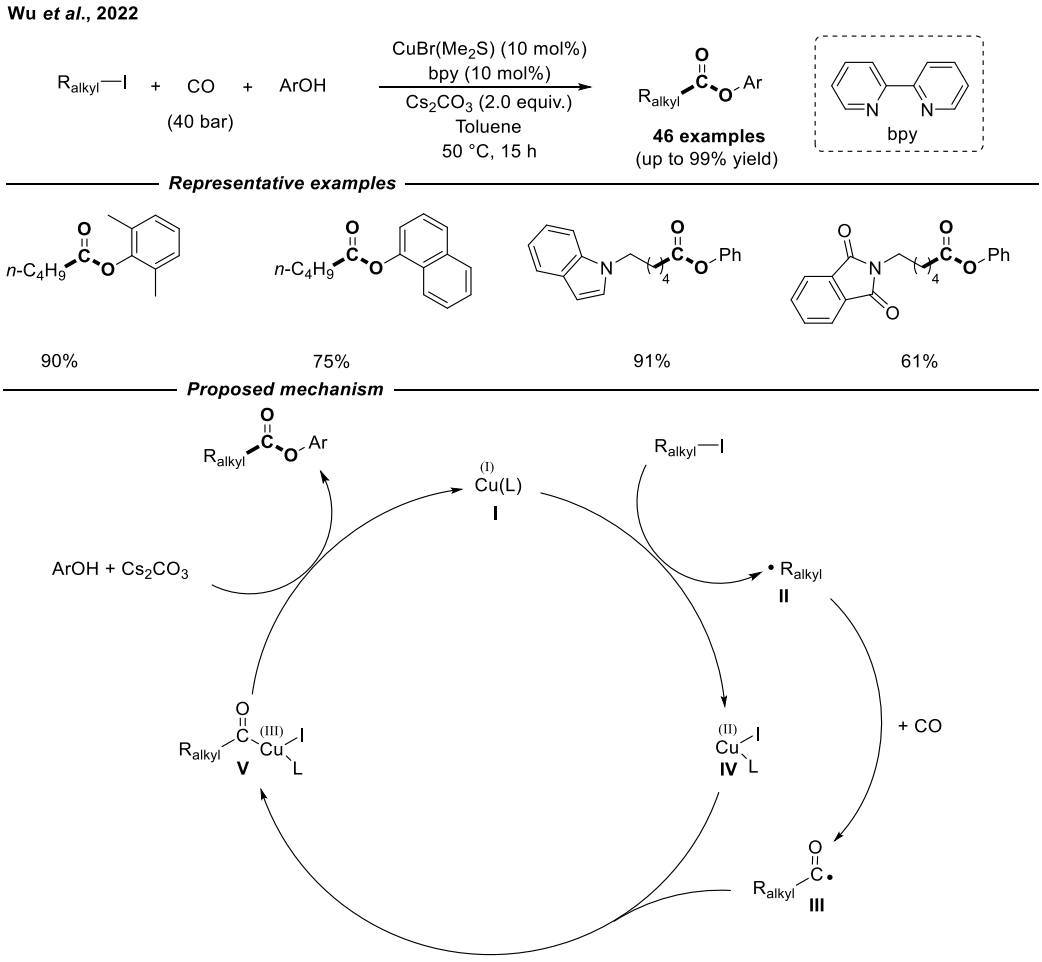


Scheme 44. Copper-catalyzed alkoxycarbonylation of unactivated alkyl iodides with alcohols.

In 2022, the Wu group reported a new copper-catalyzed cross-coupling reaction to synthetize esters with phenols as nucleophilic partners, which are known to be less nucleophilic compared to alcohols.[61] The catalytic system identified consists of 10 mol% of CuBr(Me_2S) and 10 mol% of 2,2'-bipyridyl under 40 bar of carbon monoxide in toluene at 50 °C for 15h (Scheme 45). This reaction showed good functional group compatibility, the reaction furnished the desired esters in moderate to excellent yields. Moreover, alkyl iodides containing heterocycles could be converted smoothly with moderate to excellent yields. This protocol can also be extended to the carbonylation of secondary and tertiary alkyl iodides but no reaction occurred when alkyl bromides were employed. On the basis of the results collected, the authors proposed a catalytic cycle in which the alkyl iodides are activated by a copper-catalyst **I** to form an alkyl radical **II** and a copper(II) species **IV**. Then, the alkyl radical **II**, under a pressure of carbon monoxide, is capable to capture a molecule of carbon monoxide to generate an acyl radical **III** which reacts with **IV** to give an acylcopper(III) intermediates

[61] Wu, X. F.; Bartolo, G.; Mancuso, R.; Russo, P.; Zhao, F. *J. Catal.* **2022**, *413*, 907–912.

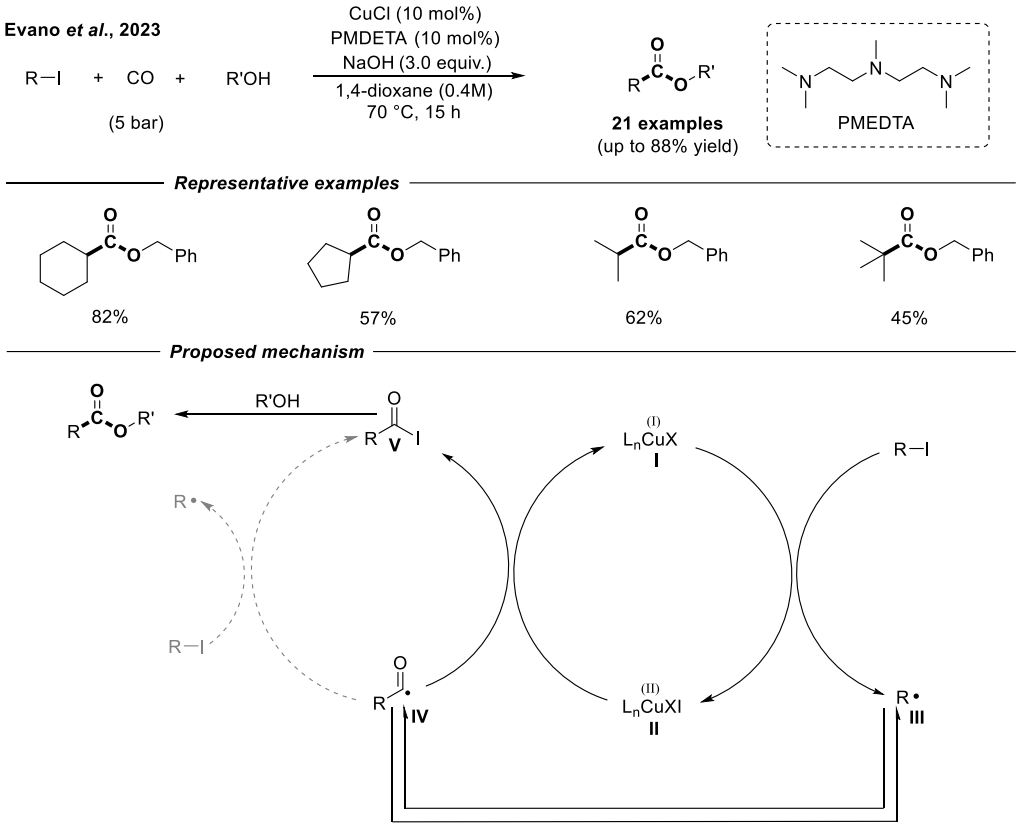
V. Finally, an anion exchange between phenols and halide on copper occurs and the target ester is formed through reductive elimination.



Scheme 45. Copper-catalyzed carbonylative coupling of alkyl iodides with phenols.

In 2023, our group reported a novel copper-catalyzed carbonylative cross-coupling between alkyl iodides and alcohols or sodium hydroxide to synthesize esters and carboxylic acids (Scheme 46).[62] Upon reaction with catalytic amounts of copper(I) chloride (10 mol%) and *N*, *N*, *N*′, *N*′′, *N*′′-pentamethyldiethylenetriamine under a mild pressure of carbon monoxide (5 bar) at 70 °C, a range of secondary and tertiary alkyl iodides are readily transformed into the corresponding esters and carboxylic acids. The main advantages of this protocol include its broad applicability, the use of an especially inexpensive and available catalytic system (€407/kg for PMDETA15 and €96/kg for CuCl) and its user-friendliness. For what concern the reaction mechanism, the authors proposed a radical pathway. The catalytic cycle is initiated by a single electron transfer from a copper(I) complex **I** to the starting alkyl halide, generating the corresponding copper(II) complex **II** and an alkyl radical species **III**. Thereafter, the addition of the alkyl radical **III** onto carbon monoxide yields a transient acyl radial intermediate **IV**, which is oxidized by the copper(II) complex **II** to furnish the corresponding acyl iodide **V**, which would close the catalytic cycle. At this point, the acyl iodide intermediate **V** reacts with an alcohol or a hydroxide anion to finally afford the desired ester or carboxylic acid, respectively.

[62] Adaoudi, O.; Le Bescont, J.; Bruneau-Voisine, A.; Evano, G. *Synthesis* **2023**.



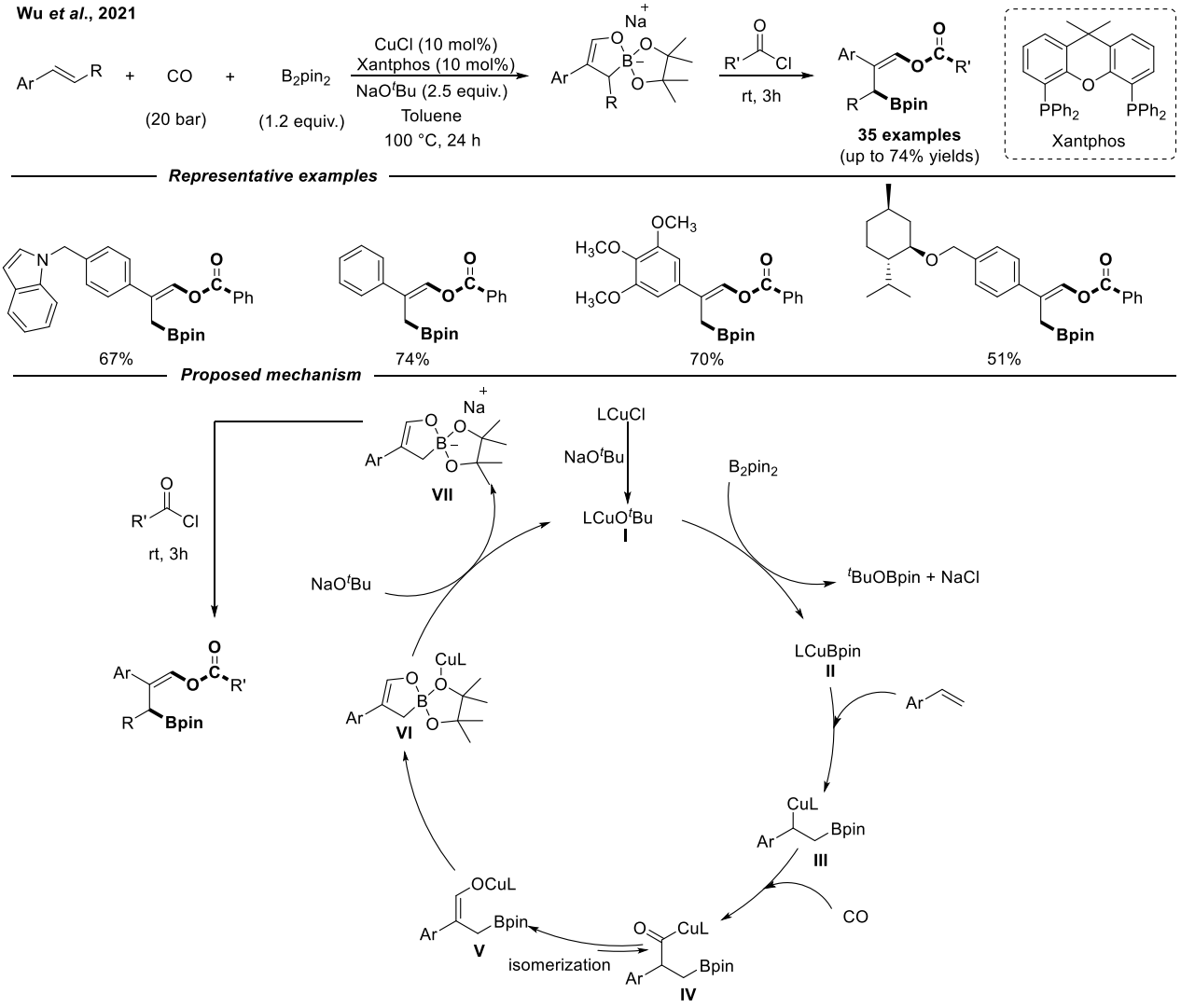
Scheme 46. Copper-catalyzed carbonylative cross-coupling of alkyl iodides with alcohols and sodium hydroxide: synthesis of esters and carboxylic acids.

Another class of highly interesting compounds that can be used to effect carbonylation reactions are alkenes. The functionalization of alkenes represents an important basis of today's chemical industry. Apart from polymerization and oxidation, carbonylation reactions using CO represent an attractive technology for the production of value-added bulk and fine chemicals from olefins. For instance, methyl propionate, an important intermediate for polymethacrylates, is produced on the scale of > 300 000 tons per annum by the palladium-catalyzed methoxycarbonylation of ethylene.[63] Besides, over 10 million tons of oxo products are produced every year from alkenes via hydroformylation and related tandem reactions.[64] For these reasons, we will continue our bibliographic study focusing our attention on the most innovative copper-catalyzed carbonylation cross-coupling reactions using alkenes as starting materials.

In 2021, the Wu group reported a copper-catalyzed multi-component borofunctionalization of styrenes with bis(pinacolato)diboron (B_2pin_2) and CO (Scheme 47) yielding cyclic borates.[65] By this one-pot borofunctionalization of alkenes, B_2pin_2, CO, and NaO^tBu in the presence of 10 mol% of Xantphos and CuCl. Due to the mild reaction conditions, the protocol showed a good functional group compatibility, allowing the formation of a huge library of vinyl esters. The catalytic cycle that the authors proposed starts with the reaction between CuCl, NaO^tBu and B_2pin_2 to give an active LCu–Bpin species **II**. Then, the borocupration of

[63] a) Jimenez Rodriguez, C.; Foster, D. F.; Eastham, G. R.; Cole-Hamilton, D. J. *Chem. Commun*. **2004**, *15*, 1720–1721. b) del Rio, I.; Claver, C.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem*. **2001**, *11*, 2719–2738.
[64] a) Zuidema, E.; Escorihuela, L.; Eichelsheim, T.; Carbo, J. J.; Bo, C.; Kamer, P. C. van Leeuwen, P. W. *Chem. Eur. J.* **2008**, *14*, 1843–1853. b) Diebolt, O. Muller, C. Vogt, D. *Catal. Sci. Technol*. **2012**, *2*, 773–777.
[65] Wu, X. F; Wu, F. P.; Yuan, Y. *Chem. Sci.* **2021**, *12*, 13777–13781.

the alkene takes place to afford the β-boroalkylcopper intermediate **III**, followed by a CO-insertion step to generate an acyl-copper intermediate **IV**, which easily undergoes isomerization to the O-bound copper enolate intermediate **V**. Subsequently, the resulting copper vinyl alkoxide **V** evolves to the final sodium cyclic borates **VII**. Due to the poor stability during purification by silica gel column chromatography the cyclic borates were treated with acyl chlorides to afford the corresponding β-boryl vinyl esters.

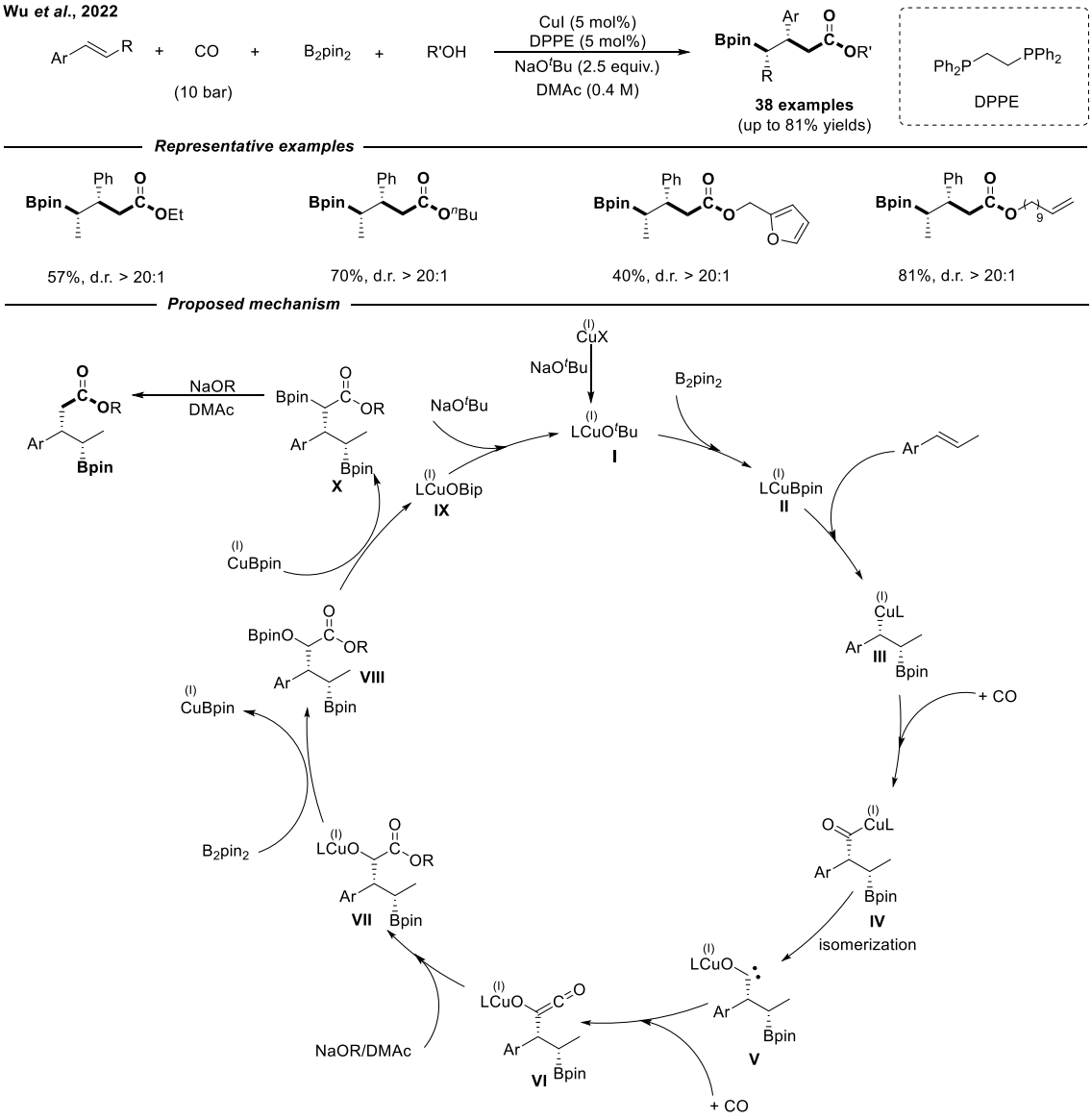


Scheme 47. Copper-catalyzed borofunctionalization of styrenes with B_2pin_2 and carbon monoxide and further conversion to esters.

Recently, the Wu group described the first protocol for the copper-catalyzed carbonylative catenation and borylation of alkenes under an atmosphere of carbon monoxide (Scheme 48).[66] The catalytic system consists of 5 mol% of CuCl as the copper source and 5 mol% of DPPE (1,2-bis(diphenylphosphino)ethane) as the ligand in DMAc with NaO^{t}Bu under a low pressure of carbon monoxide (10 bar) at 60 °C. The (*E*)-olefins reacted with B_2pin_2 and alcohols, affording the corresponding γ-boryl esters in good yields and in good diastereoselectivity. With this synthetic strategy, two molecules of carbon monoxide act as CH_2 and carbonyl group sources. In particular, through this process one molecule of CO is reduced by the β-boryl alkyl copper complex, then another molecule of CO is incorporated leading to the formation of the methylene-carbonyl group (–CH_2–CO–) in one step. More specifically, the authors proposed

[66] Wu, F. P.; Yang, Y.; Fuentes, D. P.; Wu, X.F. *Chem*. **2022**, *8*, 1982–1992.

that the catalytic cycle starts with the generation of a Cu–Bpin **II** complex through the reaction between copper salt, NaO^{t}Bu and B_2pin_2. Then, the Cu–Bpin complex reacts with olefin via a reaction of borocupration to generate an alkyl copper complex **III** which can undergoes a CO-insertion step under an atmosphere of carbon monoxide.



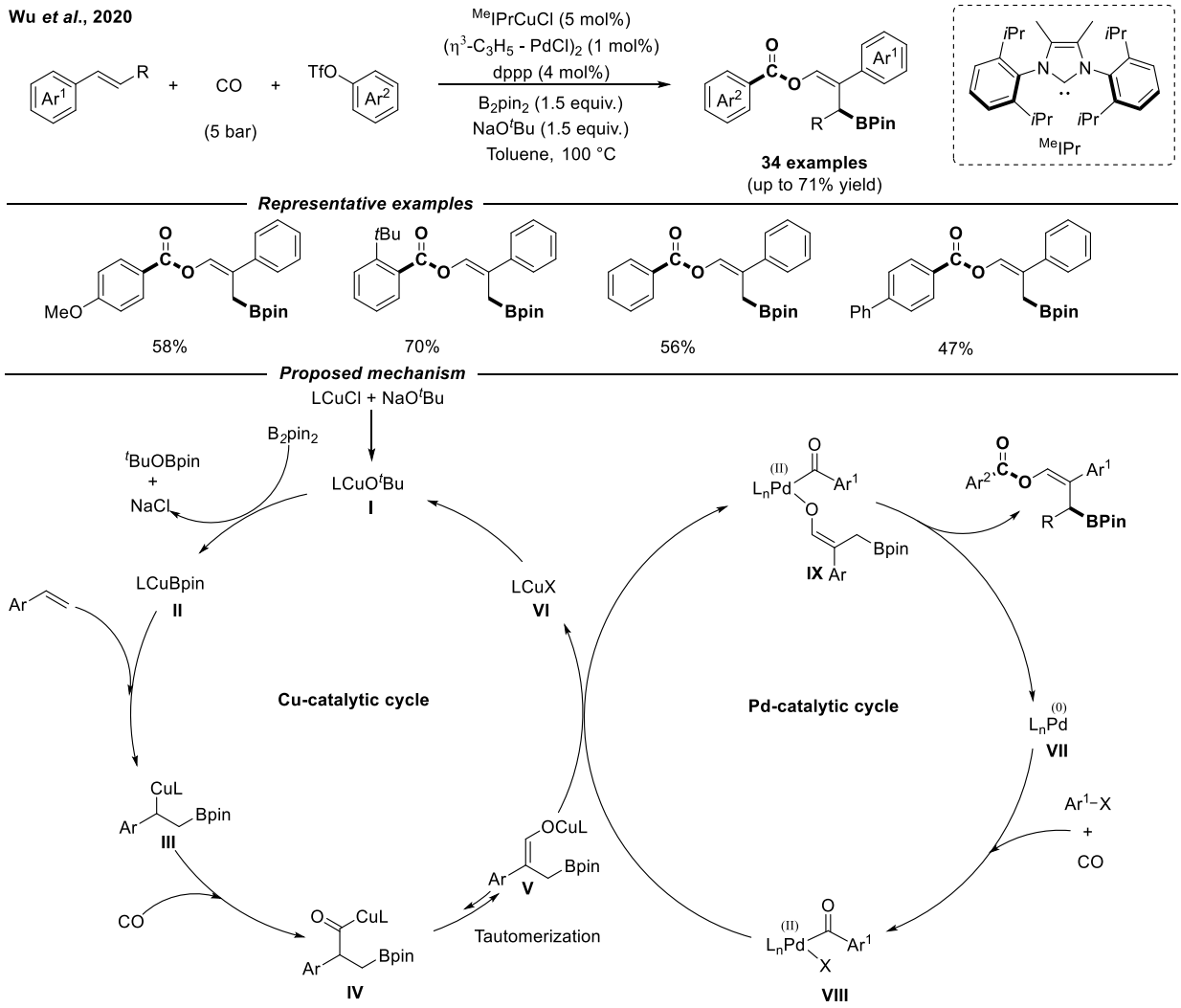
Scheme 48. Copper-catalyzed carbonylative catenation of olefins for the synthesis of γ-boryl esters.

Thus, the resulting acyl-copper complex **IV** will follow an isomerization step **V** and a second CO-insertion affording a highly reactive ketene **VI** which collapse to the corresponding ester **VII** in presence of sodium alkoxide. Afterwards, the copper alkoxide **VII** reacts with B_2pin_2 to spontaneously evolve to the desired γ-boryl esters, which is the final product of this transformation.

The Wu group also reported a more sophisticated multicomponent synthetic procedure for the preparation of β-boryl vinyl esters via a cooperative Cu/Pd catalytic system.[67] The reaction is carried out using aryl triflates, vinylarenes, B_2pin_2 and carbon monoxide as starting materials in toluene at 100 °C (Scheme 49).

[67] Wu, F.P.; Wu, X. F.; Xu, J. X.; Yuan, Y. *Angew. Chem. Int. Ed.* **2020**, *59*, 17055–17061.

With this protocol a large library of β-boryl vinyl esters were synthesized with broad functional group tolerance. The mechanism consists of two cooperative catalytic cycles involving Cu and Pd. In the copper catalytic cycle, the active species is the ^{Me}IPrCuO^{t}Bu **I** which reacts with B_2pin_2 to form a ^{Me}IPrCu-Bpin complex **II**. Thus, a borocupration of the olefin occurs affording the alkyl copper intermediate **III**, which with the CO-insertion into the Cu-C bond yields to an acyl-copper(III) intermediate **IV**.



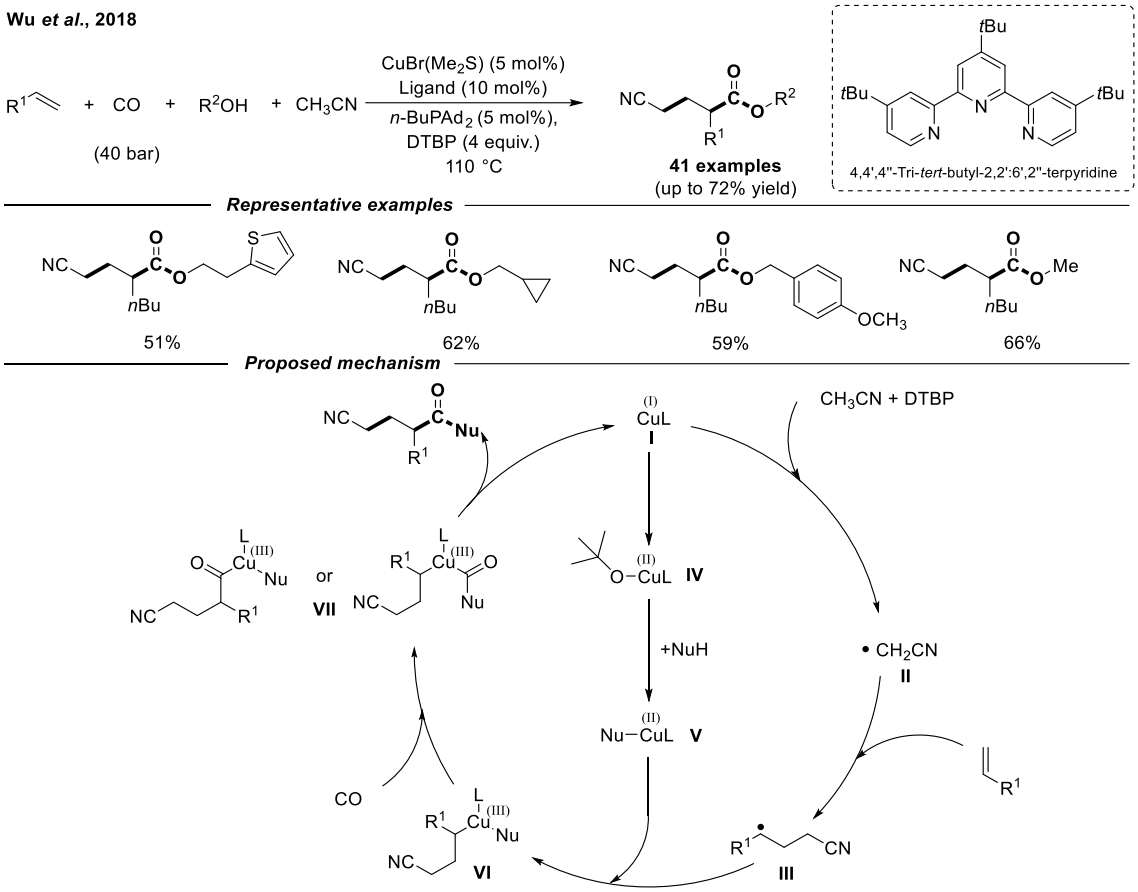
Scheme 49. Borocarbonylation of vinyltriflates by cooperative Cu/Pd catalysis for the synthesis of β-boryl vinyl esters.

At this point, the acyl-copper tautomerizes to the vinyl alkoxide copper species **V**. Concomitantly, in the Pd-catalytic cycle is generated an acyl palladium intermediate **VIII** via oxidative addition of the aryl triflate ArOTf to $L_nPd(0)$ **VII** and a CO-insertion step. Afterwards, the copper and palladium catalytic cycles begin to intersect via the transmetallation of the vinyl alkoxide copper complex **V** onto the acyl palladium species **VIII**, thus leading to an acyl-Pd-vinyl alkoxide **IX**. This intermediate collapses via reductive elimination to $L_nPd(0)$ releasing the β-boryl vinyl ester as final product.

In the same year, the Wu group developed a carbonylative four components reactions for the synthesis of 4-cyano esters (Scheme 50).[68] In this process, through a catalytic system consisting of 5 mol% of CuBr(Me_2S) and 10 mol% of terpyridine, together with $BuPAd_2$ (5 mol%) and *tert*-butyl peroxide (4 equiv.)

[68] Li, Yahui; Zhu, F.; Wang, Z.; Wu, X. F. *Chem. Commun.* **2018**, *54*, 1984–1987.

under CO pressure, the desired alkoxycarbonylated product can be isolated in good yield and excellent regioselectivity. Notably, this carbonylative multicomponent reaction can also be applied with different nucleophiles such as amides and benzenesulfonamide, even if their nucleophilicity is lower of the alcohols. The mechanism postulated for this transformation consists in the initial activation of acetonitrile under the cooperative effect of the copper catalyst and DTBP to generate the corresponding ·CH_2CN radical via hydrogen abstraction **II**. Then, the ·CH_2CN radical reacts with the olefin to give the intermediate radical **III**.



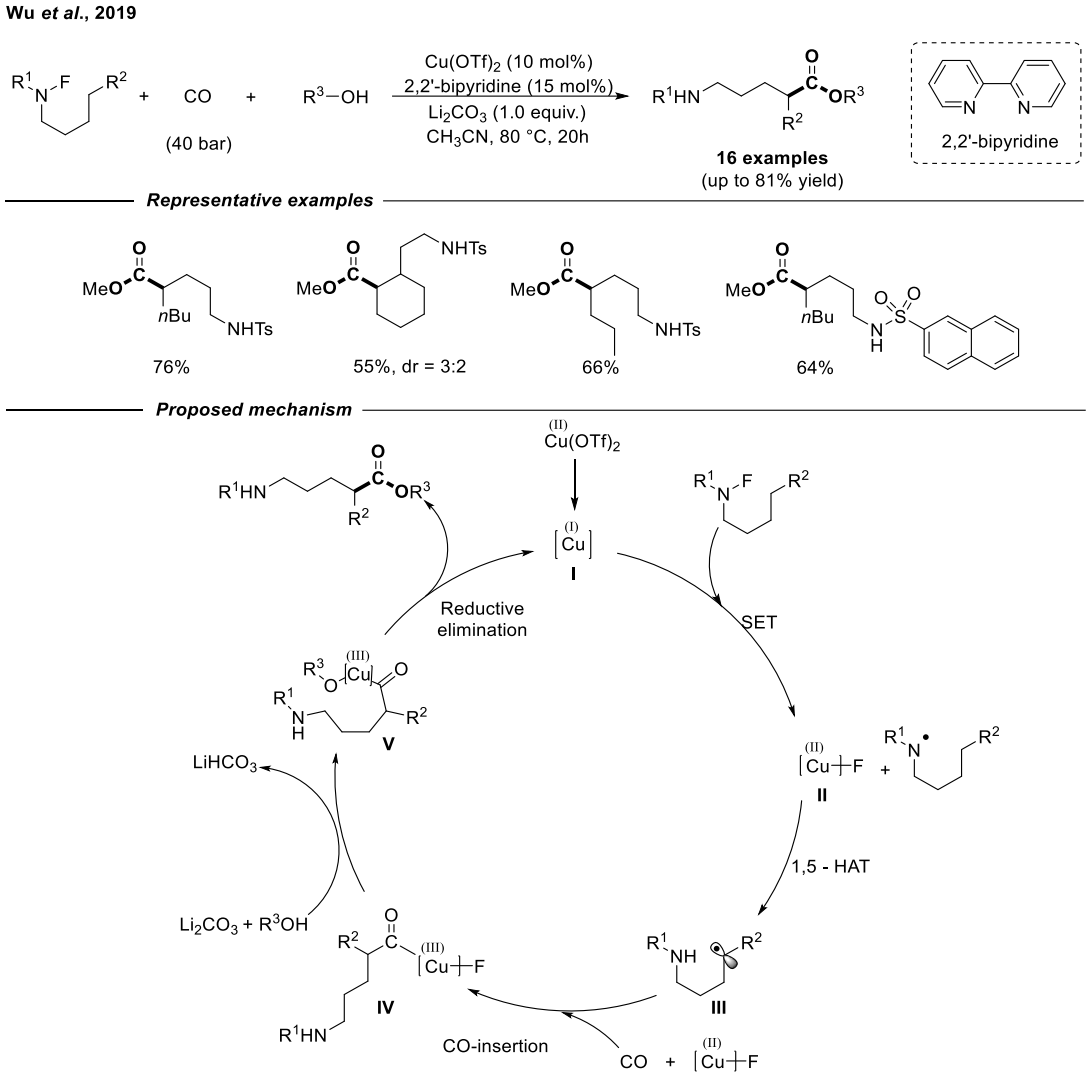
Scheme 50. Copper-catalyzed alkoxycarbonylation of alkenes for the synthesis of 4-cyano esters.

In the meantime, the copper pre-catalyst will be activated by ^{t}BuOO^{t}Bu to give intermediate **V**. Subsequently, a Cu(III)-complex **VI** is formed after the reaction between the Cu(II)-complex **V** and the alkyl radical **III**. The Cu(III)-complex after coordination and CO-insertion will form an acylcopper intermediate **VII**, to finally afford the alkoxycarbonylated product after reductive elimination.

Another class of appealing substrates that can be employed in copper-catalyzed alkoxycarbonylative cross-coupling reactions are *N*-fluorosulfonamides. Indeed, combining the Hofmann−Löffler−Freytag (HLF) reaction and the copper-catalyzed alkoxycarbonylation is possible to prepare highly functionalized esters. Notably, this approach offers the opportunity to prepare compounds, which are quite challenging to prepare with alternative procedures and with a reduced number of steps. In 2019, the Wu group developed an interesting intermolecular copper-catalyzed alkoxycarbonylation for the functionalization of a remote C(sp^3)–H bonds of *N*-fluorosulfonamides.[69] In this protocol, CO is used as a radical acceptor in combination with a 1,5-HAT/carbonylative cascade reaction for the synthesis of esters (Scheme 51). The optimized reaction

[69] Yin, Z.; Zhang, Y.; Zhang, S.; Wu, X. F. *J. Catal.* **2019**, *377*, 507–510.

conditions rely on the combination of 10 mol% of $Cu(OTf)_2$, 15 mol% of 2,2'-bipyridine and 1.0 equiv. of Li_2CO_3 in acetonitrile under 40 bar CO at 80 °C for 20h. Under standard reaction conditions the reaction tolerates different functional groups and alcohols, producing the corresponding esters in moderate to good yields.



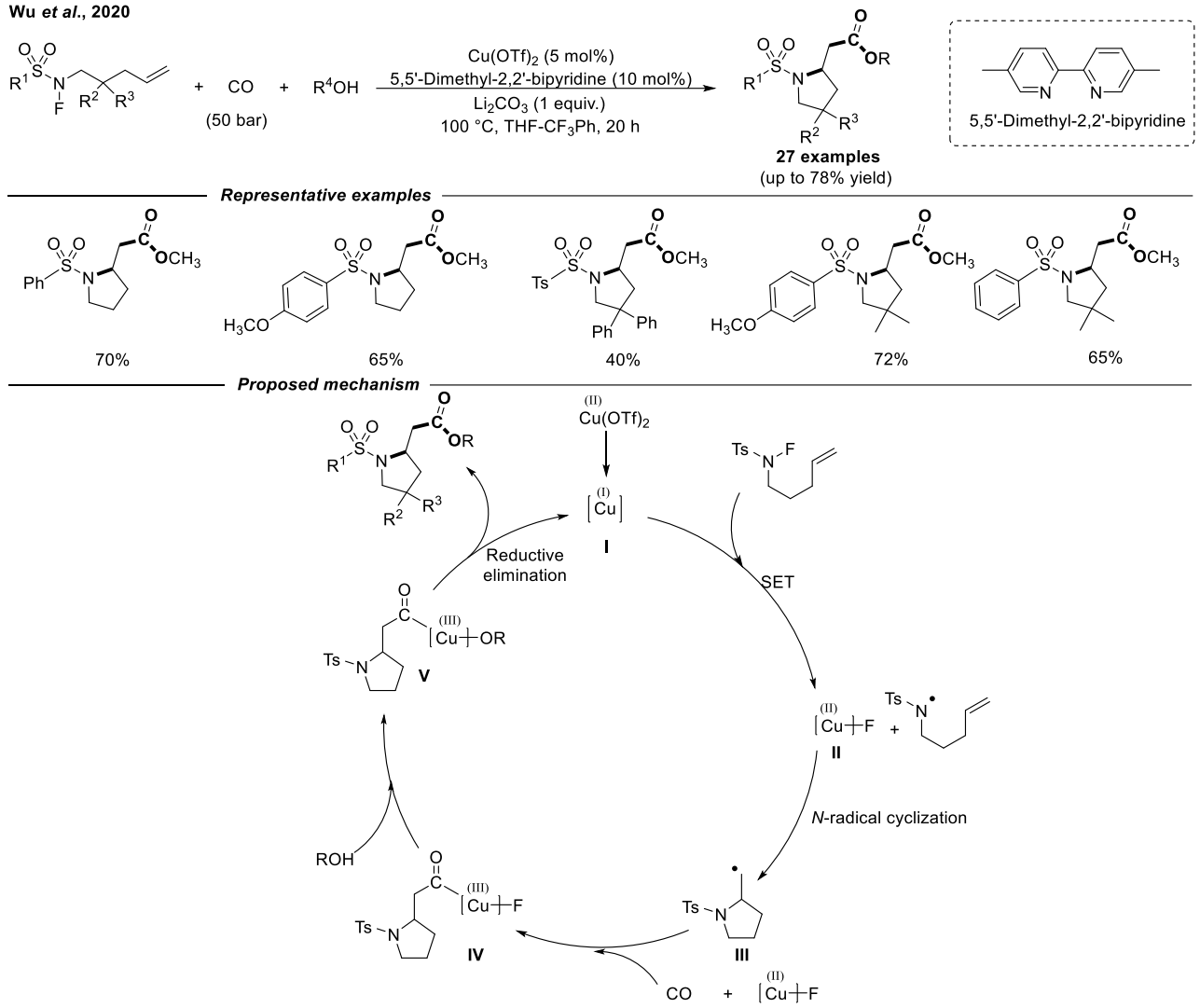
Scheme 51. Copper-catalyzed 1,5-HAT/carbonylative cascade reaction for the synthesis of esters.

The reaction mechanism begins with a Cu(I) single electron transfer onto *N*-fluorosulfonamides to form the amidyl radical and Cu(II) **II**. Then, the amidyl radical undergoes an intramolecular 1,5-HAT to provide the new carbon radical **III**, which would be captured by CO and Cu(II) species to generate an acyl-copper(III) intermediate **IV**. Finally, with a ligand exchanges and reductive elimination the target ester is obtained with the Cu(I) species regenerated for a new catalytic cycle.

In 2020, the Wu group reported a novel intramolecular copper(II)-catalyzed alkoxycarbonylation of *N*-fluoro-sulfonamides to synthesize β-homoprolines, valuable heterocycles due to their applications in biology and pharmacology (Scheme 52).[70] *N*-fluoro-sulfonamides and alcohols were treated with 5 mol % of $Cu(OTf)_2$ and 10 mol % of 5,5'-dimethyl-2,2'-bipyridine and 1 equiv. of Li_2CO_3 under 50 bar of CO pressure in a mixed solvent of THF/$PhCF_3$ (4:1) at 100 °C. The reaction proceeds via an intramolecular cyclization and

[70] Wu, X. F.; Yin, Z.; Zhang, Y. *Org. Lett.* **2020**, *22*, 1889–1893.

intermolecular carbonylation of a free radical. The scope of this reaction was explored with a wide range of alcohols and *N*-fluoro-sulfonamides bearing electron-donating or -neutral groups. In addition, also substrates with functional groups in the alkyl branched chain were all transformed smoothly into the corresponding *N*-sulfonyl-β-homoproline ester products in good yield.



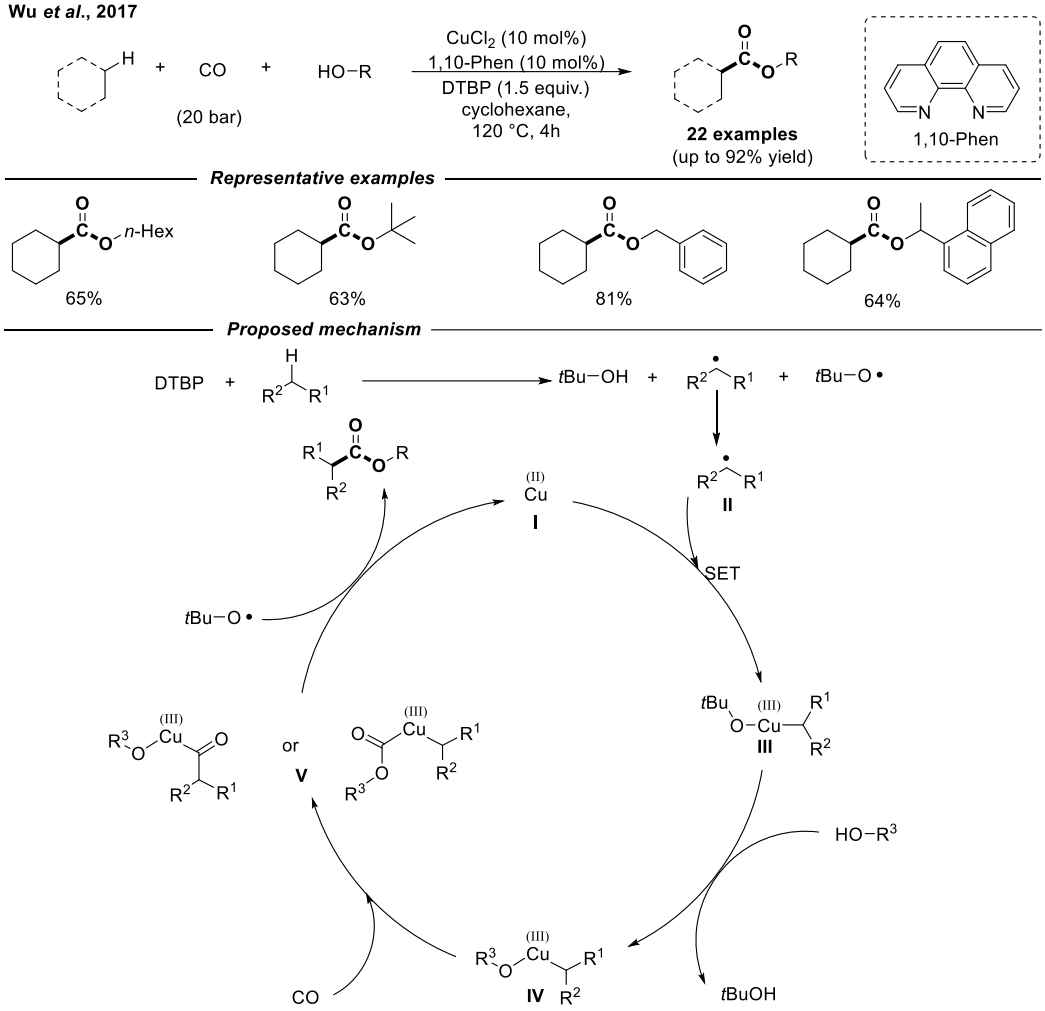
Scheme 52. Copper-catalyzed alkoxycarbonylation for the synthesis of β-homoprolines from *N*-fluoro-sulfonamides.

The proposed reaction mechanism starts with a single electron reduction in which Cu(I) promotes the generation of an amidyl radical while forming the corresponding Cu(II) complex **II**. Thus, an intramolecular cyclization of the amidyl radical takes place leading to the formation of a new C–N bond and a new cyclized radical intermediate **III**. Thereafter, the new cyclized radical intermediate **III** in combination with the Cu(II) catalyst **II** and a molecule of carbon monoxide give an acyl-copper(III) intermediate **IV**. Finally, with a ligand-exchange procedure onto the copper(III) complex the alcohols is coordinated onto the metal center **V** to provide the desired ester after reductive elimination.

Another class of attractive substrates that can be used in copper-catalyzed alkoxycarbonylative cross-coupling reactions are alkanes due to are valuable starting materials for the preparation of aliphatic esters. These compounds rank among the most ubiquitous and versatile functional groups that are present in a wide range of high-value compounds, particularly those used in the pharmaceutical, agrochemical, or polymer industries. The latest frontier of copper-catalyzed carbonylative cross-coupling reactions is the direct

alkoxycarbonylation of the C–H bond which, given its low polarity and high bond dissociation energy, continues to be a significant challenge to accomplish.

In 2017, the Wu group disclosed a new copper-catalyzed carbonylative cross-coupling for the synthesis of aliphatic esters directly from alkanes and alcohols.[71] Noteworthy, this protocol is the first example of copper-catalyzed alkoxycarbonylation of alkanes. The authors used 10 mol% $CuCl_2$ and 1,10-phenanthroline together with DTBP (1.5 equiv.) at 20 bar CO (Scheme 53), enabling a smooth carbonylation of the C(sp^3)–H bond of alkanes to the corresponding esters in moderate-to-good yields.



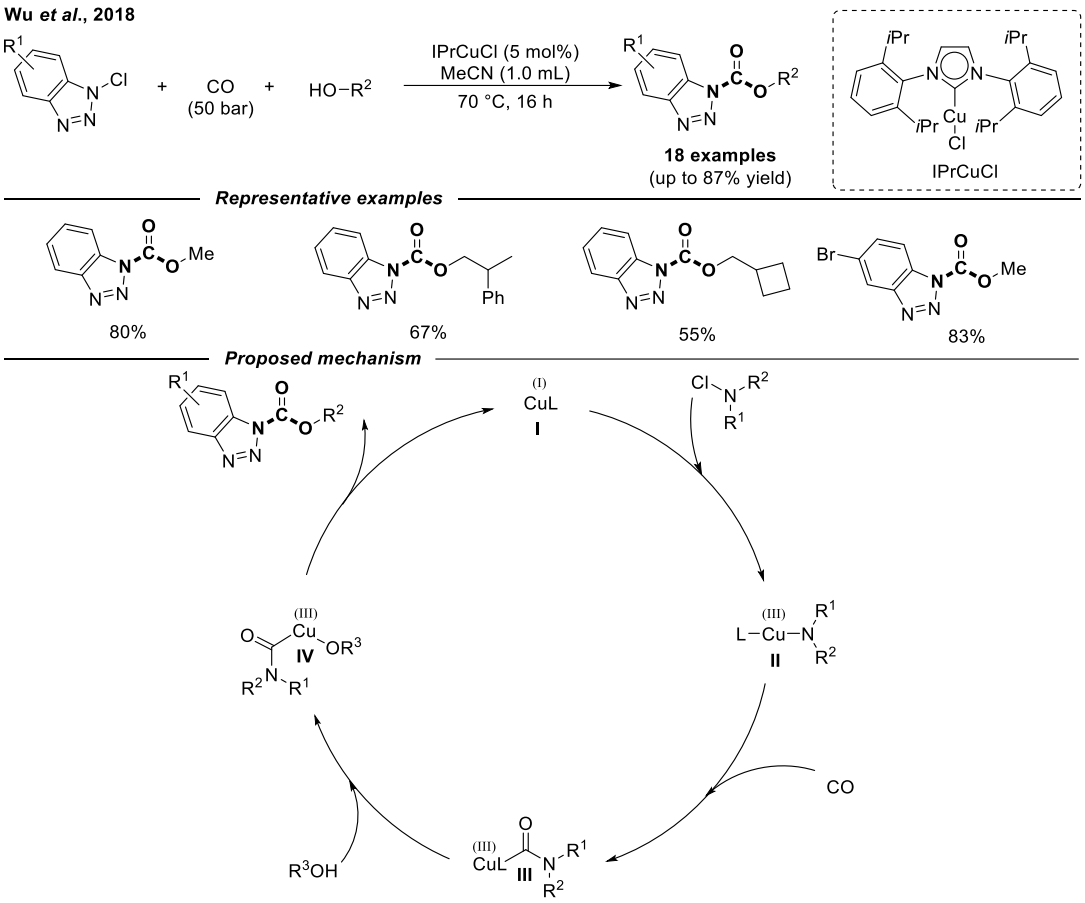
Scheme 53. Synthesis of esters via copper-catalyzed alkoxycarbonylation of alkanes.

The authors proposed that the reaction mechanism starts with an homolytic cleavage of the peroxide to generate the t*ert*-butoxy radical, which reacts with the alkane to generate the corresponding radical species **II** after hydrogen atom abstraction. At this point, the radical alkane reacts with the copper(II) species **I** to afford the alkyl copper(III) species **III**, which reacts with the alcohol to produce a copper(III) intermediate with the alkoxide coordinated onto the copper center **IV**. Thereafter, carbon monoxide is coordinated onto the metal center and inserted in the Cu–C bond to generate the intermediate **V**, which then afford the final

[71] Li, Y.; Wang, C.; Zhu, F.; Wang, Z.; Dixneuf, P.H.; Wu, X. F. *ChemSusChem*. **2017**, *10*, 1341–1345.

carbonylated product after reductive elimination. At the same time, the formed copper(I) reacts with radicals and regenerates the active copper(II) catalyst **I**.

Although, carbamates can hardly be considered as esters, their synthesis by copper-catalyzed carbonylative cross-coupling reactions will be included in this section since they are close, in terms of mechanism involved, to alkoxycarbonylations of alkyl halides. Very recently, the Wu group indeed developed a new method for the copper-catalyzed carbonylative synthesis of carbamates using *N*-chloroamines and alcohols as starting materials (Scheme 54).[72] The optimized reaction conditions were found to rely on 5 mol% of IPrCuCl at 70 °C in acetonitrile under a pressure of carbon monoxide of 50 bar. Under these reaction conditions, a library of carbamates was prepared in good yields starting from a range of alcohols and *N*-chloroamines.



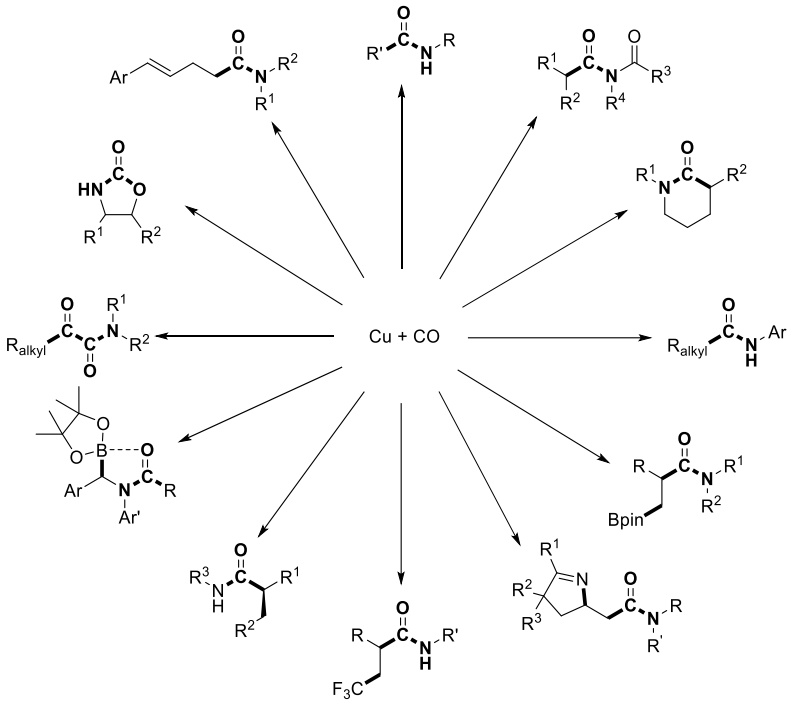
Scheme 54. Copper-catalyzed carbonylative coupling of *N*-chloroamines with alcohols: synthesis of carbamates.

Based on the previous literature and mechanistic studies, the authors proposed a possible reaction pathway that would firstly involve a dialkylaminyl copper(III) complex **II** formed by oxidative addition from the *N*-chlorodialkylamine to the IPrCuCl(I). Then, under an atmosphere of carbon monoxide, carbon monoxide is inserted into the dialkylaminyl copper species to form a carbamoyl copper intermediate **III**, which easily coordinate the alcohols to form the final intermediate **IV**, which release the product after a reductive elimination step, simultaneously regenerating the copper(I) species **I**.

[72] Yin, Z.; Wang, Z.; Wu, X. F. *Org. Biomol. Chem.* **2018**, *16*, 2643–2646.

1.5.5 Copper-catalyzed carbonylative cross-coupling reactions for the synthesis of amides

In this section, we will focus our attention to the preparation of amides, another class of important carbonyl derivatives that can also be prepared through copper-catalyzed carbonylative cross-coupling reactions. Amides are important chemicals that are widespread in pharmaceuticals, natural products, and many functional materials.[73] Hence, the development of efficient and selective protocol for new amide bonds construction is an important task for organic chemists. Among the known methodologies, aminocarbonylation is a straightforward transformation for the synthesis of amides and is an attractive alternative to the use of coupling agents.[74] However, by examining the literature, the majority of the reported carbonylation reactions for the preparation of amides are based on palladium-catalyzed carbonylative cross-coupling.[75] Lately, copper-catalyzed carbonylation to synthesize amides is emerging as an attractive area of research and great progress have been made recently. All the products that can be synthesized through the use of copper-catalyzed carbonylative cross-coupling to prepare amides and derivatives are depicted in the Scheme 55 below, and serve to give a general overview of the progress achieved in the recent years in an area of copper catalysis never explored before.

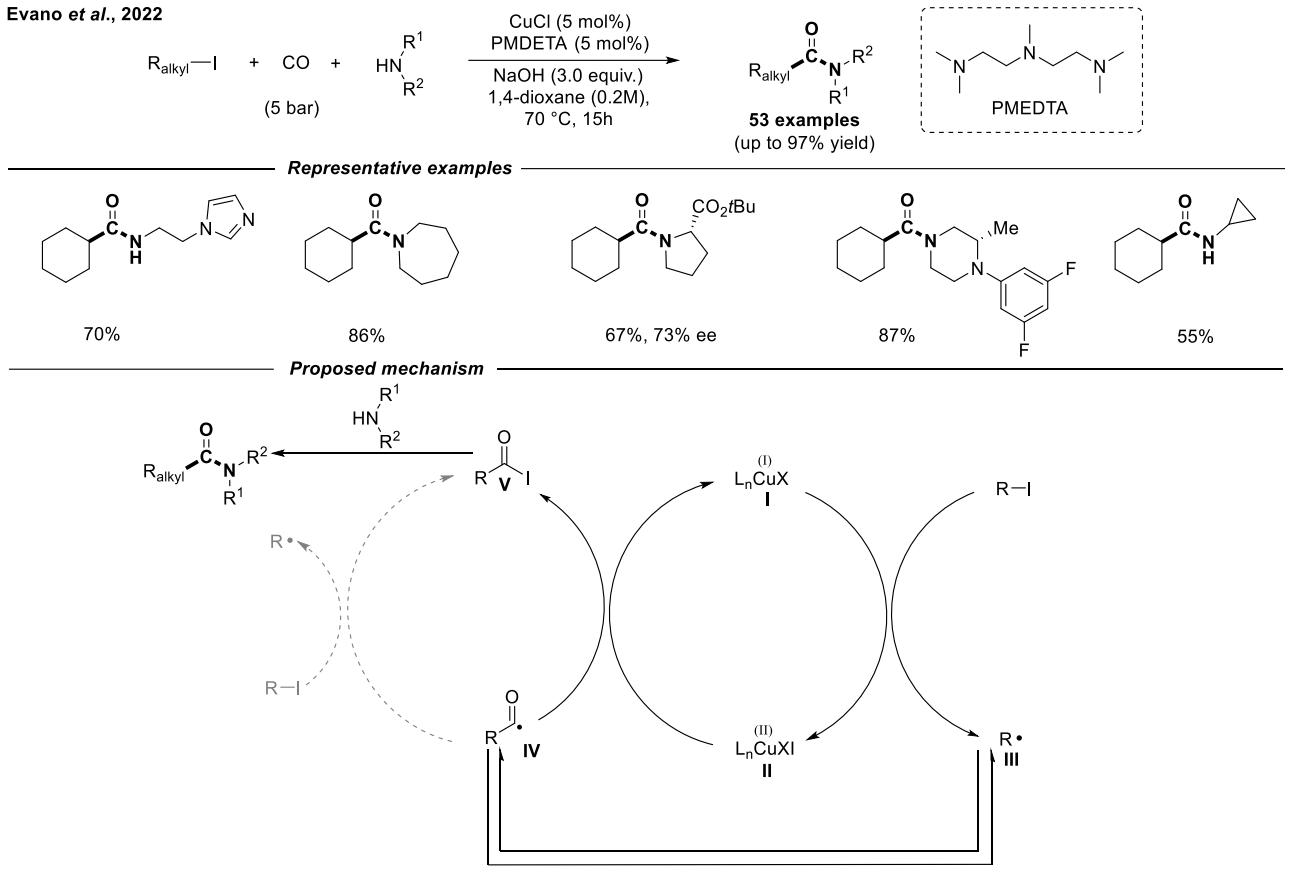


Scheme 55. Examples of compounds prepared via copper-catalyzed aminocarbonylation using carbon monoxide.

In 2022, our group described a new, efficient and broadly applicable copper-catalyzed carbonylative cross-coupling between amines and alkyl iodides for the synthesis of amides based on a catalytic system composed of copper(I) chloride and *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (PMDETA) in the presence of sodium hydroxide under a pressure of 5 bar of carbon monoxide at 70 °C for 15h (Scheme 56).[76] With this protocol, a broad range of alkyl iodides and amines can be successfully coupled to form the corresponding amides that are obtained in good moderate to good yields. Primary, secondary, tertiary alkyl iodides and all

[73] Hutchby, M. *Novel Synthetic Chemistry of Ureas and Amides*, Springer, **2013**.
[74] Beller, M.; Wu, X. F. *Transition Metal Catalyzed Carbonylation Reactions*, Springer, **2013**.
[75] Barnard, C. *Organometallics* **2008**, *27*, 5402–5422.
[76] Ling, J.; Voisine, A. B.; Journot, G.; Evano, G. *Chem. Eur. J.* **2022**, *28*.

classes of amines can be used to obtain the corresponding amides. Notably, this protocol has been useful for the carbonylation of substrates with complex structures such as L-proline ester, abietylamine and estradiol smoothly furnishing the corresponding amide derivatives. From a mechanistic point of view, a mechanism relying on a radical pathway has been proposed. The catalytic cycle is initiated by a single electron transfer from a copper(I) complex **I** to the starting alkyl halide, generating the corresponding copper(II) complex **II** and an alkyl radical species **III**. The addition of the alkyl radical **III** onto carbon monoxide yields a transient acyl radical intermediate **IV** which is oxidized by the copper(II) complex **II**, yielding a highly reactive acyl iodide **V** intermediate that reacts with the starting amine and the base to give the corresponding amide.

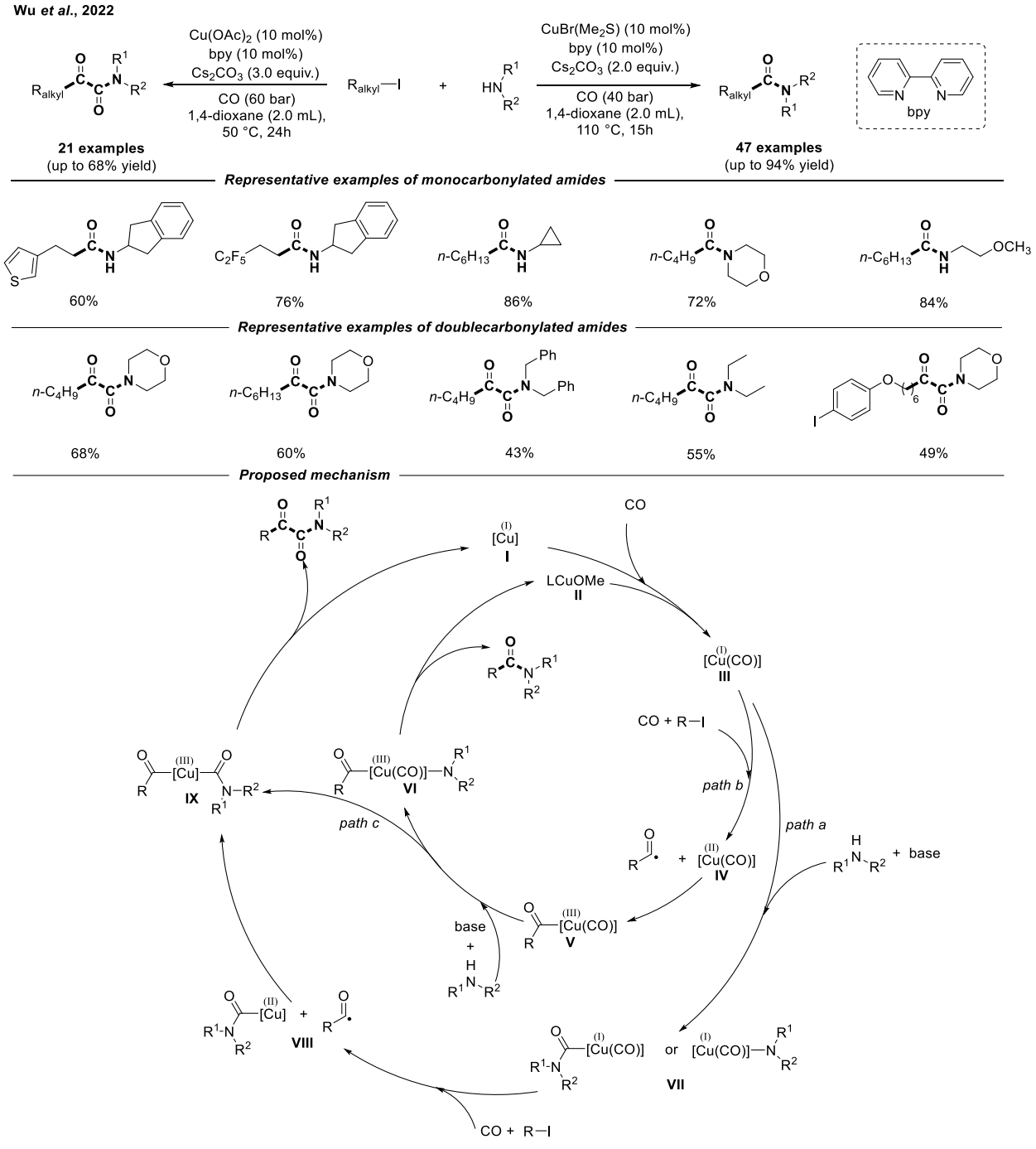


Scheme 56. Copper-catalyzed carbonylative cross-coupling of alkyl iodides and amines.

In addition to the preparation of amides also α-keto amides can be easily prepared with copper-catalyzed carbonylative cross-coupling reactions. The formation of the product of double carbonylation is obtained by the double insertion of two molecules of carbon monoxide on the starting substrate. In 2022, the Wu group developed a controllable method for the production of α-keto amides and amides from the same substrates (Scheme 57).[77] Through this protocol, it is possible to selectively promote the formation of the carbonylated product, slightly changing the reaction conditions. The ability to selectively promote the carbonylation product is possible by modifying some key parameters crucial for the course of the reaction, such as the copper source, the temperature, the pressure of carbon monoxide and the equivalents of the inorganic base. On the one hand, using 1.7 equivalent of amines, $Cu(OAc)_2$ and 2,2'-bipyridine as the catalytic system, with 3.0 equiv. of Cs_2CO_3 as base under 60 bar of CO at 50 °C for 24h, the authors reported that it was possible to obtain selectively the α-keto amides in good yield. On the other hand, by slightly altering the

[77] Wu, X. F.; Ai, H. J.; Zhao, F. *Angew. Chem. Int. Ed.* **2022**, *61*, e202200062.

reaction conditions, it was possible to change the course of the reaction and induce the insertion of a single molecule of carbon monoxide and selectively synthesize amides.



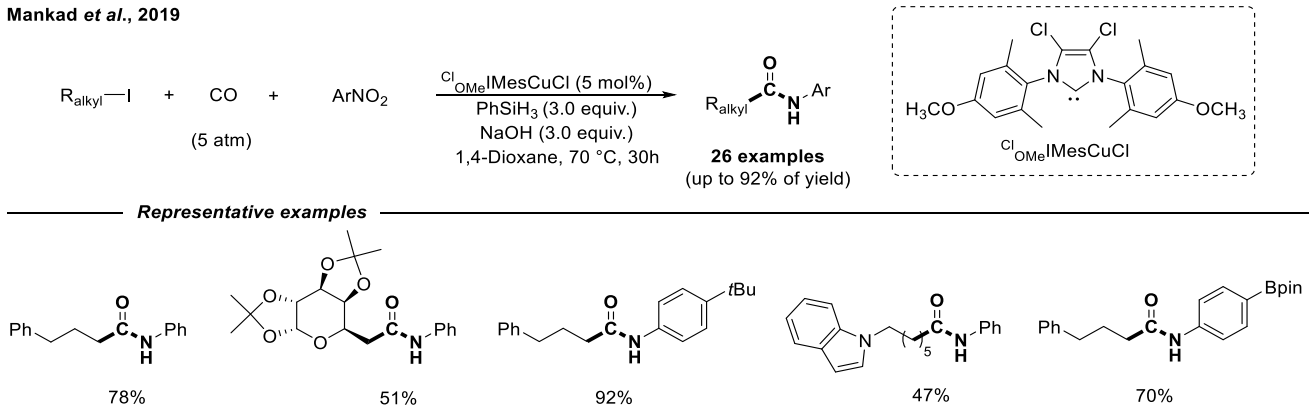
Scheme 57. Copper-catalyzed carbonylative cross-coupling of alkyl iodides and amines.

Indeed, using the CuBr·DMS as copper source, increasing the temperature at 110 °C and reducing the pressure of carbon monoxide at 40 bar, it has been possible induce selectively the formation of the single carbonylated amide, without no product of double carbonylation. For what concerns the reaction mechanism, the authors proposed that for the synthesis of amides, the catalytic cycle starts with the generation of a (carbonyl)copper complex **III** through the coordination of CO onto the copper salt **II**. Then, the copper(I) species reacts with the starting alkyl iodide by a single electron transfer (SET) to generate the corresponding copper(II) intermediate and the alkyl radical species. Further addition of the alkyl radical

species onto carbon monoxide yields a transient acyl radical intermediate **IV**. At this point, the acyl radical intermediate and the copper(II) complex **IV** evolve spontaneously to a highly reactive copper(III) complex **V**. Finally, with a ligand exchange the amine coordinates onto the copper-metal center **VI** and with a reductive elimination step, the target product of aminocarbonylation is obtained regenerating the copper complex **II** required for the next catalytic cycle.

The authors proposed that the catalytic cycle for the synthesis of α-keto amides starts with the generation of a (carbonyl)copper complex through the coordination of CO onto the copper salt **III**. Then, with a ligand exchange and the coordination of the amine onto the copper metal center a carbamoyl copper(I) intermediate **VII** is generated. At this point, the copper complex in presence of the alkyl iodide and carbon monoxide, through a single electron transfer (SET), evolve to the corresponding carbamoyl copper(II) complex and an acyl radical intermediate **VIII**. These two reaction intermediates will spontaneously evolve to a rare intermediate of carbamoyl-acyl copper(III) **IX**, which with a reductive elimination step will afford the target α-keto amide and regenerate the copper complex(I) **I**.

In continuation of their studies, the Mankad group in 2019 developed an innovative protocol for the synthesis of amides via Cu-catalyzed reductive aminocarbonylation of alkyl iodides and nitroarenes as the nitrogen source (Scheme 58).[78] In this transformation, the copper catalyst plays a double role mediating both the carbonylation of alkyl iodides and the reduction of nitroarenes, to afford *in-situ* anilines and acyl iodides, which spontaneously react together to generate the desired amide. The optimized reaction conditions are based on the use of 5 mol% of $^{Cl}_{OMe}$IMesCuCl, 3.0 equiv. of NaOH and $PhSiH_3$ under a pressure of CO of 5 atm in 1,4-dioxane at 70 °C for 30h. Using this protocol, primary, secondary and tertiary alkyl iodides underwent the reductive carbonylation with full tolerance towards sensible functional groups such as ester, nitrile, trifluoromethyl and ether as well as heterocyclic groups such as indole and furan. Good results were also obtained with a variation of the nitroarenes partner. Good functional group tolerance was identified toward halides, thioethers, protected phenols and boronic esters. Although several mechanistic experiments were carried out, no proposed mechanism has however been described in the original publication.

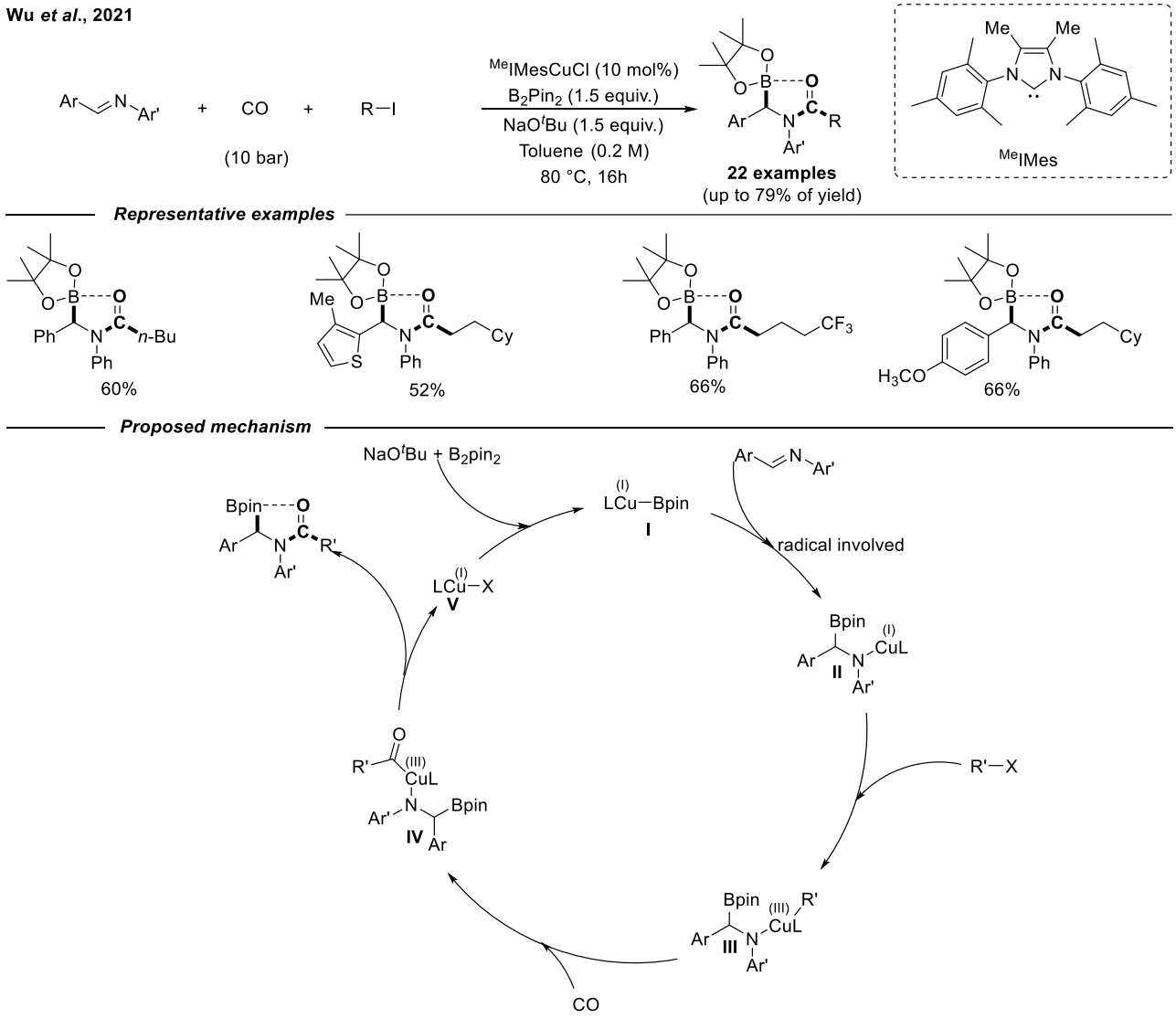


Scheme 58. Copper-catalyzed reductive aminocarbonylation of alkyl iodides with nitroarenes.

The Wu group has exploited the knowledge gained for the preparation of amides via copper-catalyzed carbonylative cross-coupling to prepare more functionalized and challenging carbonyl compounds, such as α-boryl amides (Scheme 59).[79] These bifunctional substrates serve as building blocks for the synthesis of more complex molecules and can be used for the formation of new carbon−carbon bonds through Suzuki

[78] Zhao, S.; Mankad, N. P. *Org. Lett.* **2019**, *21*, 10106–10110.
[79] Wu, X. F.; Wu, F. P. *Angew. Chem. Int. Ed*. **2021**, *60*, 695–700.

reactions. The α-boryl amides have been prepared in good yields via a copper-catalyzed borocarbonylation of imines and alkyl iodides under a low pressure of carbon monoxide (10 bar). The catalytic system consists of 10 mol% of ^{Me}IMesCuCl in the presence of B_2pin_2 (1.5 equiv.) and NaO^{t}Bu (1.5 equiv.). The scope of the reaction is wide and with a good functional group tolerance. The proposed reaction pathway starts with the generation of a LCu-Bpin complex **I** generated from CuCl, B_2pin_2 and NaO^{t}Bu which inserts into the C=N bond of imine to furnish α-boryl amido-copper complex **II**. Later on, the alkyl iodide reacts with the α-boryl amido-copper complex to generate a copper (III) complex **III**. Afterwards, carbon monoxide coordinates onto the copper metal center to afford an acyl-copper(III) intermediate **IV**. The final step is a reductive elimination which release the α-boryl amide as final product and the catalyst **V** (Scheme 59).

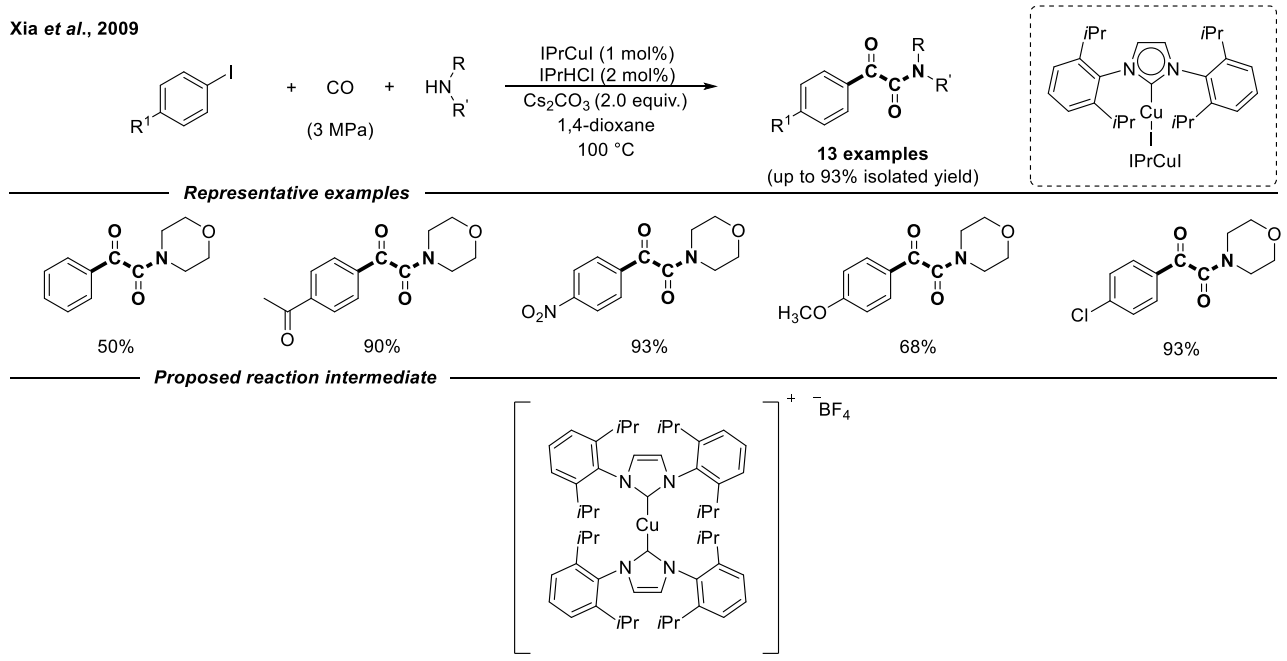


Scheme 59. Copper-catalyzed carbonylative synthesis of α-boryl amides from imines and alkyl iodides.

In addition to alkyl iodides, copper-catalyzed aminocarbonylative cross-coupling reactions can also be performed on aryl iodides as starting materials for the preparation of aromatic amides, however it is import to note that the number of procedures available in the literature is quite limited since are more difficult substrates to activate. In 2009, the Xia group developed a IPrCuI catalyzed double carbonylation of aryl iodides and secondary amines under 40 atm of carbon monoxide (Scheme 60).[80] The catalytic system

[80] Liu, J.; Zhang, R.; Wang, S.; Sun, W.; Xia, C. *Org. Lett.* **2009**, *11*, 1321–1324.

consists of IPrCuI and IPr·HCl, in presence of Cs_2CO_3 as base. Apparently, the precursor of the copper complex, IPr·HCl, is crucial for the double carbonylation. No product of mono-carbonylation has been described and only 2% of the product was obtained when IPrCuI was used as catalyst, while a combination of IPrCuI and IPr·HCl afforded the product of double carbonylation product in excellent yield under the standard reaction conditions.



Scheme 60. Copper catalyzed double carbonylation of aryl iodides and amines with IPrCuI/IPrHCl.

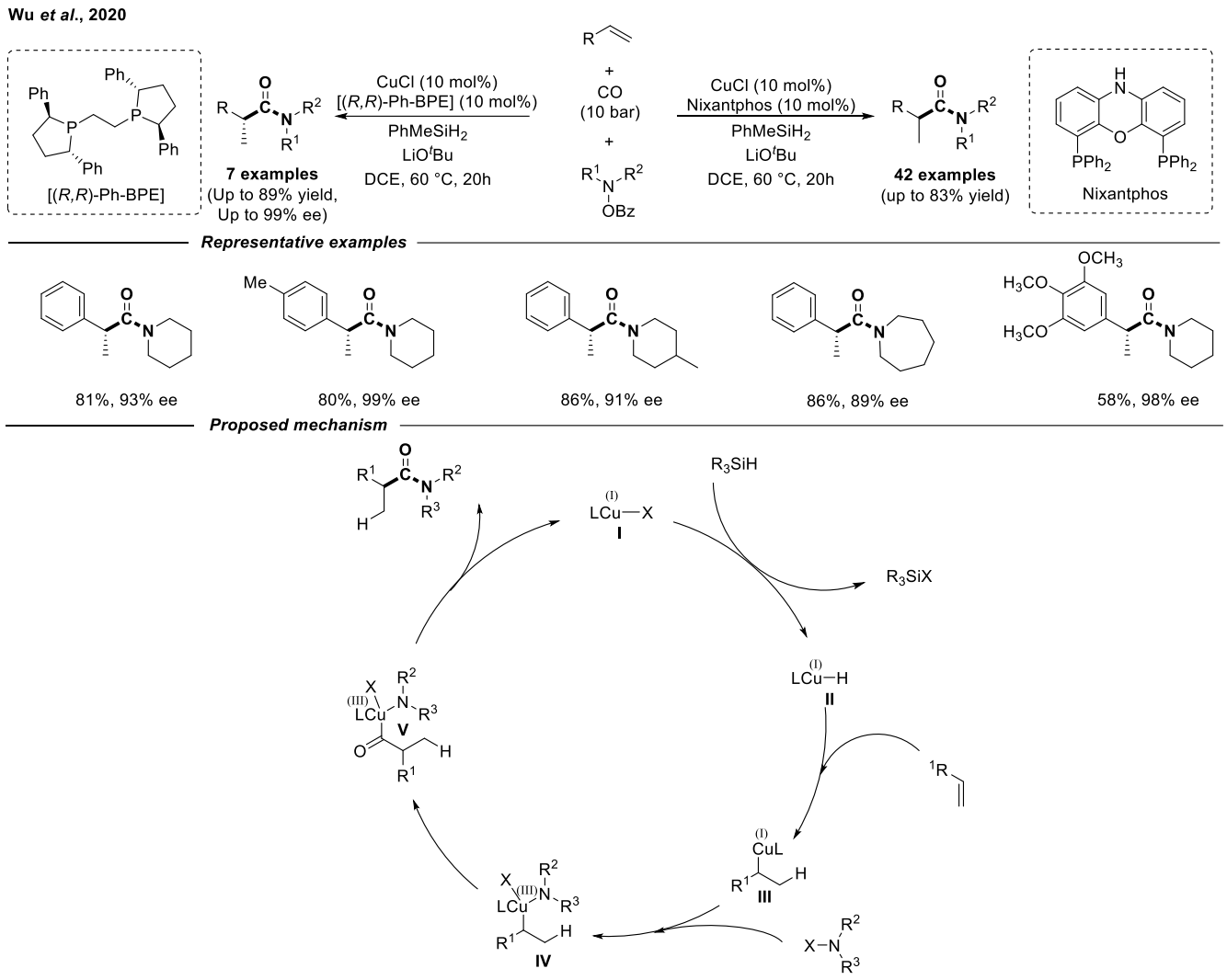
More probably, the active species is a *bis*-carbene copper complex $[Cu(IPr)_2]BF_4$ which is formed *in-situ* when supplementary NHC precursor is added in the catalytic system. Unfortunately, no reaction mechanism has been proposed by the authors.

In addition to aryl iodides, copper-catalyzed aminocarbonylative cross-coupling reactions can also be performed on alkenes as starting materials. Generally, for these substrates is required the activation of the double bond by hydrocupration, hydroboration or radical reactions as has been done in the following examples. Clearly, using olefins as starting materials it is possible to perform a double functionalization of the carbon atoms of the double bond allowing the preparation of compounds of high synthetic value.

Very recently, the Wu group has developed a novel carbonylative hydroamidation of vinylarenes with hydroxylamine derivatives to synthetize branched amides (Scheme 61).[81] Using 10 mol% of CuCl and 10 mol% of Nixantphos under a low pressure of carbon monoxide (10 bar), the reaction proceeds under mild reaction conditions and tolerates a variety of functional groups. Only traces of the desired products could be observed when using α-substituted styrene and β-substituted styrene as substrates. Furthermore, using (*R,R*)-Ph-BPE as a chiral bidentate phosphine ligand, this protocol could yield the corresponding α-chiral amides in high yields and good enantioselectivities (89-99% ee). The catalytic cycle proposed by the authors starts with the formation of a copper hydride catalyst LCuH **II** in the presence of silane and LCuX **I**. Subsequently, the copper hydride **II** follows the insertion of the olefin to form an alkyl copper intermediate **III**. At this point, the oxidative addition of the hydroxylamine derivative takes place to afford the species **IV**. Then, the CO insertion

[81] Yuan, Y.; Wu, F. P.; Schuenemann, C.; Holz, J.; Kamer, P. C.; Wu, X. F. *Angew. Chem. Int. Ed.* **2020**, *59*, 22441–22445.

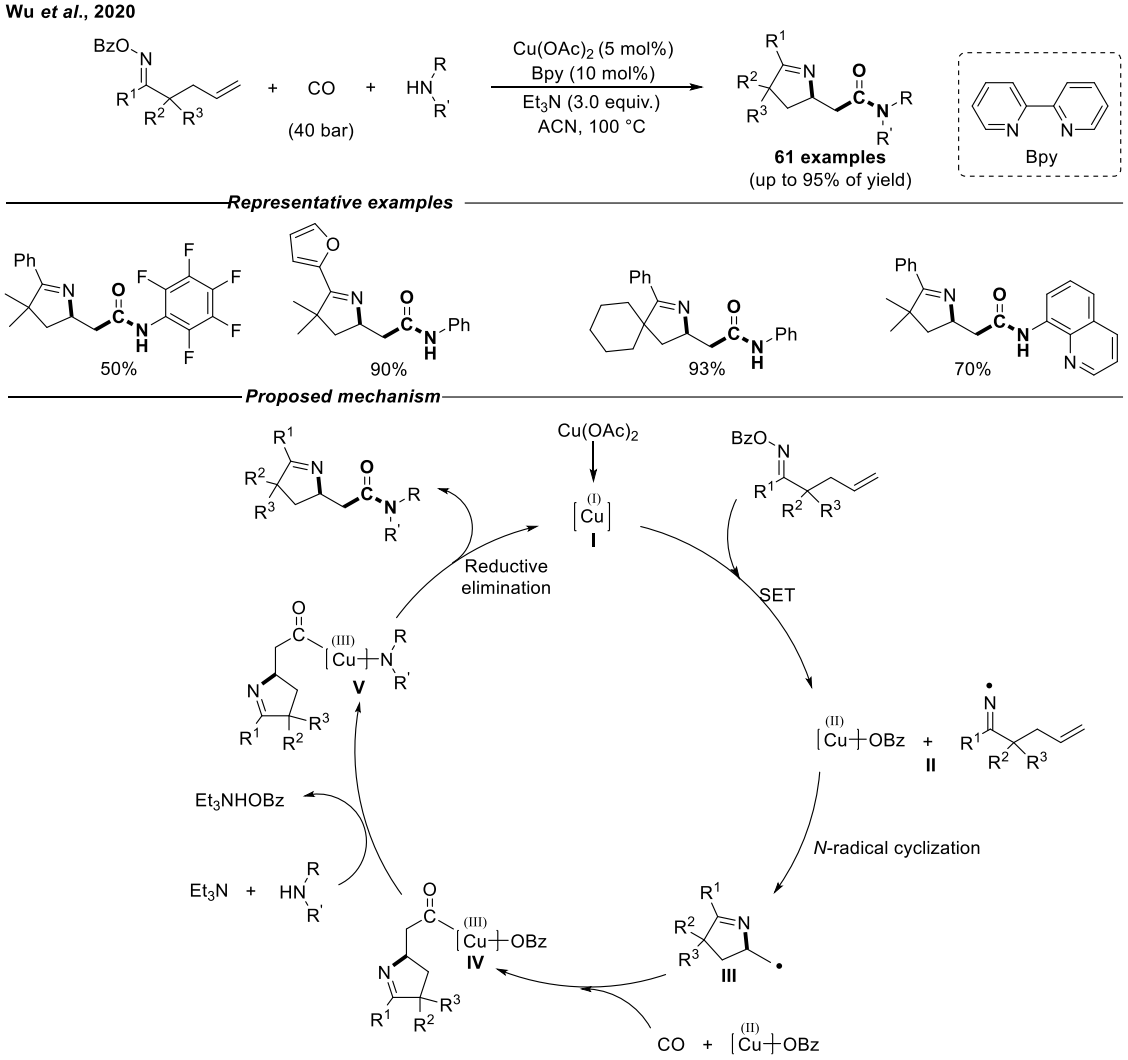
generates the acyl copper intermediate **V**. Finally, the reductive elimination releases the desired branched amides and regenerates the copper(I) catalyst **I**.



Scheme 61. Copper-catalyzed carbonylative hydroamidation of styrenes to branched amides.

In 2020, the Wu group reported a novel a copper-catalyzed carbonylative cyclization for preparing pyrrolidine-containing amides from γ, δ-unsaturated aromatic oxime esters and amines using a simple catalytic systems composed of 5 mol% of $Cu(OAc)_2$ with 10 mol% of BPy under a pressure of carbon monoxide of 40 bar (Scheme 62).[82] Under these conditions, γ, δ-unsaturated aromatic oxime esters were smoothly cyclized with broad functional group compatibility and good yields. The proposed reaction mechanism for this transformation relies on a Cu(I)-induced single electron reduction of γ,δ-unsaturated aromatic oxime esters to form a Cu(II) species **II** and an iminyl radical, which can undergo an intramolecular radical cyclization to obtain a terminal carbon radical **III**. Then, the alkyl radical reacts with carbon monoxide and generate an acyl-copper(III) intermediate **IV**. Subsequently, a ligand exchange takes place and the amine is coordinated onto the copper complex **V** to finally furnish the desired target amides with a reductive elimination that convert Cu(III) to Cu(I) regenerating the catalyst **I**.

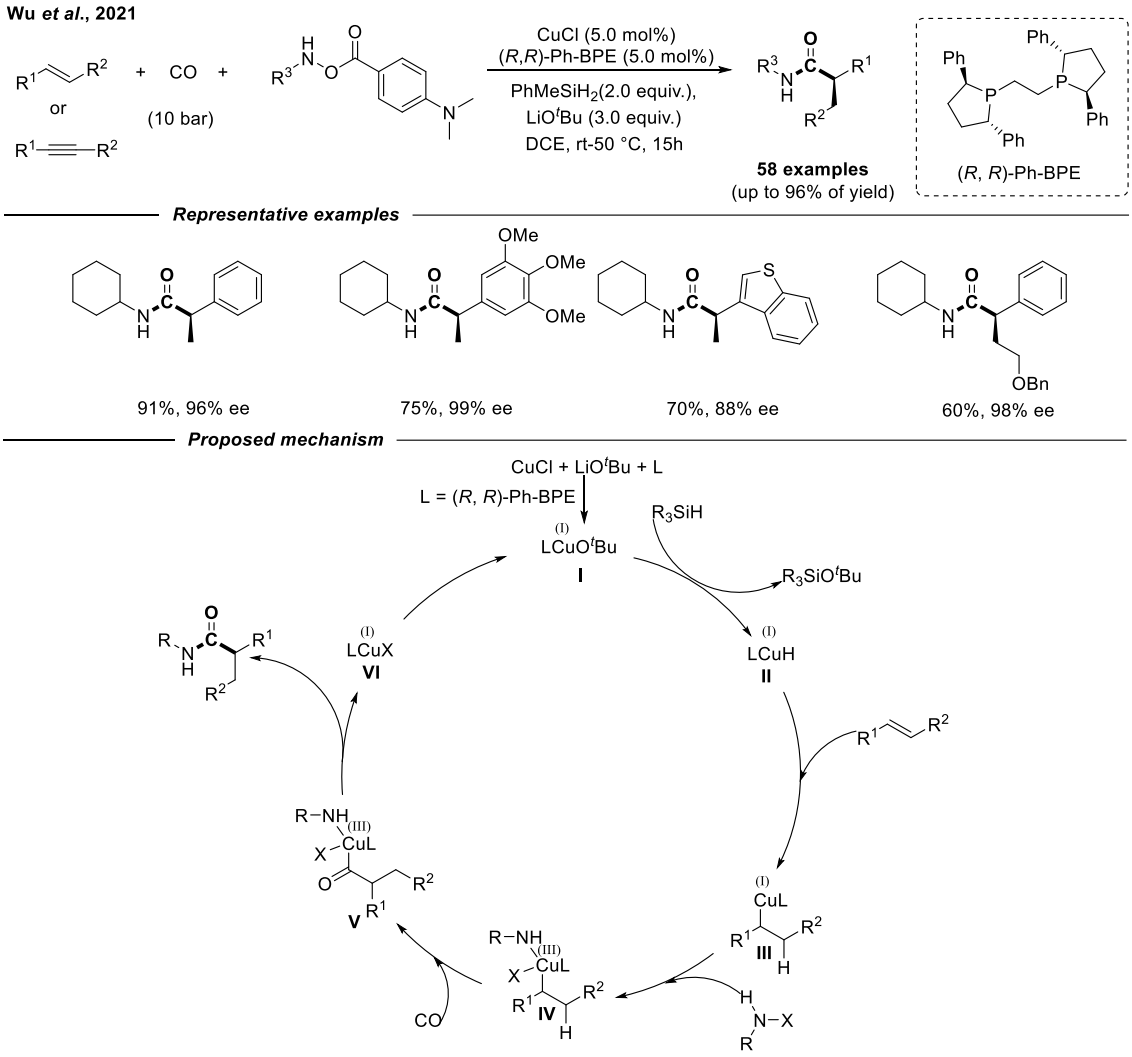
[82] Wu, X.; Ai, H.; Zhang, Y. *Org. Chem. Front.* **2020**, *7*, 2986–2990.



Scheme 62. Copper-catalyzed carbonylative synthesis of pyrrolidine containing amides.

Subsequently, the Wu group developed a new advanced protocol for the enantioselective copper-catalyzed hydroaminocarbonylation of alkenes with electrophilic hydroxylamines possessing a 4-(dimethylamino)benzoate group (Scheme 63).[83] This method is useful to directly convert styrenes to α-chiral secondary amides in good yields with excellent enantioselectivities (up to >99% ee). The catalytic system consists of 5 mol% of CuCl with 5 mol% of (*R*, *R*)- Ph-BPE as ligand in presence of 2.0 equiv. of $PhMeSiH_2$ and 3.0 equiv. of LiO^tBu under a low pressure of carbon monoxide (10 bar). This method has also been extended to alkynes to give the corresponding acrylamides. The proposed reaction mechanism consists with the formation of LCuO^tBu **I** followed by reaction with $PhMeSiH_2$ to generate a copper hydride intermediate **II**, LCu-H. At this point, the copper hydride intermediate **II** reacts with the alkene to furnish an alkyl-copper species **III**. Then, the oxidative addition with the electrophilic hydroxylamine takes place to afford an alkyl-amido copper(III) complex **IV** which undergoes carbon monoxide insertion to give the corresponding acyl-amido copper(III) species **V**, thereafter the reductive elimination step takes place with the release of the product and of the catalyst LCu-X **I**. Finally, the reaction of the intermediate **I** with LiO^tBu regenerates the catalyst LCuO^tBu.

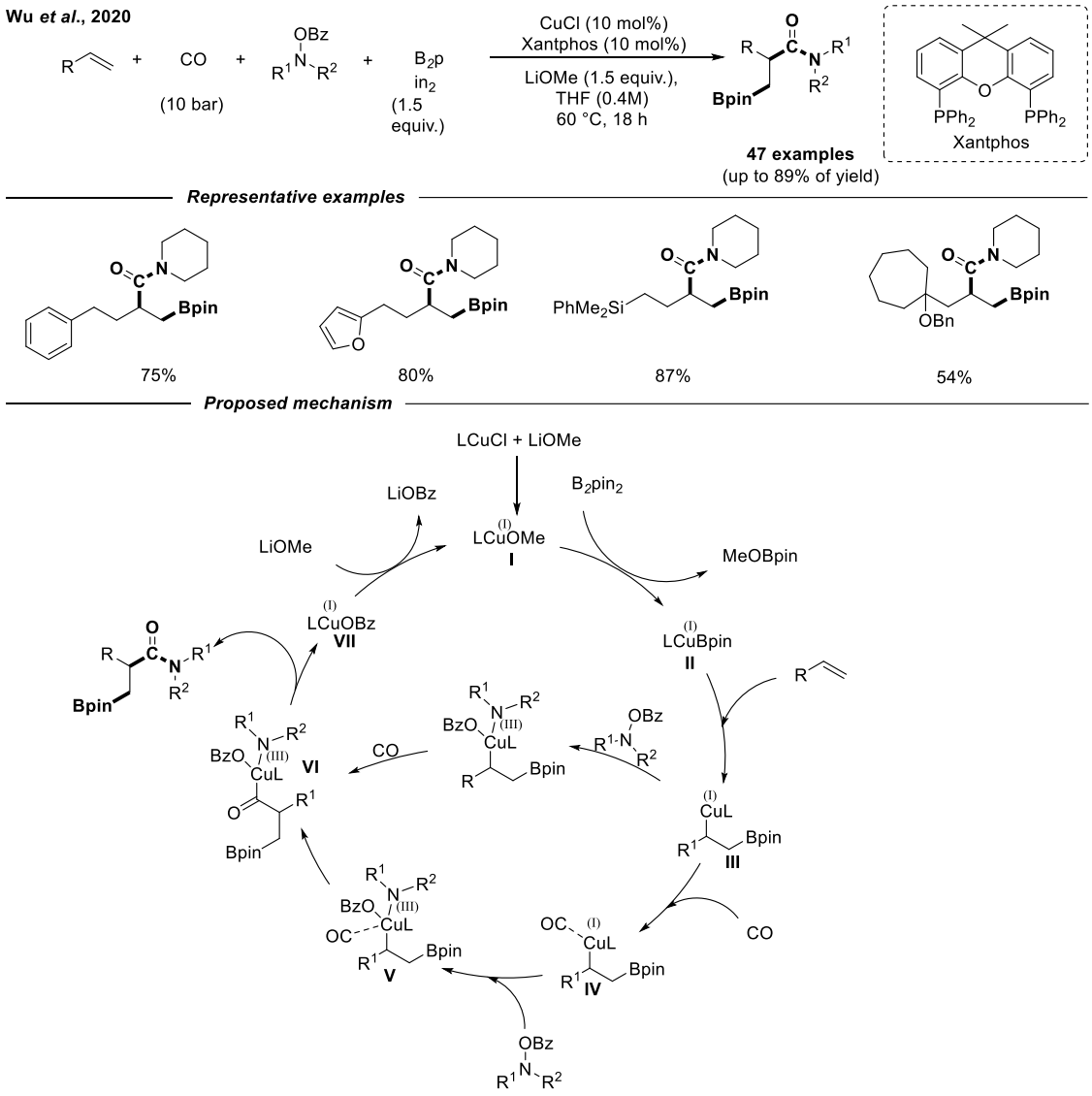
[83] Yuan, Y.; Zhao, F.; Wu, X. F. *Chem. Sci*. **2021**, *12*, 12676–12681.



Scheme 63. Copper-catalyzed enantioselective carbonylation toward α-chiral secondary amides.

In 2020, the Wu group reported a copper-catalyzed carbonylative borylamidation of olefins with hydroxylamines as electrophiles to give the corresponding amides using a combination of 10 mol% of CuCl/Xantphos under 10 bar of carbon monoxide and 1.5 equiv. of B_2pin_2 (Scheme 64).[84] With this protocol olefins were smoothly converted to the desired β-boryl amides with excellent yields. Under the standard conditions, the scope of the methodology has shown great applicability and compatibility with different functional group, including esters, sulphides, ethers and heterocyclic moieties. The suggested reaction pathway starts with the formation of a LCuBpin complex **II** which undergoes insertion into the alkene to generates the β-borylalkylcopper **III** which coordinate carbon monoxide **IV**. At this point, an oxidative addition with hydroxylamine forms an alkyl-copper(III) intermediate **V** which evolve to acyl-copper(III) **VI** through the CO-insertion into the C-Cu bond. Finally, the target β-boryl amide is obtained with a reductive elimination which regenerates the copper complex **VII** required for the next catalytic cycle.

[84] Wu, F. P.; Holz, J.; Yuan, Y.; Xiao, F. W. *CCS Chem*. **2020**, *2*, 2643–2654.

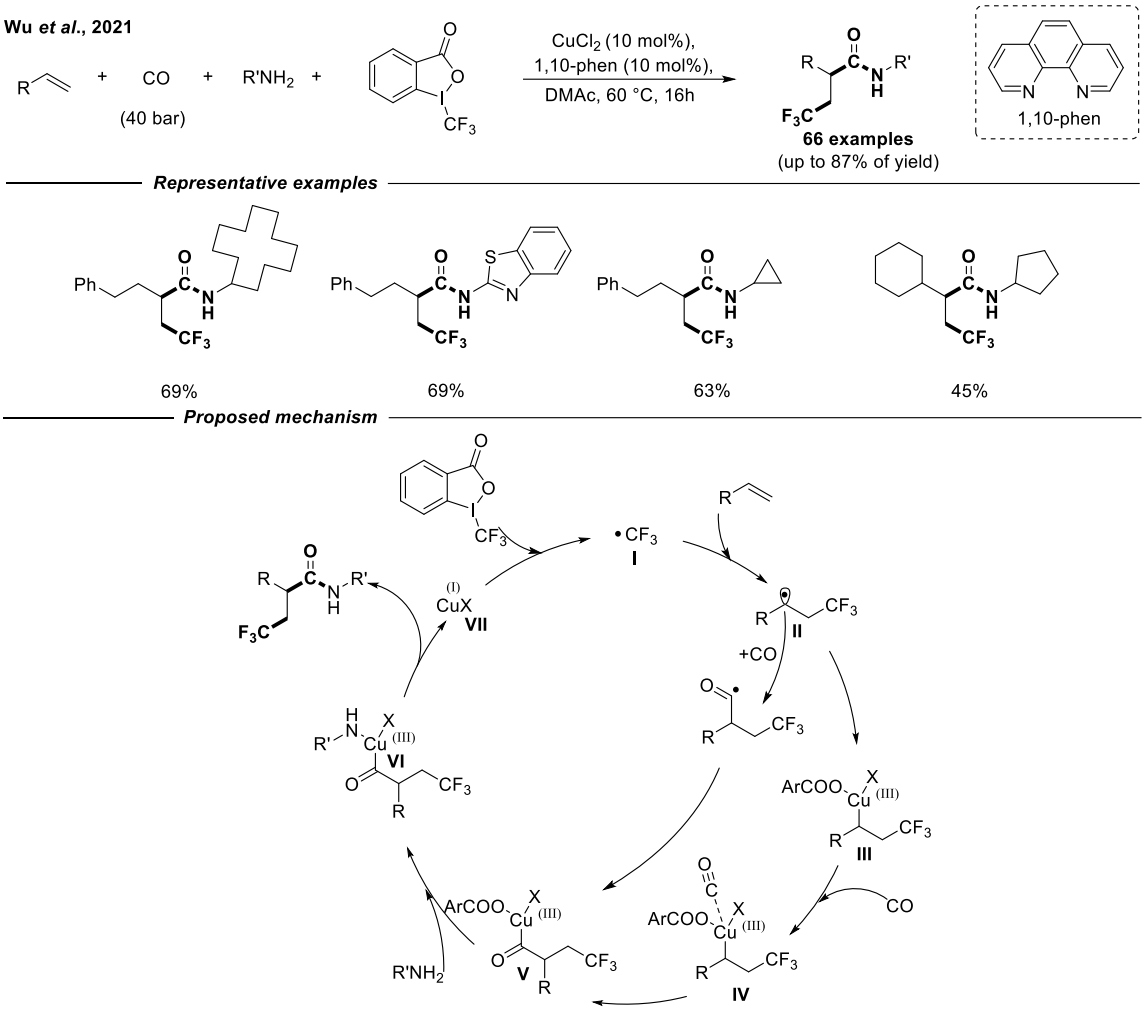


Scheme 64. Copper-catalyzed carbonylative synthesis of β-boryl amides via boroamidation of alkenes.

Based on the previous study, the Wu group next reported a novel copper-catalyzed carbonylative trifluoromethylation of unactivated alkenes to access functionalized carbonylated product as β-trifluoromethylated amides, esters and acids using the Togni reagent.[85] With this protocol β-trifluoromethylated carboxylic acid derivatives can be prepared with a catalytic system quite simple, composed of 10 mol% of $CuCl_2$ and 10 mol% of 1, 10-phenantroline in DMAc at 60 °C for 16h (Scheme 65).

The scope of the reaction is broad and a wide range of compounds has been prepared with excellent yields and good functional group tolerance such as nitriles, halogens, esters, phenols and heterocyclic moieties. Notably, this transformation works also with ethylene gas, which is an important building block in chemical industry.

[85] Wu, F. P.; Yuan, Y.; Wu, X. F. *Angew. Chem. Int. Ed.* **2021**, *60*, 25787–25792.

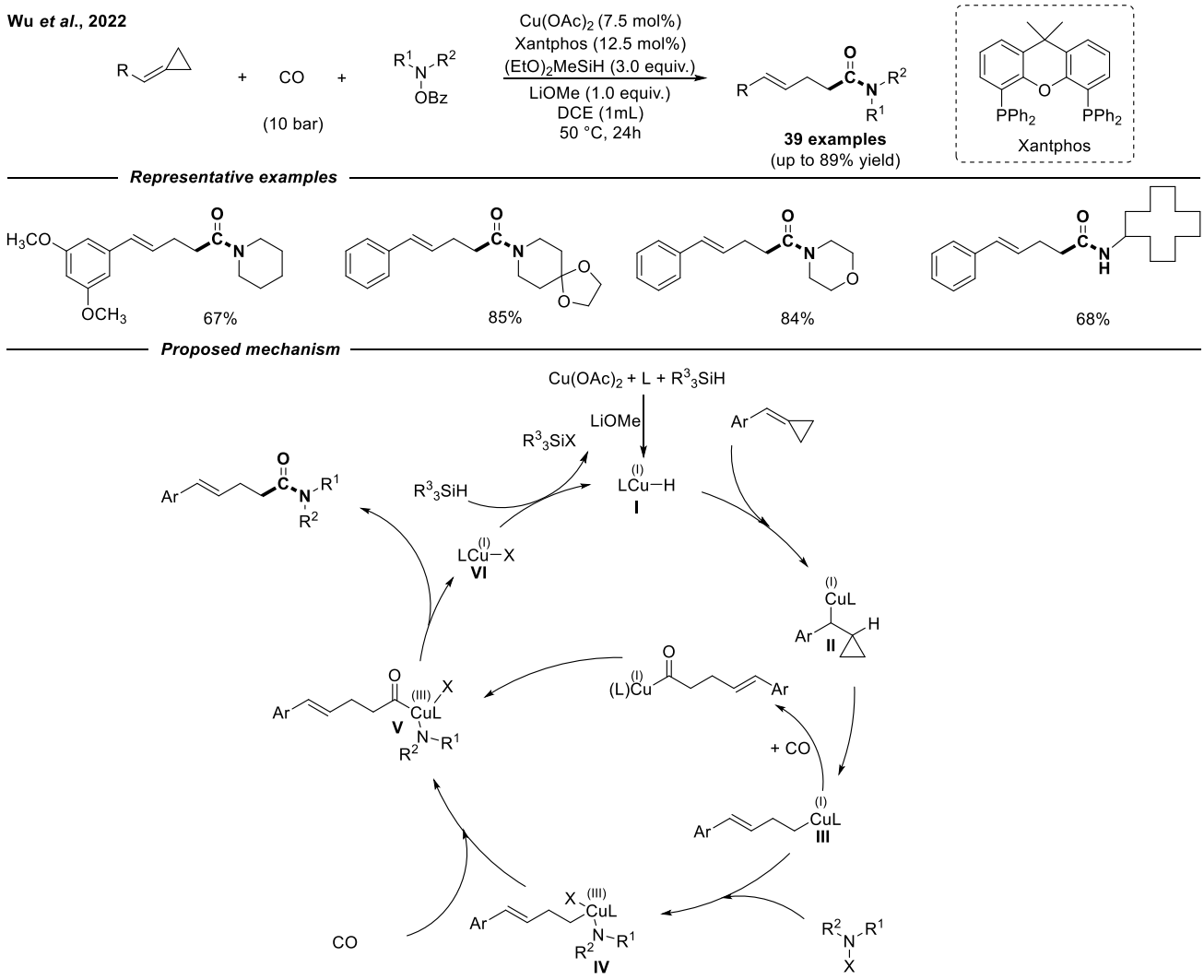


Scheme 65. Copper-catalyzed carbonylative trifluoromethylation of alkenes for the synthesis of carboxylic acid derivatives.

The mechanism proposed by the authors to address this carbonylative trifluoromethylation starts with the reaction between the copper catalyst and the Togni's reagent to generate a CF_3• radical **I** and a Cu(II) species. Then, the CF_3• radical **I** reacts with an alkene to form a new alkyl radical species **II**. At this point the Cu(II) species react with the alkyl radical **II** to furnish with an oxidation an alkyl-copper(III) intermediate **III**. Herein, after carbon monoxide coordination **IV** and insertion into the C–Cu bond an electrophilic acyl-copper(III) complex is formed **V**. Then, a ligand exchange takes place and with a reductive elimination step the final product is obtained regenerating the Cu(I) catalyst **VII** for the next catalytic cycle.

Recently, the Wu group reported in 2022 a novel protocol for the copper-catalyzed hydroaminocarbonylation of benzylidenecyclopropanes for the synthesis of γ,δ-unsaturated amides (Scheme 66).[86] With this synthetic strategy is installed onto the final product an amidic group and a double bond, which may be subject to further functionalization. This protocol requires 7.5 mol% of $Cu(OAc)_2$ and 12.5 mol% of Xantphos in presence of an excess of $(EtO)_2MeSiH$ as hydride source under a low pressure of carbon monoxide and mild reaction conditions.

[86] Geng, H. Q.; Wu, X. F. *Chem. Commun.* **2022**, *58*, 6534–6537.

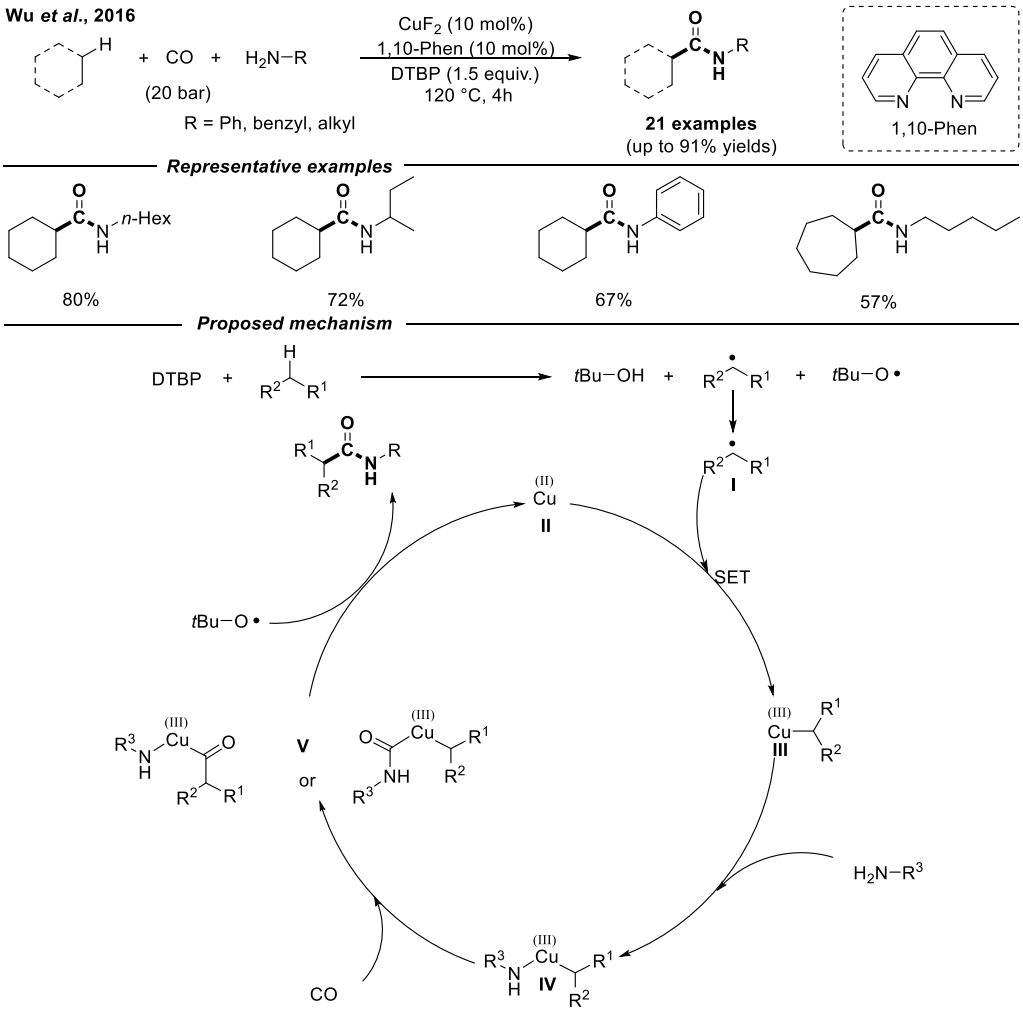


Scheme 66. Copper-catalyzed hydroaminocarbonylation of benzylidenecyclopropanes for the synthesis of γ, δ-unsaturated amides.

This transformation is highly stereoselective and compatible with a broad range of functional groups. A plausible mechanism for this copper-catalyzed carbonylation starts with the generation *in-situ* of a copper hydride species **I** through the reaction between $(EtO)_2MeSiH$ and copper acetate. Then, the copper hydride **I** attacks the benzylidenecyclopropanes with a reaction of hydrocupration to generate an alkyl-copper intermediate **II**. At this point, the highly reactive intermediate **II** follow a ring-opening of the cyclopropane moiety to generate a linear alkyl-copper species **III**, which is prone to undergo to oxidative addition in presence of a protected hydroxylamines, which is the electrophilic partner of the reaction. Finally, the alkyl-copper(III) complex **IV** undergoes CO insertion to give the corresponding acyl-copper(III) species **V**, before the reductive elimination step and the release of the final product.

Another class of attractive substrates that can be employed in copper-catalyzed aminocarbonylative cross-coupling reactions are alkanes since are useful starting materials for the preparation of aliphatic amides. Indeed, the latest frontier of copper-catalyzed carbonylative cross-coupling reactions is the direct aminocarbonylation of the C–H bond, which still remains an important challenge to achieve due to its high bond dissociation energy and low polarity.

In 2016, the Wu group reported an interesting on copper-catalyzed aminocarbonylation of alkanes for the synthesis of aliphatic and aromatic amides (Scheme 67).[87] With 10 mol% of CuF_2 and 10 mol% of 1,10-phenantroline in presence of 1.5 equiv. of DTBP under 20 bar of CO at 120 °C, C(sp^3)–H bond of alkanes can be selectively carbonylated to obtain the corresponding amides in good yields. With this protocol linear and branched, aliphatic, aromatic and benzylic amines can be smoothly coupled with alkanes to afford the corresponding amides in good yields. To investigated the reaction mechanism, experiments with TEMPO were carried out and no formation of the desired amide product can be obtained, with the exception of an adduct between the alkene and TEMPO found in GC-MS analysis. Based on the results collected, the postulated reaction mechanism starts with a copper(II)-catalyzed or thermal homolytic cleavage of a peroxide to generate the *tert*-butoxy radical, which reacts with the alkane to give an alkyl radical **I** via radical hydrogen abstraction.

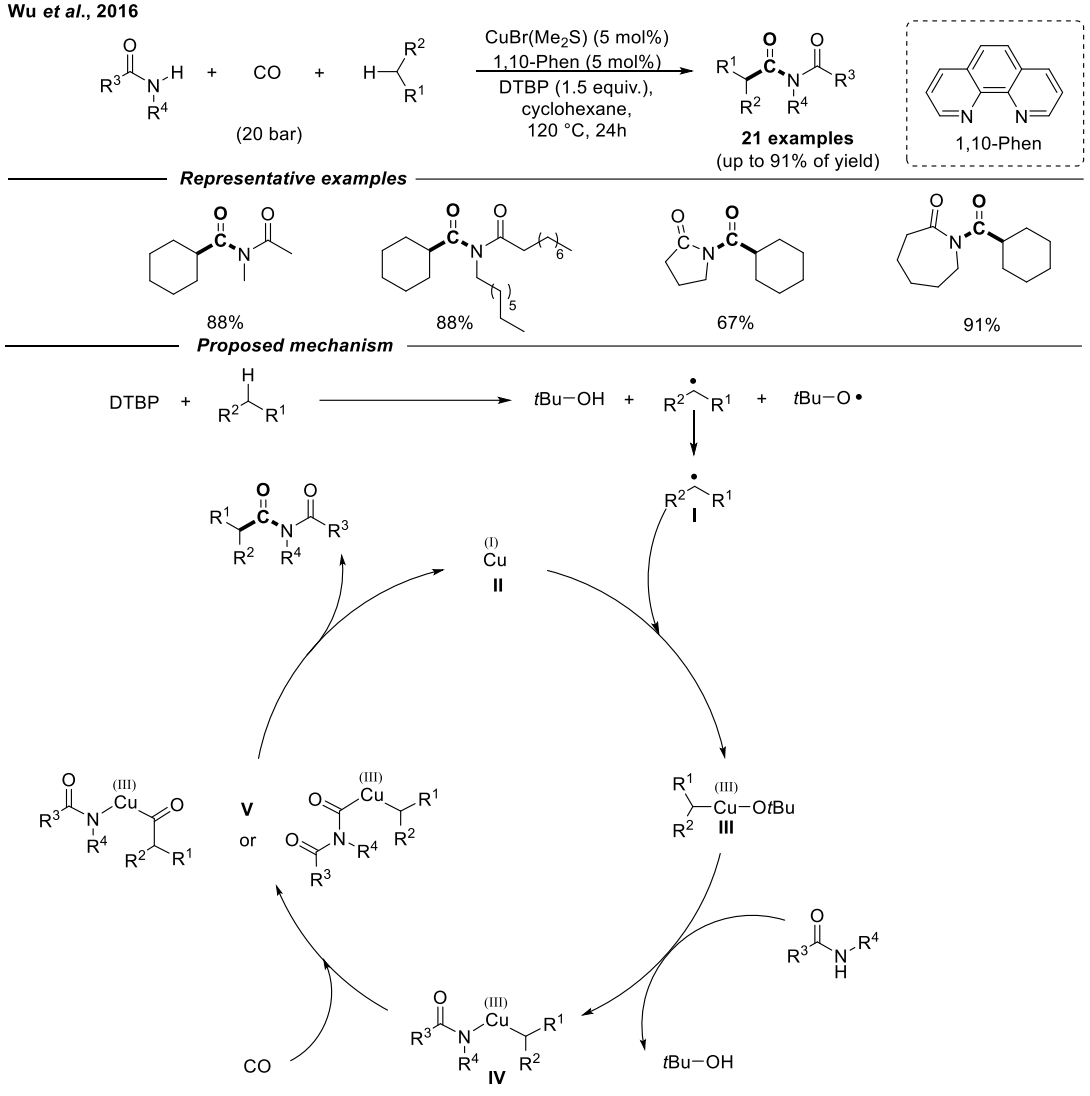


Scheme 67. Copper-catalyzed carbonylative synthesis of amides from alkanes and amines via C(sp^3)-H bond activation.

Thus, the alkyl radical reacts with the copper(II) complex **II** to furnish with a single electron transfer (SET) a Cu(III) intermediate **III**, which after ligand exchange and amine coordination onto the metal center **IV** is ready to insert carbon monoxide in the C–Cu bond to afford an acyl-Cu(III) complex **V**. Finally, the product is obtained with a reductive elimination, along with a Cu(I) intermediate, which is oxidized by the ^{t}BuO• radical to re-generate the active Cu(II) species **II** for the next catalytic cycle.

[87] Li, Y.; Zhu, F.; Wang, Z. *ACS Catal.* **2016**, *6*, 5561–5564.

In the same year, the Wu group described an extension of this method where the amine partner has been replaced with less nucleophilic amides. Indeed, the authors described the first copper-catalyzed carbonylative C(sp^3)–H activation of alkanes with amides to prepare imides.[88] This method uses 5 mol% of CuBr(Me_2S) and 5 mol% of 1,10-phenantroline together with 1.5 equiv. of DTBP under 20 bar of pressure of carbon monoxide at 120 °C (Scheme 68). For what concern the scope of the reaction, a series of imides were smoothly synthesized in good yields without discrimination between linear, branched, cyclic and acyclic amides.

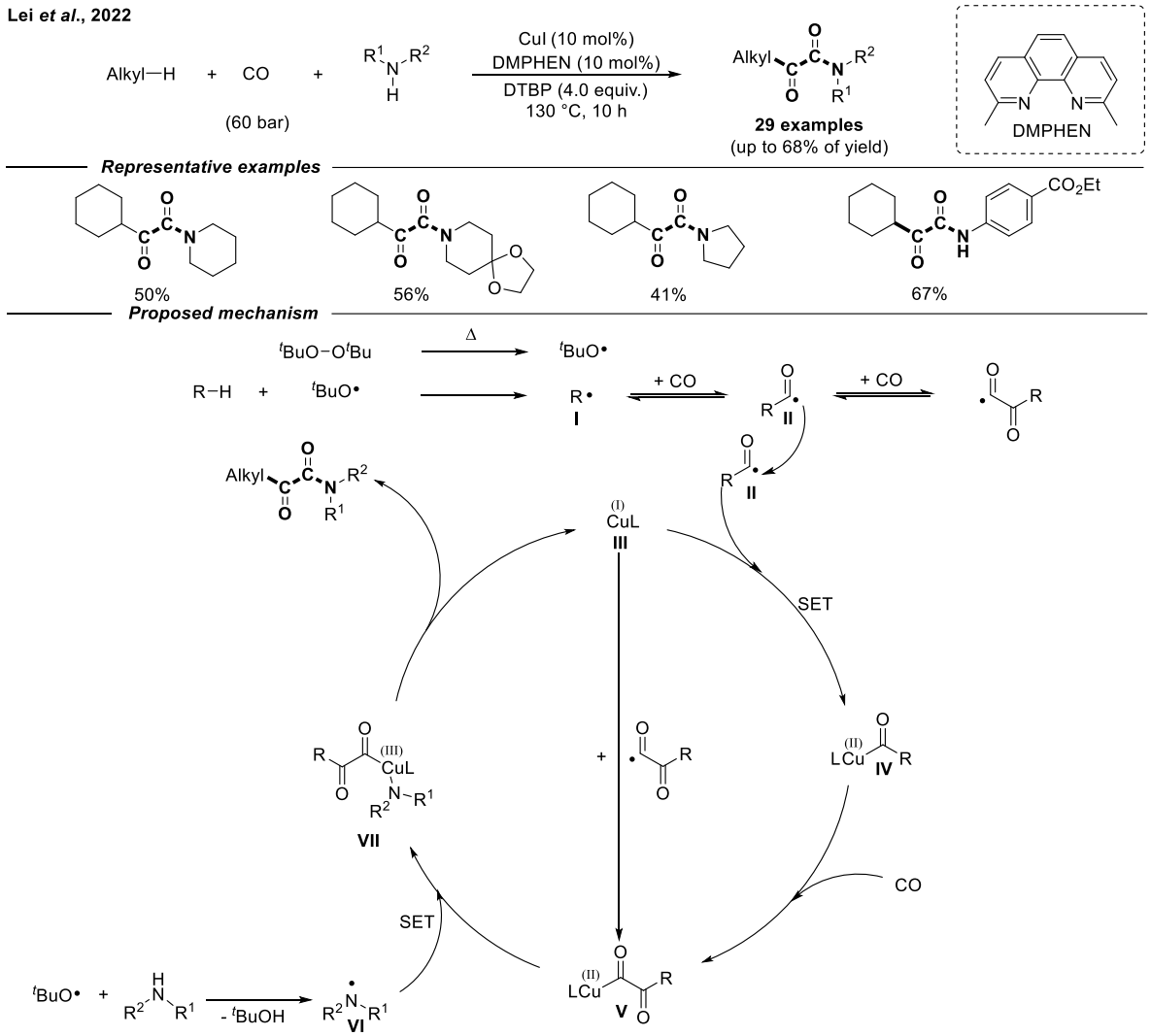


Scheme 68. Copper-catalyzed carbonylative coupling of alkanes and amides for the imide synthesis.

As in the previous case, the reaction starts with the homolytic cleavage of the peroxide to generate a *tert*-butoxy radical, which reacts with the alkane to generate an alkyl radical **I**. Then, an oxidation of the Cu(I) complex gives the Cu(III)-alkyl intermediate **III** which, with a ligand-exchange coordinate the amide at the nitrogen, to afford the intermediate **IV**. Finally, the CO insertion in the Cu–C bond occurs to generate an acyl-copper(III) complex **V**, which then affords the product of carbonylation after reductive elimination.

[88] Wu, X.F.; Wang, Z.; Zhu, F.; Dong, K.; Li, Y. *Angew. Chem. Int. Ed*. **2016**, *55*, 7227–7230.

In 2022, the Lei group reported the direct aminocarbonylation of the C–H bond. The authors developed a novel copper-catalyzed double-carbonylation reaction of alkanes with amines to prepare alkyl α-ketoamides using carbon monoxide as carbonyl source (Scheme 69).[89] The catalytic system consists of 10 mol% of CuI and 10 mol% of 2,9-dimethyl-1,10-phenanthroline under a pressure of 60 bar and a large excess of di-*tert*-butyl peroxide as oxidant. The main disadvantage of this first example of direct aminocarbonylation of the C–H bond is the use of high reaction temperature (130 °C) to promote the C–H activation. With this protocol, various amines, such as aliphatic and aromatic, were all suitable for direct double aminocarbonylation of alkenes. The use of DTBP as oxidant is essential to start the activation of the alkane and induce the homolytic cleavage of the C–H bond to generate the alkyl radical required to initiate the catalytic cycle.



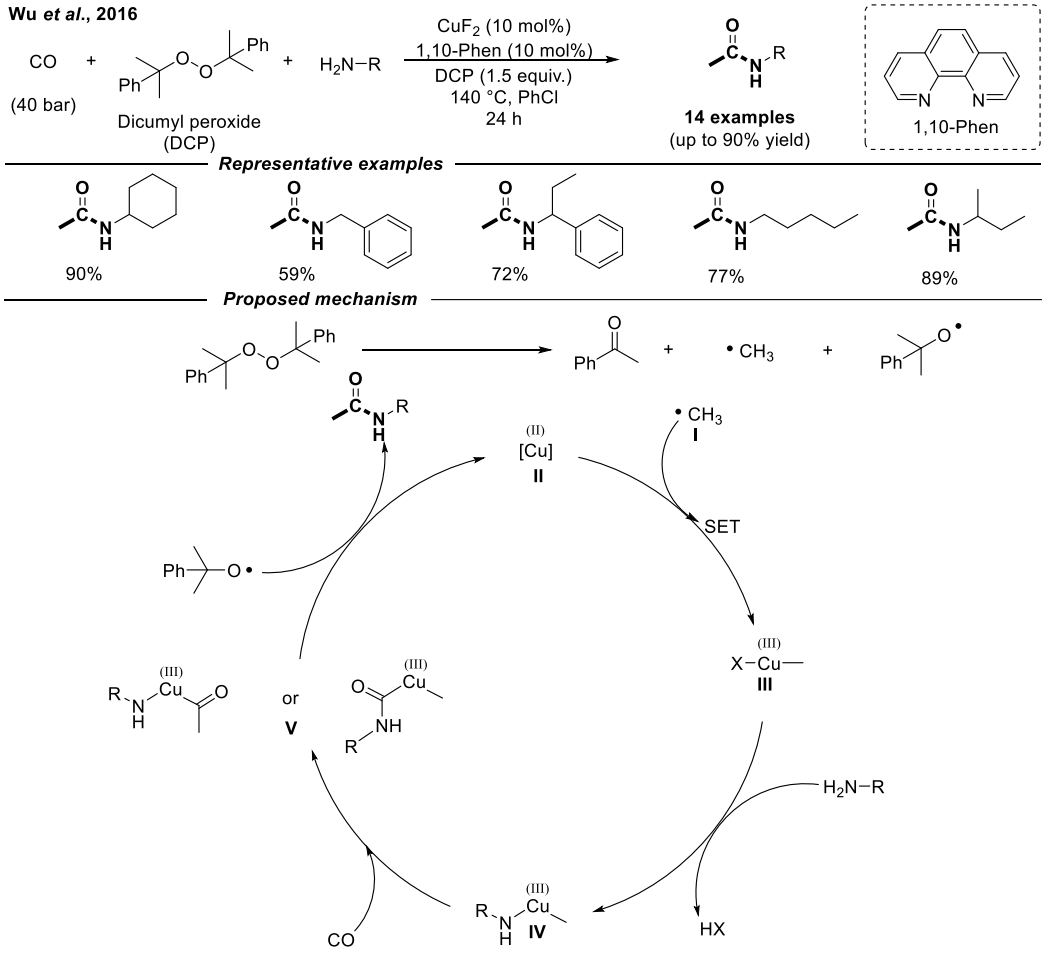
Scheme 69. Copper-catalyzed double-aminocarbonylation of C(sp^3)–H bonds of unactivated alkanes with carbon monoxide.

For what concern the reaction mechanism, the authors proposed that the reaction pathway starts with the generation of *t*BuO· radical through the homolysis of *tert*-Butyl peroxide, then the *t*BuO· radical promotes the homolytic cleavage of the C–H bond of alkane to furnish an alkyl radical **I**. Then, the alkyl radical

[89] Lu, L.; Qiu, F.; Alhumade, H.; Zhang, H.; Lei, A. *ACS Catal.* **2022**, *12*, 9664–9669.

I under a pressure of carbon monoxide reacts with carbon monoxide to generate an acyl-radical intermediate **II**. Then, the catalytic cycle starts with the reaction of the copper(I) complex **III** with the acyl-radical intermediate **II** via a single electron transfer (SET) to forma an acyl-copper(II) complex **IV**. Under a high pressure of carbon monoxide, a second molecule of carbon monoxide can be inserted to furnish an alkyl glyoxal copper(II) complex **V**. Spontaneously, the di-carbonyl radical copper(II) complex **V** reacts with the aminyl radical **VI** via a second single electron transfer (SET) to form a copper(III) complex **VII**. Finally, the copper(III) complex **VII** follows a reductive elimination step to regenerate the catalyst **III** for a new catalytic cycle and releasing the α-ketoamides as final product.

Lastly, the Wu group reported in 2017 a new synthetic strategy for the carbonylative acetylation of amines (Scheme 70).[90] The catalytic system consists of 10 mol% of CuF_2 and 10 mol% of 1,10-phenantroline under a pressure of 40 bar of carbon monoxide. A library of *N*-acetyl amides was prepared with good yields and with good functional group compatibility. In presence of the copper catalyst, dicumyl peroxide decompose into the corresponding acetophenone, methyl radical **I** and alkoxy radical. Then, the methyl radical **I** reacts with CuF_2 **II** to give a methyl copper(III) complex **III** which coordinate the amine **IV** and, under a pressure of carbon monoxide, generates an acetyl-copper(III) complex **V**. Finally, a reductive elimination step takes place to close the catalytic cycle with the simultaneous formation of a copper(I) complex, before to be re-oxidized to Cu(II) through the 2-phenylpropan-2-oxy radical.

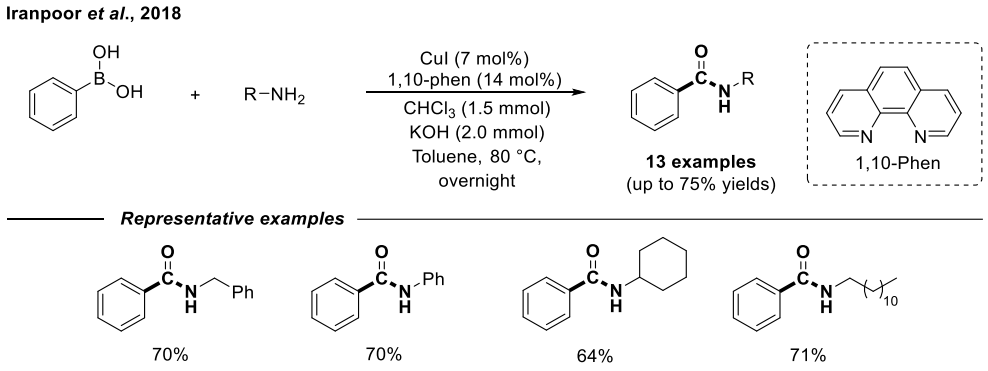


Scheme 70. Copper-catalyzed carbonylative acetylation of amines.

[90] Li, Y.; Wang, C.; Zhu, F.; Wang, Z.; Soulé, J. F.; Dixneuf, P. H.; Wu, X.F. *Chem. Commun.* **2017**, *53*, 142–144.

Another class of compounds that can be used as starting materials for the preparation of amides are boronic acids, these reagents are very attractive due to their stability, commercially availability and low toxicity. Despite these advantages, their use for the development of new copper-catalyzed carbonylative cross-coupling reactions is still limited to few examples.

Recently, the Iranpoor group reported a novel copper-catalyzed protocol for the synthesis of benzamides using a catalytic system based on 7 mol% of CuI and 14 mol% of 1,10-phenantroline in toluene at 80°C overnight (Scheme 71).[91] Under these conditions, aryl boronic acids can be successfully coupled with amine under a pressure of carbon monoxide generated by the decomposition of $CHCl_3$ under basic conditions. With this protocol aliphatic, aromatic and benzyl amines can be easily converted to the corresponding benzamides through the incorporation of carbon monoxide generated *in-situ* with $CHCl_3$ as CO surrogate. Unfortunately, the tolerance towards functional groups installed onto the boronic acids is not wide, indeed the scope is restricted to aromatic rings containing halogens or aliphatic chains. No mechanism has been proposed in the original paper.

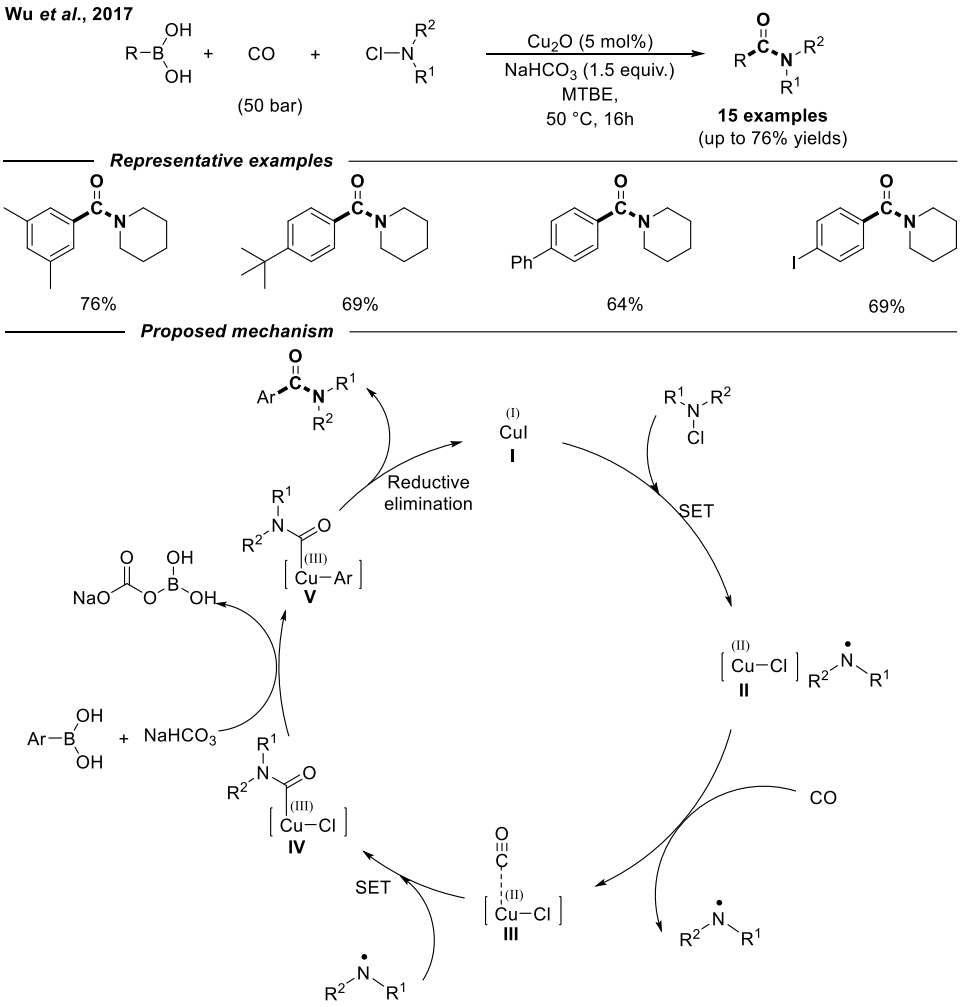


Scheme 71. Copper-catalyzed carbonylation reaction of organoboranes with amines.

More recently, in 2017 the Wu group reported the first example of copper-catalyzed carbonylative cross-coupling of arylboronic acids with *N*-chloroamines for the straightforward synthesis of aryl amides.[92] With the combination of 5 mol% of Cu_2O and 1.5 equiv. of $NaHCO_3$ under 50 bar of CO atmosphere at 50°C for 16 h, various desired amide compounds were prepared in moderate to good yields (Scheme 72). Using this protocol, a wide range of boronic acids were successfully coupled with *N*-chloroamines as coupling partner. Notably, the attempts to use primary and aromatic chloramine analogues as substrates were met with failure due to substrate decomposition. Clearly, the main disadvantage of this procedure lies in the need to prepare before the cross-coupling the *N*-chloroamines which can be slightly unstable. The mechanism of this transformation is based on the generation of a dialkylaminyl radical from the *N*-chloro dialkylamine by a single electron transfer (SET) process under which the Cu(I) species is oxidized to Cu(II) complex **II**.

Thereafter, CO is coordinated onto the Cu(II) complex **III** which through the reaction with the dialkylaminyl radical generates a carbamoyl-copper complex **IV**. This intermediate undergoes transmetallation with the boronic acid to afford the final intermediate **V** and the amide product after reductive elimination.

[91] Etemadi-Davan, E.; Iranpoor, N.; Arshad, P. *Asian J. Org. Chem.* **2018**, *7*, 683–687.
[92] Yin, Z.; Wang, Z.; Li, W.; Wu, X.F. *Eur. J. Org. Chem.* **2017**, *13*, 1769–1772.

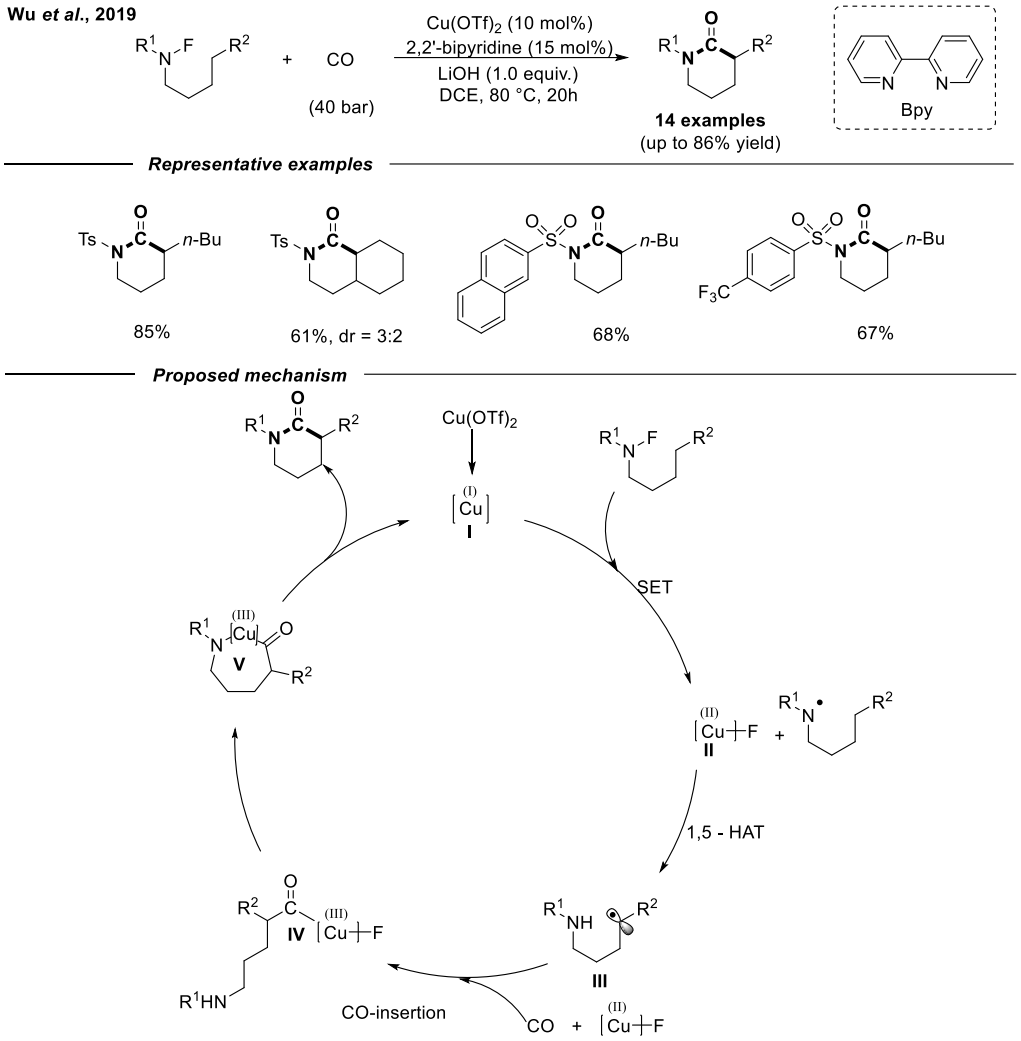


Scheme 72. Copper-catalyzed carbonylative cross-coupling of arylboronic acids with *N*-chloroamines for the synthesis of benzamides.

Subsequently, the Wu group successfully described a new method for the copper-catalyzed intra- and intermolecular carbonylation for the functionalization of a remote C(sp^3)–H bonds of *N*-fluorosulfonamides (Scheme 73).[93] The final optimized reaction conditions allowed the preparation of lactams using 10 mol% of $Cu(OTf)_2$, 15 mol% of 2, 2'-bipyridine and 1.0 equiv. of LiOH in DCE under 40 bar CO at 80 °C. The substrate scope is broad and the methodology showed to be robust. Various substituted groups on the alkyl chain have been tested exhibiting excellent δ-position regioselectivity for a series of lactams which were prepared in moderate to good yields. Besides the acyclic system, cyclic carbon radical can also provide successfully the target bicycle-lactam. Furthermore, the scope was explored considering *N*-fluoro sulfonamides bearing different electron-donating groups or electron-withdrawing groups on the aromatic ring, all the examples tested furnished the target product in good yields. The proposed reaction mechanism begins with a single electron transfer of the Cu(I) complex **I**, which is required to trigger the reduction of *N*-fluorosulfonamides to form the amidyl radical and a Cu(II) complex **II**.

[93] Yin, Z.; Zhang, Y.; Zhang, S.; Wu, X. F. *J. Catal*. **2019**, *377*, 507–510.

Then, the amidyl radical undergo an intramolecular 1,5-hydrogen atom transfer (HAT) to afford a new alkyl radical **III** which would be trapped by CO and Cu(II) species to form an acyl-Cu(III) intermediate **IV**. Finally, the acyl-Cu(III) complex **IV** undergoes an intramolecular ligand exchange in sequence with a reductive elimination step which afford the final target product regenerating the Cu(I) complex **I** for the next catalytic cycle.

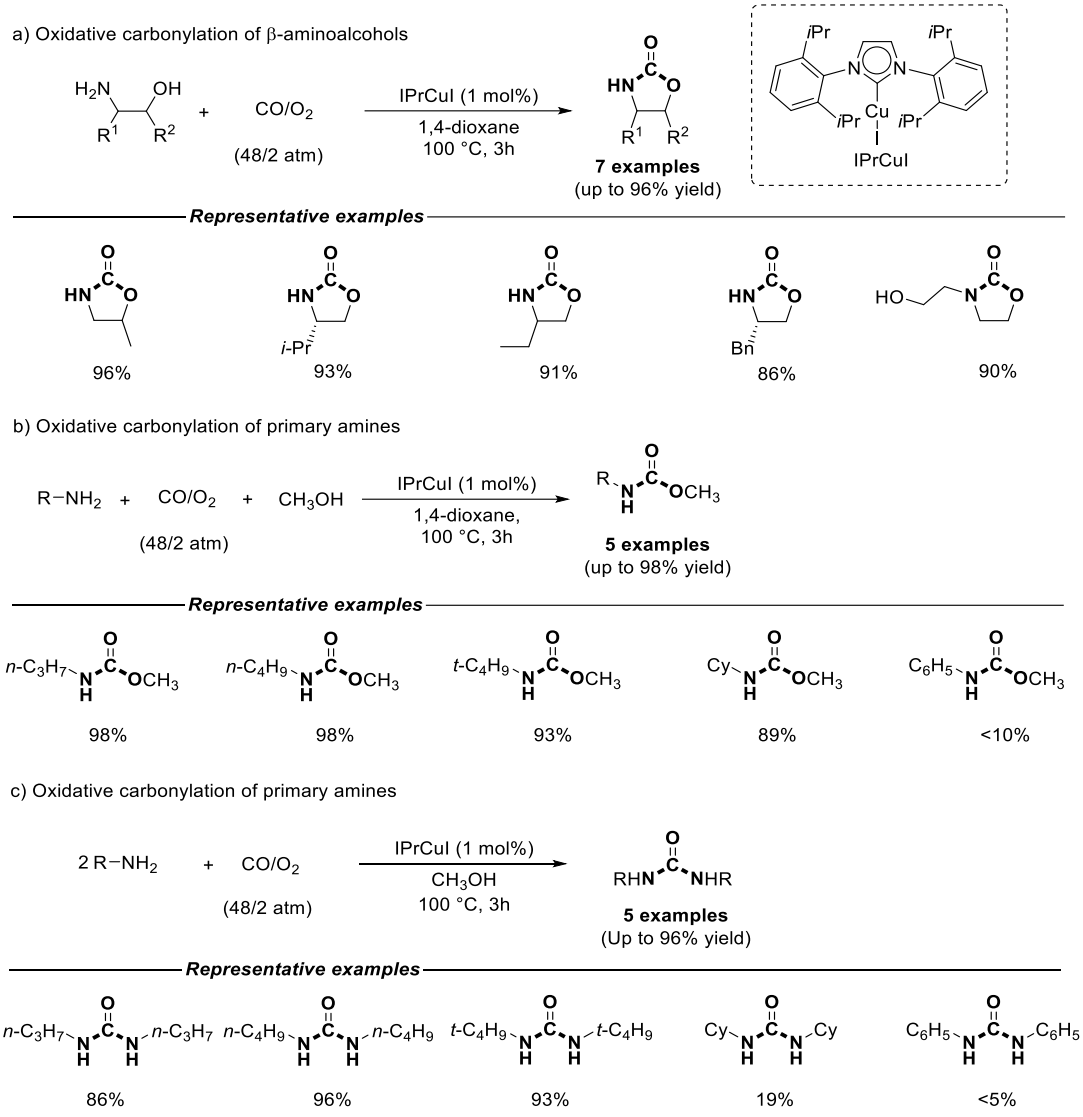


Scheme 73. Copper-catalyzed carbonylative synthesis of lactames through functionalization of C(sp^3)–H bonds of *N*-fluorosulfonamides.

In 2007, the Xia group reported a copper-catalyzed carbonylation using a stable IPrCuI complex, which was used to promote the oxidative carbonylation of amino compounds for the preparation of 2-oxazolidinone, urea, and carbamate in good yields (Scheme 74).[94] The authors reported the preparation of 2-oxazolidinone via an oxidative carbonylation of β-aminoalcohols under a relatively low pressure of carbon monoxide/oxygen (48/2 atm). Under the same reaction conditions, the oxidative carbonylation of amines and methanol gave the corresponding methoxy carbamates as final products in good to excellent yields. Alternatively, replacing methanol with two equivalents of amines, using the same catalytic system also ureas can be synthetized in high yields. Unfortunately, the number of examples reported by the authors is limited. The limitation of this protocol is the use of aromatic amines, which are not sufficiently nucleophilic to be converted in the desired products.

[94] Zheng, S.; Li, F.; Liu, J.; Xia, C. *Tetrahedron Lett.* **2007**, *48*, 5883–5886.

Xia *et al.*, 2007



Scheme 74. Copper-catalyzed oxidative carbonylation of amino compounds to synthetize 2-oxazolidinone, urea and carbamate.

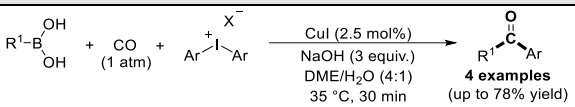
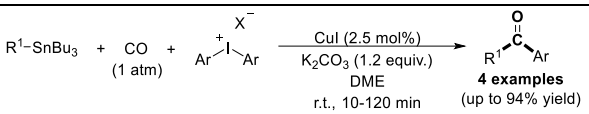
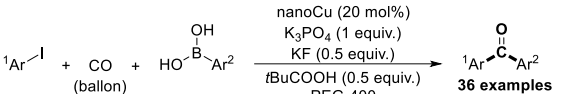
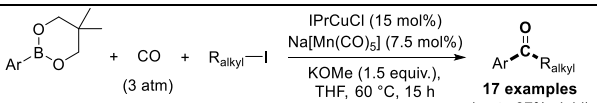
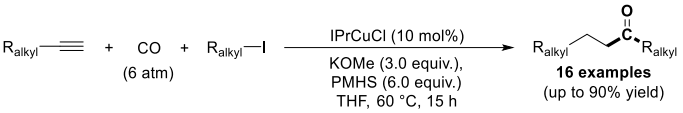
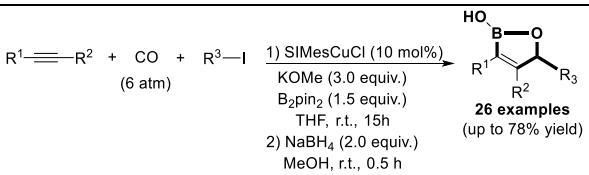
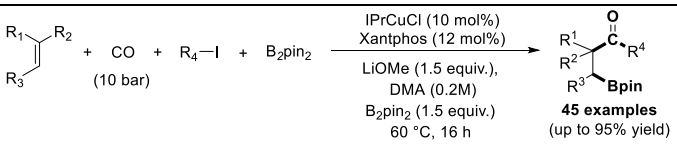
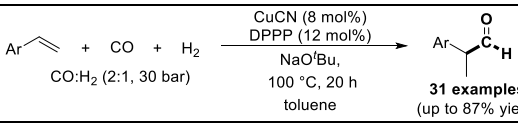
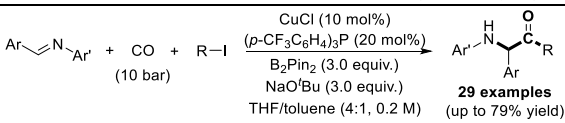
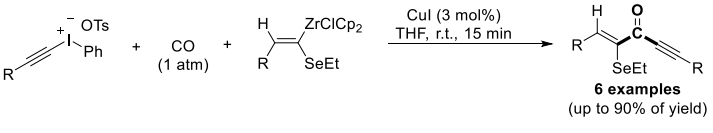
1.5.6 General conclusions on copper-catalyzed carbonylative cross-coupling reactions

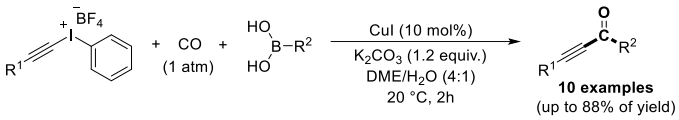
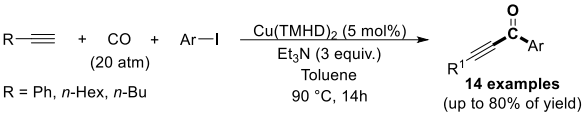
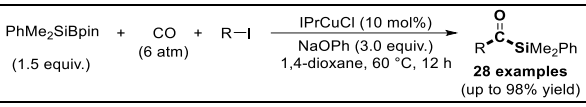
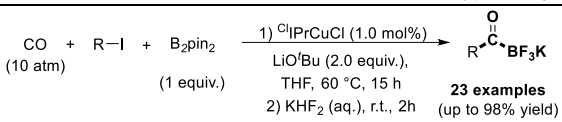
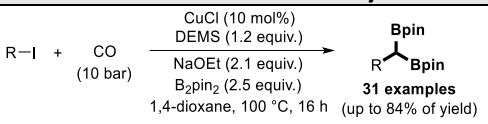
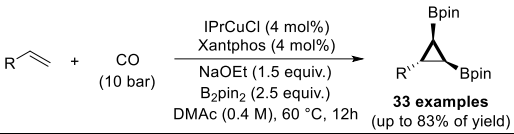
In conclusion, throughout the course of this bibliographical introduction, we have dedicated our efforts to explain in detail the developments that have been achieved in the last years in an area of research not yet sufficiently explored and dedicated to the development of new copper-catalyzed carbonylative cross-coupling reactions. Indeed, over the past few decades, carbonylation reactions have been the subject of extensive research. Efficient methods for the production of a broad variety of carbonyl compounds are provided by these innovative carbonylative processes. However, noble metals have been used to create the majority of this field's accomplishments. The usefulness of inexpensive copper catalysts in carbonylation reactions is demonstrated in this first chapter of our manuscript. Monovalent copper salts like CuI, CuCl, CuBr, and others are the most common types of copper catalysts. Divalent copper salts like $Cu(OAc)_2$ and CuO can also be employed as catalysts. To have catalytic activity in the reaction system, copper can be used alone or in conjunction with ligands, like nitrogen containing and phosphine ligands. Additionally, also cheap *N*-heterocyclic carbenes can be applied in copper-catalyzed carbonylation with carbon monoxide. Although the catalyst loadings are relatively high in the known procedures, this method is more practical and environmentally friendly. Clearly, the copper-catalyzed protocols described still do not have activity levels which are equivalent or more efficient to palladium or rhodium catalysts in the carbonylation of aryl halides and other substrates such alkynes, alkenes, alkanes etc. More work must therefore be done in this area.

In this perspective, our attention has been devoted to the development of new copper-catalyzed carbonylative cross-coupling reactions for the synthesis of carbonyl compounds. The research done to develop a new copper-catalyzed reaction for the aminocarbonylation of aryl iodides will be covered in the following chapter.

1.5.7 Summary table of the copper-catalyzed carbonylative cross-coupling reactions

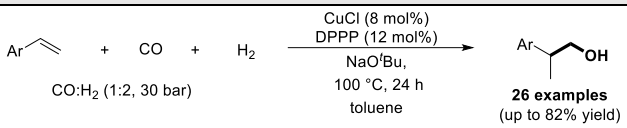
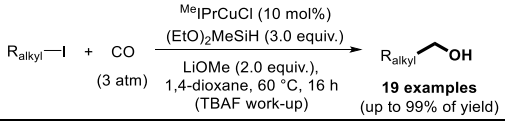
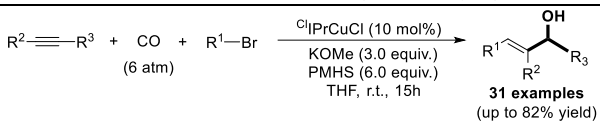
In this section, all reactions overviewed are collected through a graphical and tabulative approach so that the reader can easily have an overview of this field.

Copper-catalyzed carbonylative cross-coupling reactions			
Synthesis of ketones, aldehydes and derivatives			
Group	**Reaction and conditions**	**Advantages**	**Disadvantages**
Kang *et al.* 1996		-Mild reaction conditions -Short reaction time -Room temperature	-Need to prepare aryl iodonium salts as starting material -Narrow scope
Kang *et al.* 1996		-Mild reaction conditions -Short reaction time -Weak base	-Toxicity of tin compounds - Need to prepare aryl iodonium salts as starting material -Narrow scope
Han *et al.* 2014		-Effective -Wide scope -Short reaction time -Low pressure of carbon monoxide	
Mankad *et al.*, 2017		-Mild reaction conditions	
Mankad *et al.*, 2017		-Mild reaction conditions	-Large excess of PMHS
Mankad *et al.*, 2018		-Room temperature	-Large excess of KOMe
Mankad *et al.*, 2020		-Effective -Wide scope -Mild reaction conditions -Effective -Wide scope	
Wu *et al.*, 2021			-High temperature -Long reaction time
Wu *et al.*, 2021		-Mild reaction conditions	-Large excess of B_2pin_2 -Large excess of NaO^{t}Bu
Huang *et al.*, 1996		-Room temperature -Short reaction time -Low pressure of carbon monoxide	-Narrow scope - Need preparation of alkynyl(aryl)iodonium salts - Need preparation of alkynyl selenides

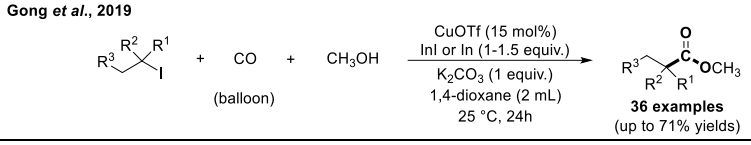
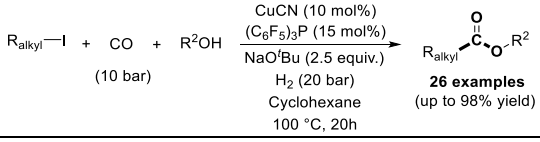
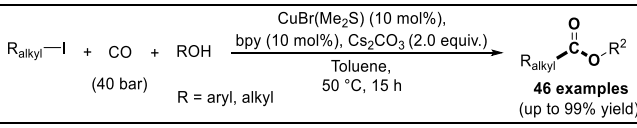
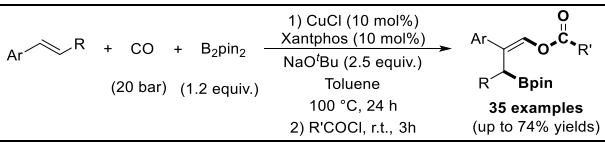
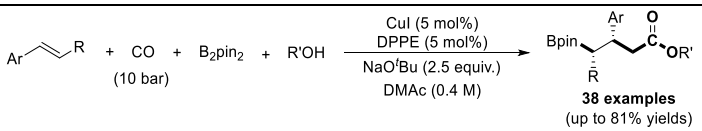
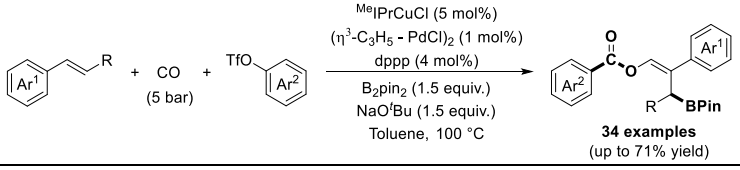
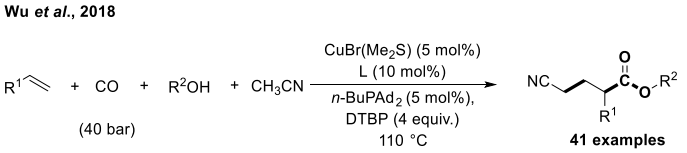
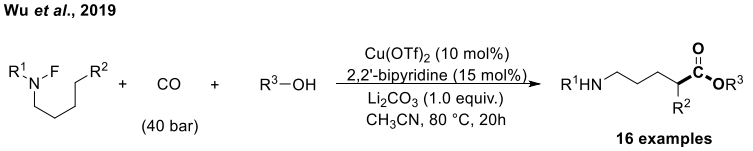
Copper-catalyzed carbonylative cross-coupling reactions			
Synthesis of ketones, aldehydes and derivatives			
Group	**Reaction and conditions**	**Advantages**	**Disadvantages**
Yu *et al.*, 2005	 **10 examples** (up to 88% of yield)	-Room temperature -Short reaction time -Low pressure of carbon monoxide -Inorganic weak base	-Narrow scope -Need preparation of alkynyl(aryl)iodonium salts
Bhanage *et al.*, 2008	 R = Ph, *n*-Hex, *n*-Bu **14 examples** (up to 80% of yield)	-Commercially available starting material	-Large excess of Et_3N -Narrow scope
Mankad *et al.*, 2018	 **28 examples** (up to 98% yield)	-Mild reactions conditions	-Large excess of NaOPh
Mankad *et al.*, 2021	 **23 examples** (up to 98% yield)	-Low catalytic loading -Mild reactions conditions	-Large excess of LiO^tBu
Synthesis of other products			
Mankad *et al.*, 2021	 **31 examples** (up to 84% of yield)	-Wide scope	-Large excess of NaOEt -High reaction temperature
Wu *et al.*, 2020	 **33 examples** (up to 83% of yield)	-Low catalytic loading -Wide scope -Mild reaction conditions	

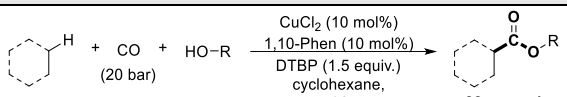
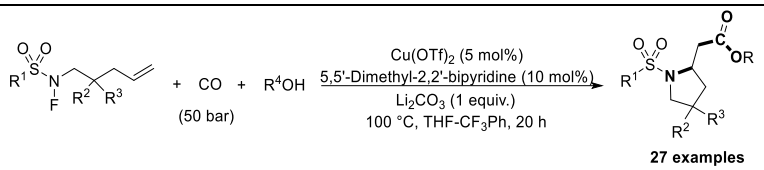
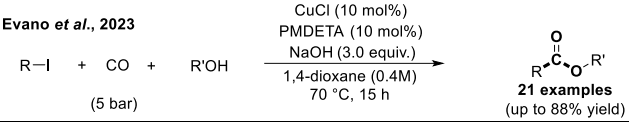
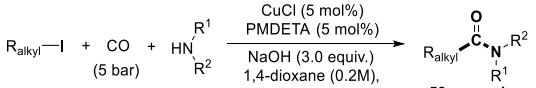
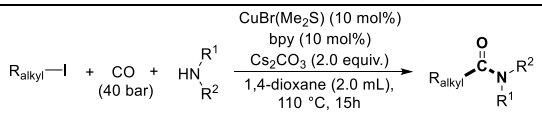
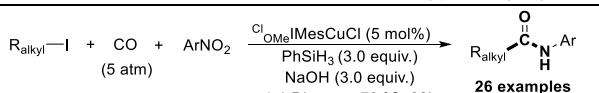
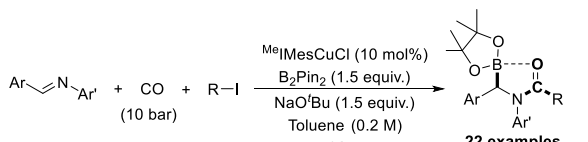
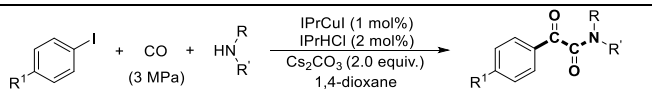
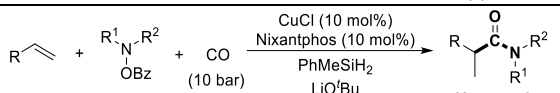
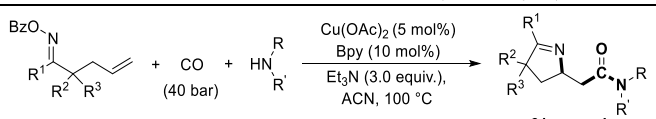
Copper-catalyzed carbonylative cross-coupling reactions

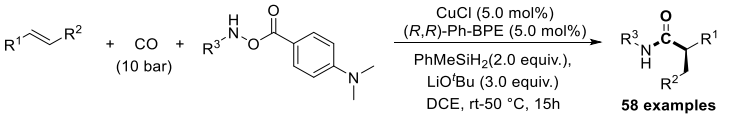
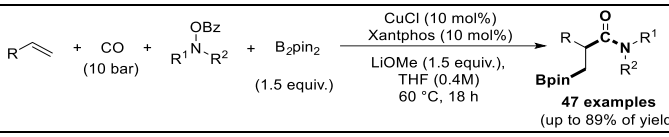
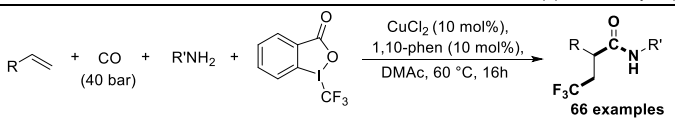
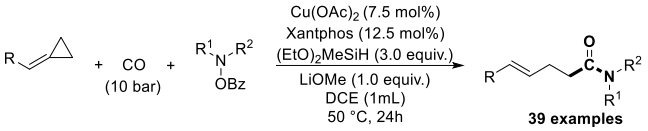
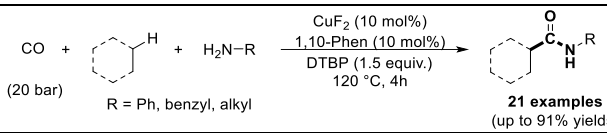
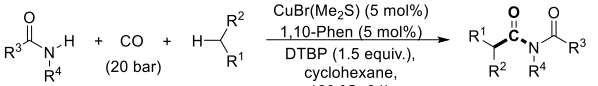
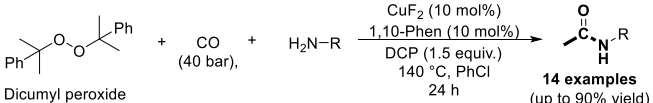
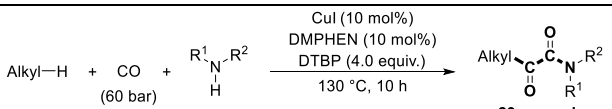
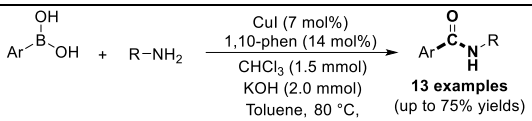
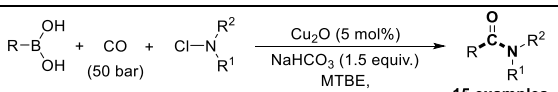
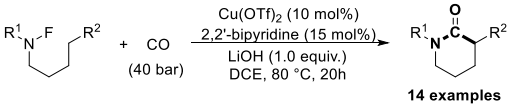
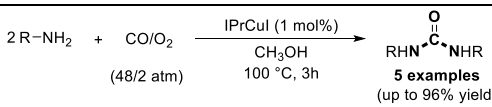
Synthesis of alcohols

Group	Reaction and conditions	Advantages	Disadvantages
Wu et al., 2021		-Good yields	-High reaction temperature -Excess of NaO*t*Bu
Mankad *et al.*, 2018		-Mild reaction conditions	-Large excess of $(EtO)_2MeSiH$ -Large excess of LiOMe
Mankad *et al.*, 2018		-Reaction with alkyl bromide (higher bond dissociation energy) -Room temperature	-Large excess of PMHS -Large excess of KOMe

Synthesis of esters

Group	Reaction and conditions	Advantages	Disadvantages
Gong *et al.*, 2019	**Gong *et al.*, 2019** 	-Mild reaction conditions -Low pressure of carbon monoxide	-Not clear mechanism -Limited to methylester
Wu *et al.*, 2021		-Effective -Wide scope	-High temperature -Long reaction time -Large excess of NaO*t*Bu
Wu *et al.*, 2022		-Effective -Wide scope -Mild reaction conditions	-High pressure of carbon monoxide
Wu *et al.*, 2021		-Effective -Wide scope	-High temperature -Long reaction time -Large excess of NaO*t*Bu
Wu *et al.*, 2022		-Effective -Wide scope	-Large excess of NaO*t*Bu
Wu *et al.*, 2020		-Low catalytic loading	-High temperature -Need of preparation of aryl triflates, reagents not commercially available
Wu *et al.*, 2018	**Wu *et al.*, 2018** 	-Effective -Wide scope -Good yields	-High temperature -Large excess of peroxides
Wu *et al.*, 2019	**Wu *et al.*, 2019** 	-Effective -Wide scope -Good yields	-Need of preparation of *N*-fluoroamines

Synthesis of esters			
Group	**Reaction and conditions**	**Advantages**	**Disadvantages**
Wu *et al.*, 2017	 **22 examples** (up to 92% yield)	-Short reaction time	-High temperature -High pressure of carbon monoxide
Wu *et al.*, 2020	 **27 examples** (up to 78% yield)	-Low catalytic loading	-High temperature -Long reaction time -High pressure of carbon monoxide -Fluorinated solvent as waste
Wu *et al.*, 2018	 **18 examples** (up to 87% yield)	-Low catalytic loading	-High pressure of carbon monoxide -Need of preparation of 1-chloro-benzotriazoles
Evano *et al.*, 2023	**Evano *et al.*, 2023**  **21 examples** (up to 88% yield)	-Low catalytic loading -Inexpensive reagents	
Synthesis of amides			
Group	**Reaction and conditions**	**Advantages**	**Disadvantages**
Evano *et al.*, 2022	 **53 examples** (up to 97% yield)	-Effective -Wide scope	-Large excess of NaOH as strong base
Wu *et al.*, 2022	 **47 examples** (up to 94% yield)	-Effective -Wide scope	-High temperature
Mankad *et al.*, 2019	 **26 examples** (up to 92% of yield)	-Commercially available starting material -Low pressure of carbon monoxide	-Large excess of NaOH as strong base -Large excess of $PhSiH_3$ -Long reaction time
Wu *et al.*, 2021	 **22 examples** (up to 79% of yield)	-Mild reaction conditions	-Need preparation of Schiff base
Xia *et al.*, 2009	 **13 examples** (up to 93% isolated yield)	-Low catalytic loading	-High reaction temperature -Narrow scope
Wu *et al.*, 2020	 **42 examples** (up to 83% yield)	-Effective -Wide scope	-Long reaction time - Need preparation of protected hydroxylamines
Wu *et al.*, 2020	 **61 examples** (up to 95% of yield)	-Effective -Wide scope	-High pressure of carbon monoxide -High reaction temperature - Need preparation of γ,δ-unsaturated aromatic oxime esters

Synthesis of amides			
Group	**Reaction and conditions**	**Advantages**	**Disadvantages**
Wu *et al.*, 2021		-Effective -Wide scope -Mild reaction conditions	- Need preparation of electrophilic hydroxylamines -Large excess of LiO^{t}Bu -Large excess of PhMeSiH$_2$
Wu *et al.*, 2020		-Effective -Wide scope -Mild reactions conditions	-Need preparation of protected hydroxylamines
Wu *et al.*, 2021		-Effective -Wide scope -Mild reaction conditions	-High pressure of carbon monoxide
Wu *et al.*, 2022		-Effective -Wide scope -Mild reaction conditions	-Excess of (EtO)$_2$MeSiH -Long reaction time -Need preparation of the starting material -Need preparation of oxime esters
Wu *et al.*, 2016		-Short reaction time	-High reaction temperature
Wu *et al.*, 2016			-High reaction temperature -Long reaction time -High pressure of carbon monoxide
Wu *et al.*, 2016		-Good yields	-High reaction temperature -Narrow scope -High pressure of carbon monoxide -Chlorinated Solvent
Lei *et al.*, 2022		-Commercially available starting material	-High pressure of carbon monoxide -High temperature -Large excess of DTBP peroxide
Iranpoor *et al.*, 2018		-No need of a cylinder of carbon monoxide -CHCl$_3$ as carbon monoxide surrogate	-Narrow scope -Large excess of KOH as strong base
Wu *et al.*, 2017		-Mild reaction conditions	-Need of preparation of *N*-chloro amines
Wu *et al.*, 2019		-Mild reaction conditions -Efficient	-High pressure of carbon monoxide -Narrow scope -Long reaction time -Need preparation of *N*-fluoro amines
Xia *et al.*, 2007		-Low catalytic loading	-High reaction temperature -Narrow scope -High pressure of carbon monoxide

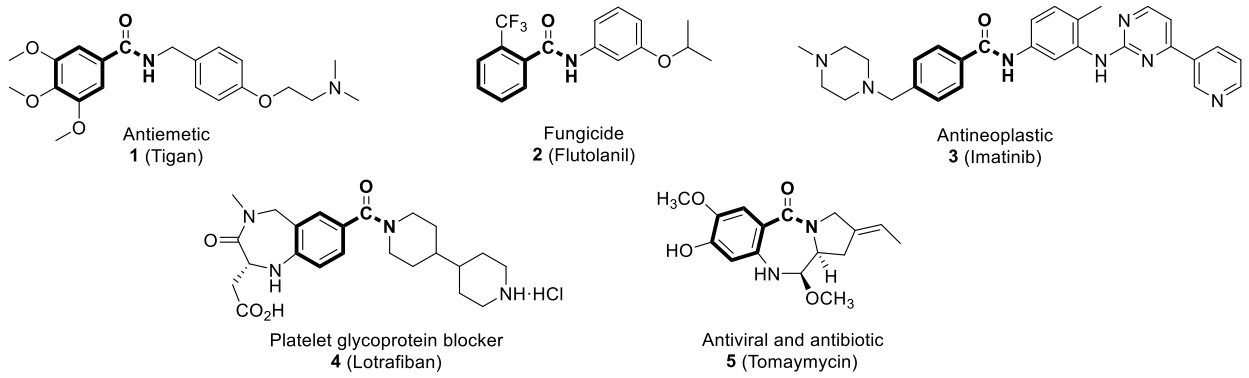
First part: Carbonylative cross-coupling reactions

Chapter 2: Copper-catalyzed carbonylative cross-coupling of aryl iodides and amines

Chapter 2. Copper-catalyzed carbonylative cross-coupling of aryl iodides and amines

2.1. Introduction

As overviewed in the previous chapter, even if tremendous progresses have been made in copper-catalyzed carbonylative cross-coupling reactions, especially in recent years, this area is still understudied and further development are clearly needed. Indeed, and especially, compared to palladium catalysis, the range of substrates that are amenable to such carbonylative processes is still too narrow, which limits further application. Among these substrates, cross-coupling involving aryl halides are hardly reported, despite a strong potential. Being able to use aryl halides in carbonylative copper-catalyzed cross-coupling reactions with various nucleophiles would indeed represent an interesting and potentially economically viable entry to carbonyl and carboxyl derivatives that could be obtained in a straightforward manner and with good atom-economy. For this main reason, we decided to investigate such reactions and decided to focus our efforts on the copper-catalyzed carbonylative cross-coupling between aryl iodides, whose activation is easier than the corresponding bromides or chlorides, and amines to the corresponding benzamides. Such compounds are indeed of broad interest since they can be found in a variety of agrochemicals, polymers, pharmaceutical compounds and a large number of naturally occurring molecules with biological activity, as shown with representative examples in the Scheme 75 below. Among these examples, it is possible to mention aromatic benzamides of relevant interest such as Tigan **1** (an antiemetic used to treat nausea),[95] Flutolanil **2** (a fungicide with both protective and curative properties for controlling *Rhizoctonia solani* and some other *Basidiomycete* fungi in rice and vegetables),[96] Imatinib **3** (an oral chemotherapy medication use to treat cancer),[97] Lotrafiban **4** (an orally-active platelet GPIIb/IIIa blocker for treatment of coronary and cerebrovascular disease)[98] and Tomaymycin **5** (a potent antiviral and antibiotic compound).[99]

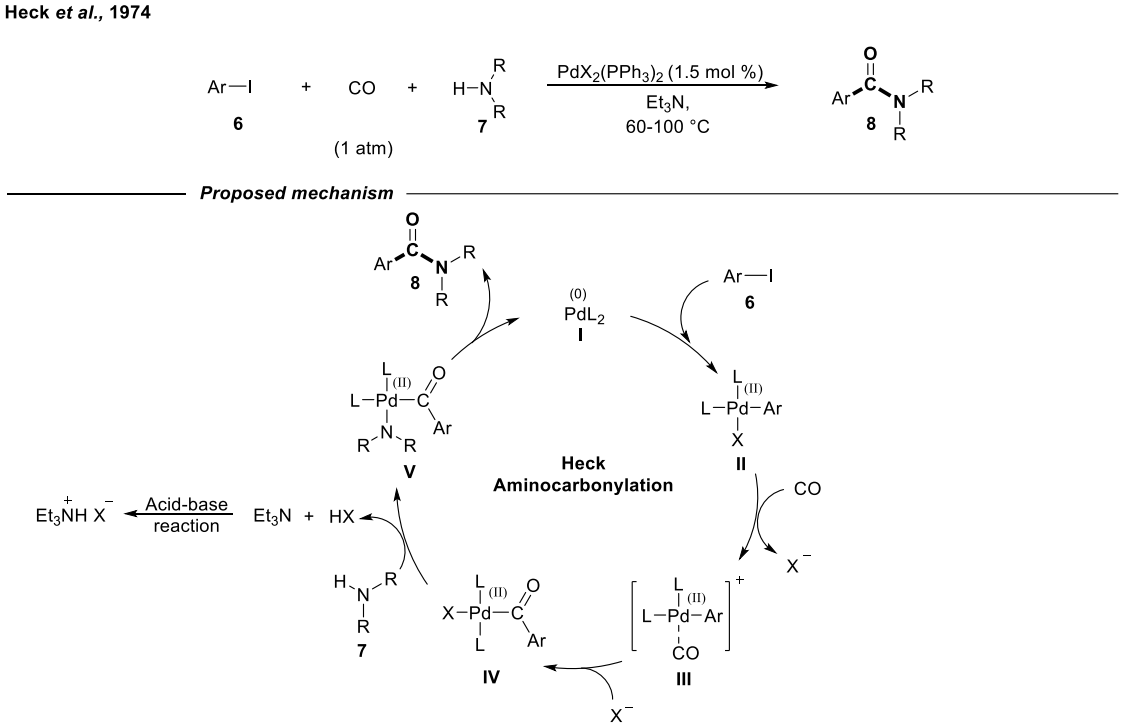


Scheme 75. Examples of benzamides with biological activity.

[95] Neelakandan, K.; Manikandan, H.; Santosha, N.; Prabhakaran, B. *Org. Process Res. Dev.* **2013**, *17*, 981–984.
[96] Motoba, K.; Uchida, M.; Tada, E. *Agric. Biol. Chem.* ***1988****, 52,* 1445–1449.
[97] Iqbal, N.; Iqbal, N. *Chemother Pract.* ***2014****,* 1–9.
[98] Atkins, R. J.; Banks, A.; Bellingham, R. K.; Breen, G. F.; Carey, J. S.; Etridge, S. K.; Hayes, J. F.; Hussain, N.; Morgan, D. O.; Oxley, P.; Passey, S. C.; Walsgrove, T. C.; Wells, A. S. *Org. Proc. Res. Dev.* **2003**, *7*, 663–675.
[99] Arima, K.; Kosaka, M.; Tamura, G.; Imanaka, H.; Sakai, H. *J. Antibiot.* **1972**, *8*, 437–444.

Despite the fact that benzamides can be easily made from amines and benzoic acids, which involves the pre-activation of the benzoic acid via a stoichiometric activating agent and produces unwanted waste, a variety of other methods for amide bond creation have been described.[100]

Among these, the three-component cross-coupling between aryl halides, amines and carbon monoxide is one of the most appealing options. This reaction has been pioneered by the Heck group who reported a general palladium-catalyzed aminocarbonylation of aryl iodides and bromides in 1974.[101] They demonstrated that secondary and tertiary amides **8** are conveniently obtained from the corresponding (hetero)aryl iodides **6** and primary or secondary amines **7** under a low pressure of carbon monoxide at 60–100 °C in the presence of 1.5 mol% $PdX_2(PPh_3)_2$, and found that stoichiometric amounts of a tertiary amine were required to neutralize the formed acid when weakly basic amines were employed as nucleophiles (Scheme 76).



Scheme 76. Palladium-catalyzed Heck's aminocarbonylation of aryl halides with amines.

After this discovery, the importance of this chemical reaction has been demonstrated by its numerous applications, such as several total syntheses of numerous natural compounds of pharmacological interest as depicted in Scheme 77. Examples include the works of Walsh (**9**, 2000)[102], Mori (**10**, 1986)[103], Wentland (**11**, 2001)[104], Gangjee (**12**, 2002)[105] and Carey (**13**, 1986)[106] where an aminocarbonylation was chosen as a key step to prepare the target molecules due to its effectiveness to construct new C–C bonds incorporating carbon monoxide as useful C1-building block.

[100] For selected review articles, see: a) Figueiredo, R. V.; Suppo, J. S.; Campagne, J. M. *Chem. Rev.* **2016**, *116*, 12029–12122. b) Sabatini, M. T.; Boulton L. T.; Sneddon, H. F.; Sheppard, T. D. *Nat. Catal.* **2019**, *2*, 10–17. c) Santos, A. S.; Silva, A. M. S.; Marques, M. M. B. *Eur. J. Org. Chem*. **2020**, *17*, 2501–2516.

[101] Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327–3331.

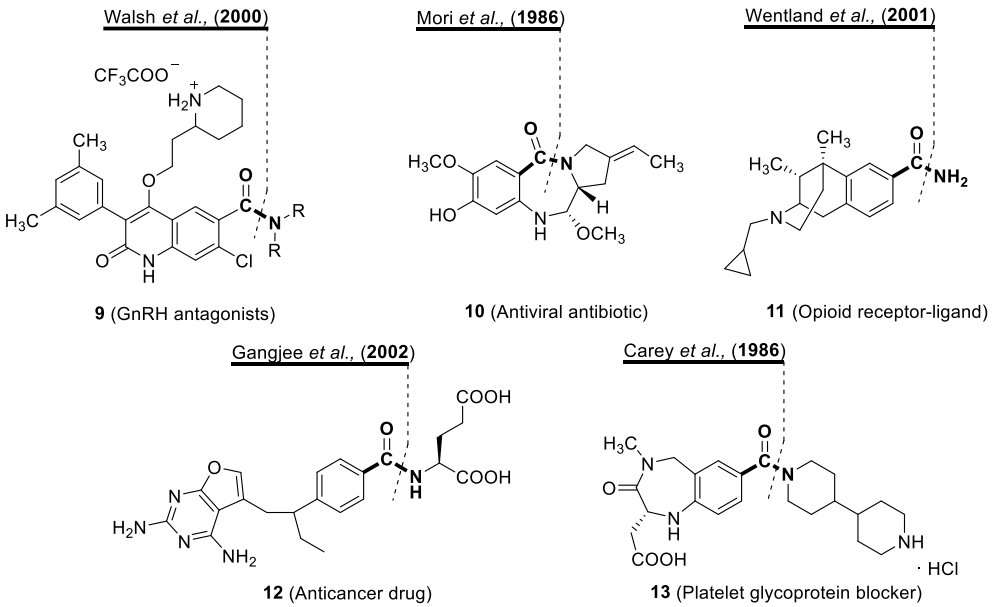
[102] Walsh, T. F.; Toupence, R. B.; Yang, Y. T.; Cheng, K.; Smith, R.G. *Bioorg*. *Med*. *Chem*. **2000**, *5*, 443–447.

[103] Mori, M.; Uozumi, Y.; Kimura, M.; Ban, Y. *Tetrahedron,* **1986**, *42*, 3793–3806.

[104] Wentland, M. P.; Lou, R.; Ye, Y.; Cohen, D. J.; Richardson, G. P.; Bidlack, J. M. *Bioorg*. *Med*. *Chem*. **2001**, *5*, 623–626.

[105] Gangjee, A.; Zeng, Y.; McGuire, J. J.; Kisliuk, R. L. *J. Med. Chem.* **2002**, *9*, 1942–1948.

[106] Andrews, I. P.; Atkins, R. J.; Carey, S. J.; Etridge, S. K.; Hayes, F. J. *Tetrahedron Lett.* **2001**, *42*, 4915–4917.



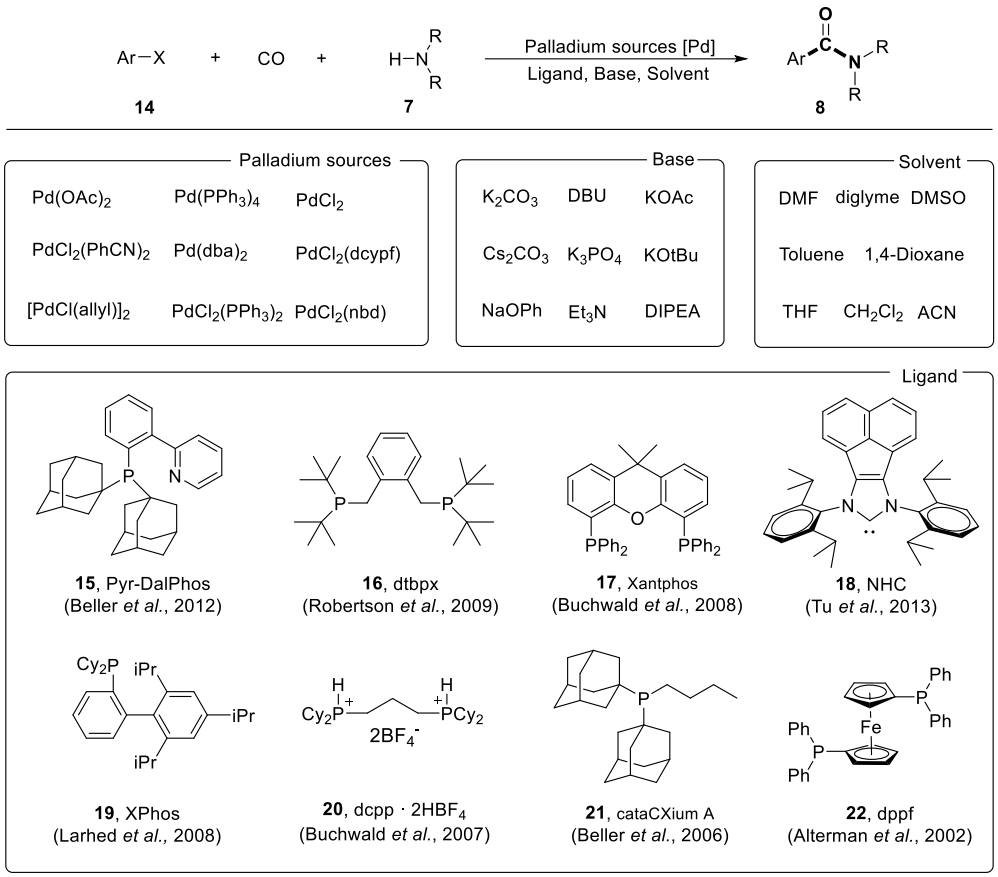
Scheme 77. Examples of biologically active molecules prepared through a palladium-catalyzed aminocarbonylation reaction.

2.2. Brief overview on the synthesis of aromatic amides through palladium-catalyzed carbonylative cross-coupling reactions from aryl halides and amines

As presented in the previous section, the interest for palladium-catalyzed aminocarbonylative cross-coupling reactions exploded at the end of the 20th century and many catalytic systems have been developed as variants of the Heck's original protocol for the direct synthesis of benzamides.[107] Scheme 78 represents a brief overview of the partners that are possible to combine in order to perform Heck's aminocarbonylation, as well as the palladium sources, ligands, bases and solvents most commonly used. Usually, the preferred palladium sources used are salts of Pd(II), as less sensitive to atmospheric oxygen, in polar solvents with a high boiling point. Generally, the bases used are weak inorganic salt, easily removable through an aqueous work-up, although also the use of more soluble organic bases can sometimes promote a more efficient coupling. A compendium of the most important ligands used today in literature is reported below and clearly a large majority includes phosphines as privileged structures, although in recent years also *N*-heterocyclic carbenes revealed to be efficient ligand to promote aminocarbonylative catalysis.[108]

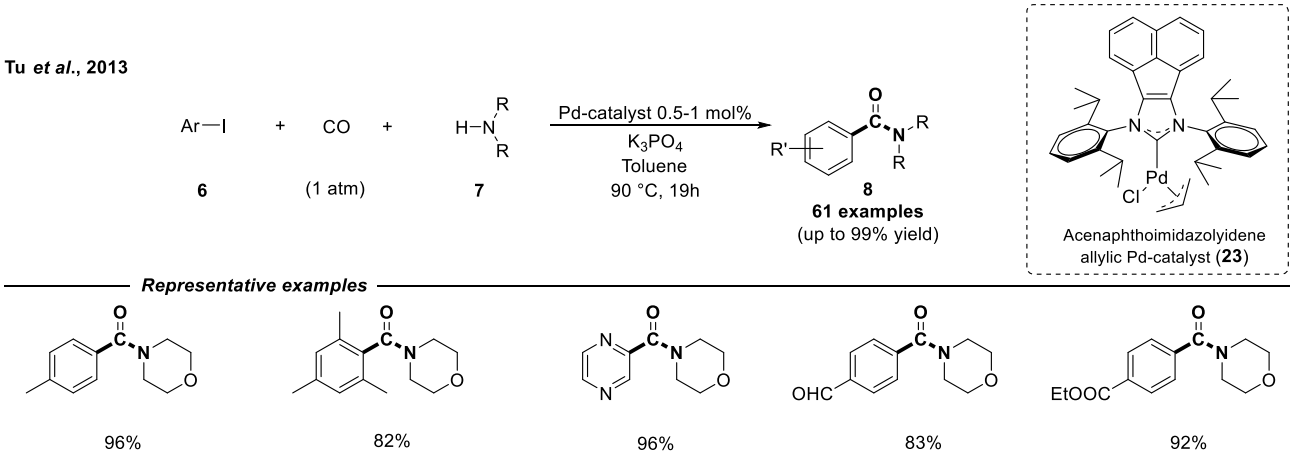
Aryl iodides are advantageous starting materials that are simple to functionalize due to the low bond dissociation energy of the C–I bond's of only 272 kJ/mol. Due to their propensity to undergo oxidative additions, which is the first step of aminocarbonylation's catalytic cycle, these substrates are therefore the most often employed ones.

[107] Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402–5422.
[108] (a) Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev*. **2011**, *40*, 5151–5169. (b) Veige, A. S. *Polyhedron* **2008**, *27*, 3177–3189.



Scheme 78. Current methods to carry out aminocarbonylation reactions.

In 2013, the Tu group published one of the most efficient protocols in which the authors utilized a robust palladium complex of *N*-Heterocyclic carbene **23** as catalyst towards the aminocarbonylation of a wide variety of (hetero)aryl iodides **6**, demonstrating its excellent catalytic activity (Scheme 79).[109] *N*-heterocyclic carbenes (NHCs) were chosen as strong σ-donor and weak π-acceptor ligands able to promote, catalyze and accelerate the oxidative addition of the palladium metal center into the C–I bond of the aryl iodides. This approach is particularly appealing since it is simple, effective and provides a practical access a large variety of aryl amides **8** despite the minimal catalytic loading and low pressure of carbon monoxide utilized.

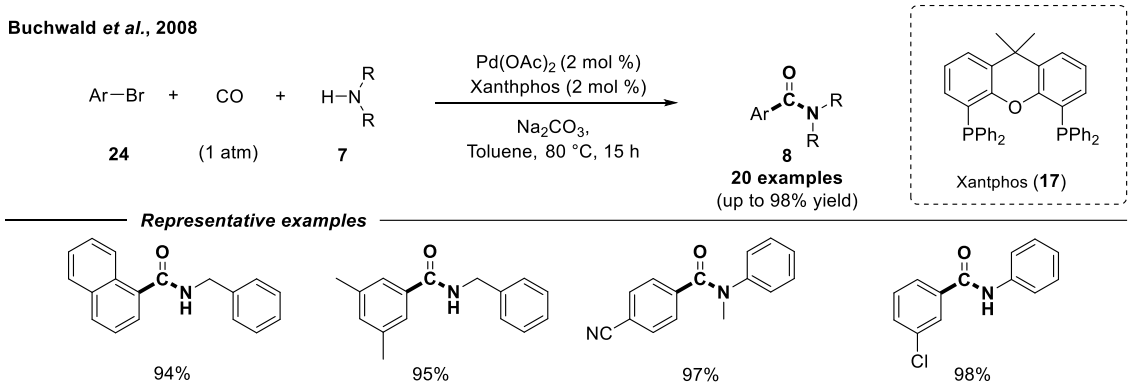


Scheme 79. Aminocarbonylation of iodoarenes at atmospheric pressure catalyzed by palladium complex.

[109] Fang, W.; Deng, Q.; Xu, M.; Tu, T. *Org. Lett.* **2013**, *15*, 3678–3681.

Based on the C–X bond dissociation energy, the rate of the oxidative addition of the aryl halide to a metal complex decreases along the sequence: C–I > C–Br > C–Cl > C–F. The higher bond dissociation energy of the C–Br bond is automatically translated into a reduced reactivity in carbonylative cross-coupling reactions due to the oxidative addition being less energetically favoured. Because of this, new ligands and reaction conditions that can enhance the aminocarbonylation of aryl bromides and the simultaneous lowering of all energy barriers are needed.

In 2008, the Buchwald group reported the development of a novel carbonylation process using palladium(II) acetate and Xantphos as ligand **17** (Scheme 80).[110] This catalytic system demonstrated to be effective for the synthesis of amides **8** from the corresponding aryl bromides **24**. With this approach, the carbonylation reaction is promoted at a relatively low pressure (1 atm) and temperature (80 °C). Due to its broad bite-angle, Xantphos is hypothesized to stabilize chemical intermediates and aid the carbonylation process in operating at lower temperatures (80 °C) and pressure (1 atm).

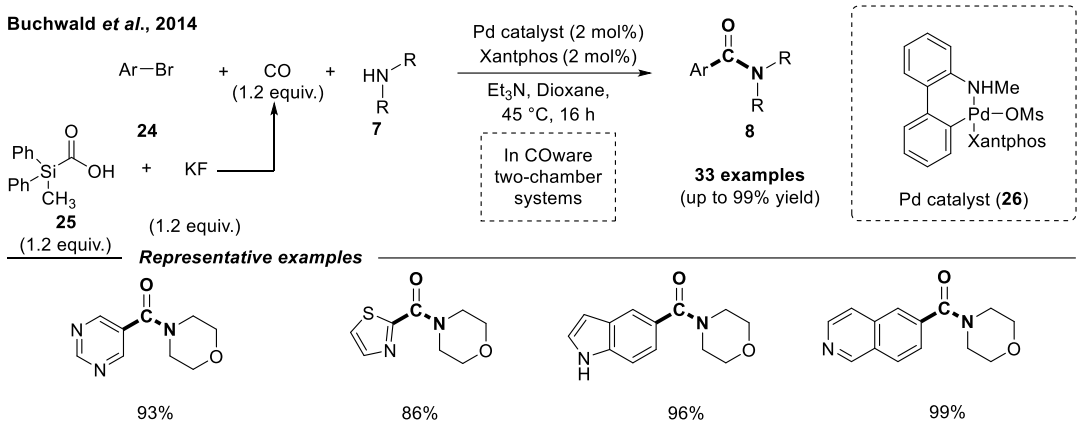


Scheme 80. Pd-catalyzed carbonylation of aryl bromides with Xantphos and $Pd(OAc)_2$ with the Buchwald's protocol.

In 2014, the Bulchwald group reported a major advance in this field by developing the first low temperature aminocarbonylation of (hetero)aryl bromides **24**.[111] The catalytic system consists of only 2 mol% of a palladacycle precatalyst **26** in combination with Xantphos as the ligand under a low pressure of carbon monoxide. Since carbon monoxide is produced safely using carbon monoxide surrogate in a two-chambers reactor (CO-ware) and the reaction is conducted at an exceptionally low temperature of only 45 °C, this new carbonylation procedure is quite attractive (Scheme 81).

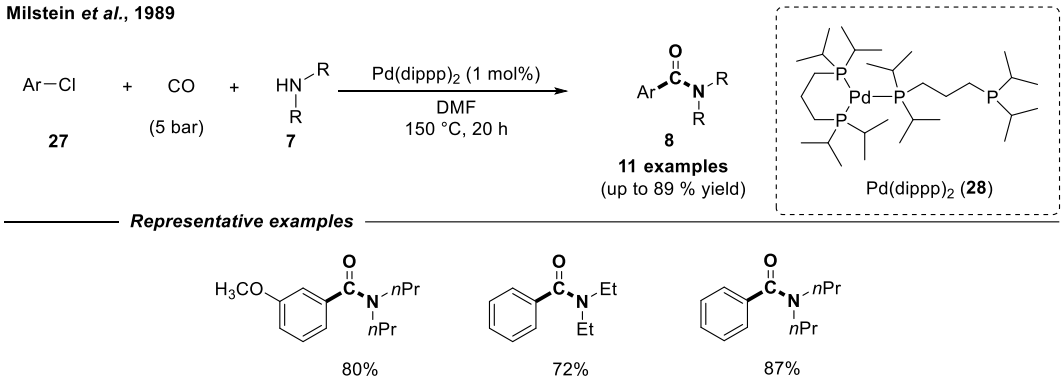
Even though aryl chlorides **27** are arguably the most useful class of aryl halides due to their high abundance, lower cost, and greater variety of available compounds, reports of palladium-catalyzed carbonylative cross-couplings with such substrates are limited. Indeed, the oxidative addition onto the Pd(0) metal center is difficult with the aryl chlorides because of the strength of the C–Cl bond.

[110] Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *18*, 7102–7107.
[111] Friis, S. D.; Skrydstrup, T.; Buchwald, S. L. *Org. Lett.* **2014**, *16*, 4296–4299.



Scheme 81. Pd-catalyzed carbonylation of aryl bromide with the Buchwald's protocols.

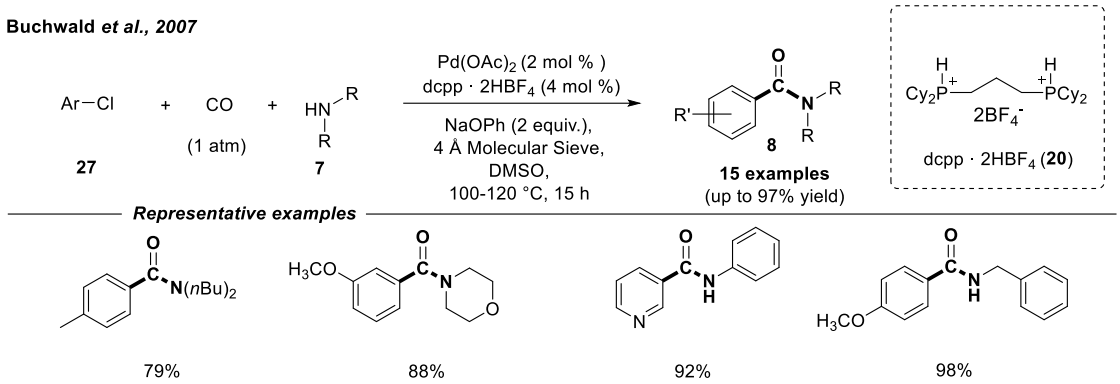
The first example of a palladium-catalyzed aminocarbonylation of aryl chlorides **27** was documented by the Milstein group in 1989 (Scheme 82).[112] The success of this reaction is due to the use of a specific palladium complex containing a large and donating *bis*(diisopropylphosphino)propane ligand **28**. The use of an electron-rich chelated Pd(0) complex allowed the synthesis of a small library of aromatic amides **8** consisting of only three representative examples. Despite its profound innovation, the main drawbacks of this methodology are its limited application (only three example), the use of high temperatures between 150 and 200 °C, and the use of polar solvents that are difficult to remove, such as DMF.



Scheme 82. Aminocarbonylation of aryl chloride palladium catalyzed.

In 2007, the Buchwald group published a further advancement for the aminocarbonylation of aryl chlorides **27**, reporting a generic and useful procedure performed at atmospheric carbon monoxide pressure and relatively low temperature (100-120 °C), which is considerably a lower temperature compared to the previously reported conditions (Scheme 83).[113] The best ligand proved to be an electron-rich air-stable bulky bisphosphine **20** (dcpp 4-5 mol %) in combination with $Pd(OAc)_2$ (2 mol %). In this process, for the success of the aminocarbonylation reaction was found to be critical the use of sodium phenoxide as additive.

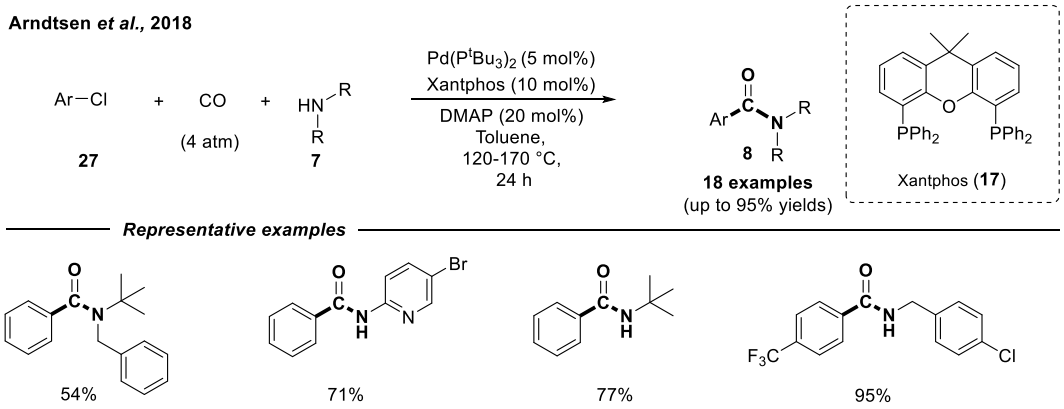
[112] Milstein, D.; Portnoy, M.; Ben-David, Y. B. *J. Am. Chem. Soc.* **1989**, *23*, 8742–8744.
[113] Martinelli, R. J.; Clark, P. T.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2007**, *46*, 8460–8463.



Scheme 83. Palladium-catalyzed aminocarbonylation of aryl chlorides at atmospheric pressure in presence of NaOPh.

Indeed, this additive is capable of facilitating the transformation by serving as both a base and an acyl transfer agent. Moreover, the phenoxide anion may also play a role as a ligand to the metal center by displacement of chloride. The use of anhydrous sodium phenoxide resulted in even more dramatic improvements, providing complete conversion of the aryl chlorides **27** and an excellent yield of the desired amides **8**. Primary, secondary, and aromatic amines **7** are all readily converted into amides. Additionally, electron-rich, -neutral, and poor aryl chlorides are all compatible with these aminocarbonylation conditions.

A last report on the aminocarbonylation of aryl chlorides **27** which is important to be mentioned is one by the Arndtsen group who reported in 2018 the use of an acyl-transfer agent, 4-dimethylaminopyridine (DMAP), to obtain *in-situ* a highly reactive electrophilic aroyl-DMAP intermediate (Scheme 84).[114] Under the optimized reaction conditions, amines **7** were successfully coupled with aryl chlorides **27** affording the products **8** in good isolated yields and at low carbon monoxide pressure (4 atm).



Scheme 84. Palladium-catalyzed aminocarbonylation of aryl chlorides to electrophilic aroyl-DMAP Salts.

As briefly overviewed, palladium catalysis is especially efficient for the aminocarbonylation of aryl halides and a variety of catalytic systems have been reported, greatly increasing the scope of the Heck's original procedure.[115] These catalytic systems have advantages in terms of reactivity and efficiency, but their widespread use is still constrained by their high prices, toxicity, and requirement for even more costly, non-reusable phosphine ligands. The exploration of non-noble catalysts in organic synthesis to catalyze

[114] Lagueux-Tremblay, P. L.; Fabrikant, A.; Arndtsen, B. A. *ACS Catal*. **2018**, *8*, 5350–5354.

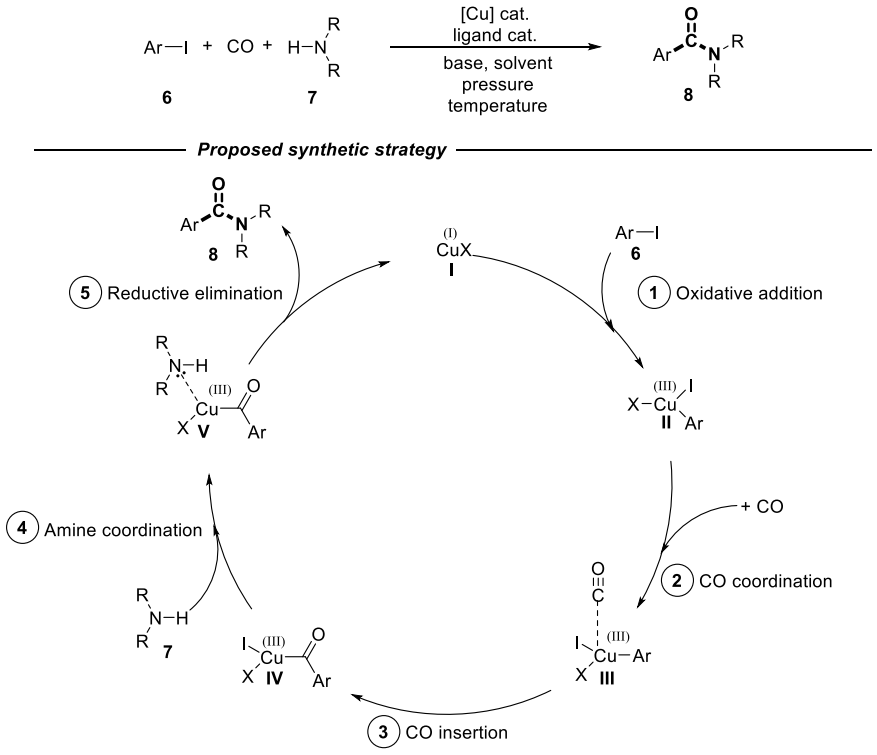
[115] (a) Beller, M. *Catalytic Carbonylation Reactions*, 1th ed.; Vol. 1; Springer Berlin, **2006**. (b) Beller, M.; Neumann, H.; Wu, X. F. *Chem. Soc. Rev.* **2011**, *40*, 4986–5009. (c) Wu, X. F. Neumann, H.; Beller, M. *Chem. Rev*. **2012**, *113*, 1–35. (d) Wu, X. F.; Fang, X.; Wu, L.; Jackstell, R.; Neumann, H.; Beller, M. *Acc. Chem. Res*. **2014**, *47*, 1041–1053. (e) Skoda-Foldes, R.; Kollar, L. *Curr. Org. Chem*. **2002**, *6*, 1097–1119. (f) Wu, X. F. Neumann, H. *ChemCatChem*, **2012**, *4*, 447–458. (g) Zhu, F.; Wang, Z.; Li, Y.; Wu, X. F. *Chem. Eur. J.* **2017**, *23*, 3276–3279.

carbonylative cross-coupling reactions has proved to be one of the best alternatives because of their benefits including availability, low cost and low toxicity.[116]

Based on our ongoing research interests and considering all the advantages of non-noble metals, we became interested to investigate a novel carbonylative copper-catalyzed cross-coupling reaction of aryl halides with amines.

2.3. Objectives

Specifically, we envisaged a strategy based on the *in-situ* generation and reactivity of acylcopper(III) complex, RCOCu(III), such intermediate can be generated through a range of elementary mechanisms (Scheme 85). The most convenient option would involve an oxidative addition step of the copper(I) catalyst and an aryl iodide **6**. Then, the aryl-Cu(III)-complex after coordination and CO-insertion would yield a transient acylcopper(III) intermediate that evolve to the target benzamide **8** after coordination of the amine **7** and a reductive elimination step. Noteworthy, the proposed catalytic cycle has been adapted considering the one proposed by Heck and co-workers in his pioneering work with palladium.[117] According to the literature that is currently available, copper has the potential to replace palladium as a catalyst. Indeed, every elementary step of the catalytic cycle has already been reported in the specialized literature dedicated to copper.



Scheme 85. Proposed synthetic strategy for the development of a new copper-catalyzed carbonylative cross-coupling of aryl halides and amines.

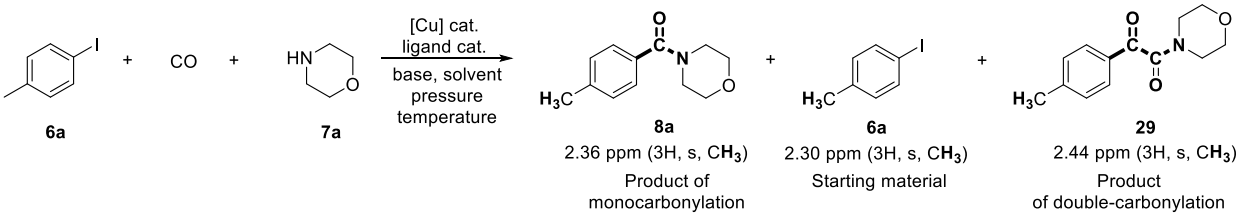
[116] Wu, X. F.; Hu, Y.; Li, Y. *Chem. Soc. Rev.* **2018**, *47*, 172–194.

[117] Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318–3326; (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327–3331.

Based on this strategy, we will summarize in this chapter the efforts that have been made to develop the first copper-catalyzed aminocarbonylation of aryl iodides. The model system used for our investigation will be discussed first, after which the optimization for the development of the copper-catalyzed carbonylative cross-coupling by a systematic variation of all crucial parameters (nature of the copper salt, ligand, base, additives, solvent, temperature, and pressure) will be presented and followed by a study of the scope and limitations of this process as well as it use for the synthesis of biologically active compounds. Finally, a discussion of the experiments that were run to try to understand the reaction's mechanism and any potential intermediates involved will be presented and discussed.

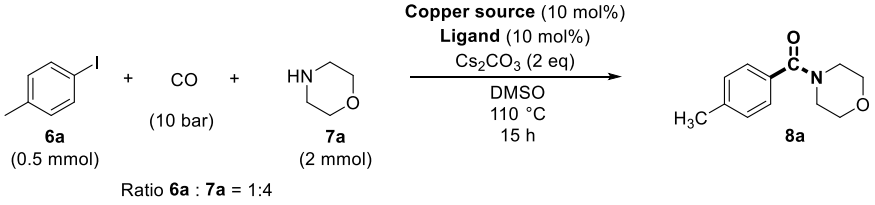
2.4. Optimization of the reaction conditions

To test the feasibility of our strategy and then to optimize it, we first had to choose a simple model substrates: 4-iodotoluene and morpholine were selected. Noteworthy, 4-iodo-toluene was selected as aryl halide partner of the reaction because of its high reactivity due to the low dissociation energy of the C(sp^2)–I bond. Aside from the simplicity of the model substrate, 4-iodotoluene was selected for the optimization phase due to its advantageous spectroscopic characteristics. Indeed, 4-iodotoluene **6a** and its carbonylated derivatives have characteristic sharp signals in the ^{1}H-NMR spectra, which easily allow to evaluate the ^{1}H-NMR yield of each reaction product. Specifically, the methyl onto the phenyl ring of 4-iodo-toluene **6a** has a sharp signal at 2.30 ppm, while in the product of mono-carbonylation **8a** is at 2.36 ppm and in the product of double carbonylation **29** is at 2.44 ppm (Scheme 86). In order to analyse the various preliminary tests collected during the optimization phase, it was agreed to avoid systematic isolation of the desired benzamide and the ^{1}H-NMR yield was evaluated using 1,1,2,2-tetrachloroethane as internal standard.



Scheme 86. Model reaction under investigation.

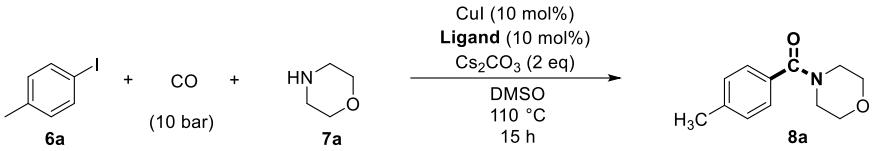
At the beginning of the investigation phase, we considered all possible parameters that could be important for the course of the reaction such as the type of copper source, the type of ligand, the reaction solvent, the reaction temperature, the pressure of carbon monoxide and many others. Considering the complexity of the reaction system at this point, we kept some reaction parameters unchanged and we concentrated mainly on the most crucial reaction parameters. The ligand and copper(I) source, which are recognized to be the main parameters, have received special attention as the most crucial variables. In this preliminary phase, the carbonylation reaction under investigation was carried out using standard values frequently used in the literature. Specifically, we kept fixed five reaction parameters such as the pressure of carbon monoxide (10 bar), the base (Cs_2CO_3, 2 equiv.), the solvent (DMSO), the temperature (110 °C) and the reaction time (15 hours), (Scheme 87).



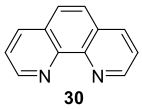
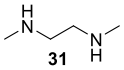
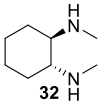
Scheme 87. Model system of study.

2.4.1. Influence of the nature of the ligand

We have begun the investigation for the development of a new copper-catalyzed aminocarbonylation reaction evaluating the influence of the nature of the ligand onto the model system chosen (Scheme 88). One of the most important factors is the nature of the ligand since it can be crucial for the solubility of the copper catalyst and can also play an important role in stabilizing some reaction intermediates such as the frequently evoked copper(III) intermediates, which are stabilized by strongly donating ligands favouring a square planar geometry. For these reasons we carried out a screening of a library of ligands commonly used in copper catalysis with the intention of identifying the most suitable candidate. Specifically, we focused our attention on ligands such as β-diketones,[118] aminoacids,[119] phenanthroline derivatives,[120] diamines[121] and diphosphine[122]. The efficacy of these ligands was evaluated for the aminocarbonylation in the presence of 10 mol% of copper iodide, one of the most common copper source. Notably, in these initial trials, a 1:1 ratio of copper/ligand was selected. The results obtained with respect of the nature of the ligands are collected in the Table 1. Most initial attempts were regrettably unsuccessful since in most cases, only traces of the product were found. The only positive result was actually obtained when a bidentate phosphine ligand, Xantphos, was used. In this case, traces of the product were identified in the ^{1}H-NMR analysis of the crude mixture. Therefore, it was decided to evaluate the Xantphos **17** efficiency in the presence of other copper sources in order to maximize the yield of the desired product.



Scheme 88. Screening of ligands onto the model reaction.

Entry	Ligand	Yield (%)[a]
1	1,10-Phenanthroline  **30**	-
2	*N, N*-Dimethylethylenediamine  **31**	-
3	*trans-N, N'*-Dimethylcyclohexane-1,2 diamine  **32**	-

[a] Yields determined by NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

Table 1. Screening of the ligands.

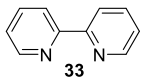
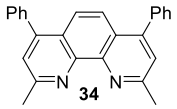
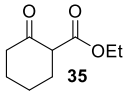
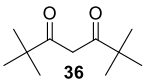
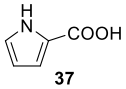
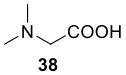
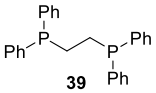
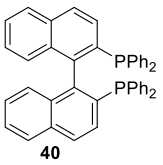
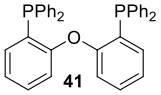
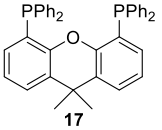
[118] (a) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742–8743. (b) Shafir, A.; Lichtor, P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *72*, 3863–3867. (c) Bao, W.; Lv, X. *J. Org. Chem*. **2007**, *10*, 3863–3867.

[119] (a) Cai, Q.; Ma, D. *Acc. Chem. Res.* **2008**, *11*, 1450–1460. (b) Deng, W.; Wang, Y.; Zou, W.; Liu, L.; Guo, Q. *Tetrahedron Lett*. **2004**, *45*, 2311–2315.

[120] (a) Buchwald, S. L.; Koval, E. D.; Altman, R. A. *J. Org. Chem.* **2007**, *16*, 6190–6199.; (b) Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657–2660.

[121] Surry, D. S.; Buchwald, S. L. *Chem. Sci*. **2010**, *1*, 13–31.

[122] van Leeuwen, P. W.N.M.; Kamer, P. *Catal. Sci. Technol*. **2018**, *8*, 26–113.

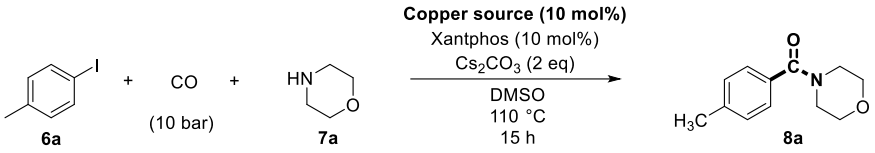
Entry	Ligand	Yield (%)[a]
4	2,2′-Bipyridine  **33**	-
5	Bathocuproine  **34**	-
6	Ethyl 2-oxocyclohexanecarboxylate  **35**	-
7	2, 2, 6, 6-Tetramethyl-3,5-heptanedione  **36**	-
8	Pyrrole-2-carboxylic acid  **37**	-
9	*N, N*-Dimethylglycine  **38**	-
10	Ethylenebis(diphenylphosphine)  **39**	-
11	rac-BINAP  **40**	-
12	DPEphos  **41**	traces
13	**Xantphos**  **17**	**16**

[a] Yields determined by NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

Table 1. Screening of the ligands.

2.4.2. Influence of the nature of copper catalyst

We indeed next turned our attention to the nature of the copper source (Scheme 89), which is a crucial parameter as the chemical reactivity, solubility in the organic solvents and stability of the copper source used is dependent of the counter ion and the ligand used. According to the data gathered from the screening of the copper sources, CuTC (copper(I) thiophene-2-carboxylate, entry 9, Table 2) showed a slightly increased production of the product with a 21% ^{1}H-NMR yield in the reaction crude. Unfortunately, the majority of the screened catalysts were found to furnish the product in lower yields.



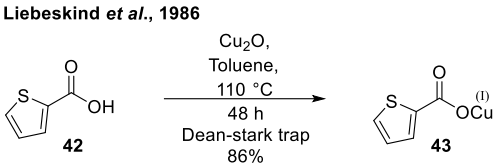
Scheme 89. Screening of the copper sources.

Entry	Copper Source	Yield (%)[a]
1	CuCN	6
2	CuCl	8
3	CuBr·DMS	8
4	CuBr	11
5	$(CF_3SO_3Cu)_2 \cdot C_6H_6$	13
6	Cu_2O	14
7	CuSCN	17
8	CuI	16
9	**CuTC**	**21**

[a] Yields determined by NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

Table 2. Screening of the copper sources.

The CuTC **43** used was prepared from high purity copper(I) oxide and 2-thiophenecarboxylic acid **42** following the Liebeskind's protocol (Scheme 90).[123] The higher yield obtained for the desired product was attributed to the thiophene-2-carboxylate anion, which can enhance the solubility of the catalyst due to its organic nature.

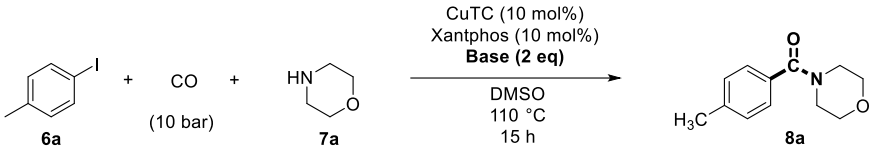


Scheme 90. Synthesis of CuTC through the Liebeskind's protocol.

[123] Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *11*, 2748–2749.

2.4.3. Influence of the nature of base

Several bases were next tested, as listed in Table 3 (entry 1-9), but unfortunately no significant increase was observed in most cases, rather fluctuations in ^{1}H-NMR yields were obtained. Using Li_2CO_3 and CsF (entry 10 and 11 of Table 3) gave the first interesting results, since to our greatest delight the target product was detected with 56% and 61% of yield, respectively. Later, inspired by recent literature and considering that the problematic step in the catalytic process might be transfer of the acyl group from the copper center to the amine, we decided to explore the use of sodium phenoxide as an organic base that might also act as an acyl transfer agent to promote the aminocarbonylation.[124] Unfortunately, the addition of sodium phenoxide ($NaOC_6H_5$, entry 3) did not significantly increase the formation of the desired product which was obtained with only 20% yield. At this point, we decided to investigate the use of electron-poor phenoxides as they could increase the electrophilicity of the corresponding acyl transfer agent. Thus, sodium 4-fluorophenoxide ($NaOC_6H_4F$, entry 11, Table 3) and sodium pentafluorophenoxide ($NaOC_6F_5$, entry 12, Table 3) were tested. Gratifyingly, a significant improvement was observed with the addition of sodium pentafluorophenoxide providing in 71% yield the target product.



Scheme 91. Screening of the base.

Entry	Base	Yield (%)[a]
1	KO^tBu	13
2	K_3PO_4	17
3	Cs_2CO_3	21
4	Na_2CO_3	22
5	KOAc	23
6	DBU	23
7	K_2CO_3	37
8	Li_2CO_3	56
9	CsF	61
10	PhONa	20
11	4-F-PhONa	35
12	**C_6F_5ONa**	**71**

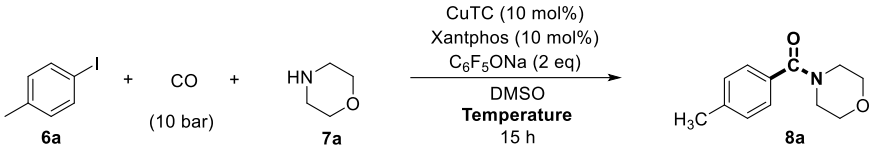
[a] Yields determined by NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

Table 3. Screening of the base.

[124] (a) Quesnel, J. S.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2013**, *135*, 16841–16844. (b) Quesnel, J. S.; Kayser, L. V.; Fabrikant, A.; Arndtsen B. A. *Chem. Eur. J.* **2015**, *21*, 9550–9555. (c) Lagueux-Tremblay, P. L.; Fabrikant, A.; Arndtsen, B. A. *ACS Catal.* **2018**, *8*, 5350–5354. (d) Martinelli, J. R.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2007**, *46*, 8460–8463.

2.4.4. Influence of additional parameters

With this promising phenoxide in hand, we next attempted to further improve the yield by screening additional reaction parameters such as the temperature, the equivalent of base and the catalytic loading of the copper source. Lower reaction temperatures were initially attempted, however regrettably when the reaction temperature was reduced at 25 and 70 °C, only traces of the product were identified in the crude of the reaction (entry 1 and 2, Table 4). This outcome is in line with the majority of carbonylative cross-coupling reactions described in the literature, most of which take place at high temperatures. We then decided to keep the reaction temperature at 110 °C (entry 3, Table 4) and additional tests were then carried out in an effort to reduce the number of sodium pentafluorophenoxide ($NaOC_6F_5$) equivalents used, from 2.0 to 1.2 equivalents (entry 4 and 5, Table 5). Notably, it was shown that the amount of sodium pentafluorophenoxide could be decreased without impacting the product yield. Finally, increasing the loading of Xantphos to 20 mol%, we were able to slightly increase the reaction yield, *p*-tolyl-iodide **6a** being smoothly aminocarbonylated with morpholine **7a** in a reproducible 84% isolated yield to furnish the desired product **8a** (entry 7, Table 6).

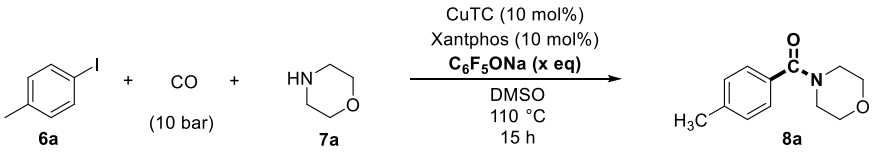


Scheme 92. Screening of the temperature.

Entry	Temperature	Yield (%)[a]
1	25 °C	traces
2	70 °C	10
3	110 °C	71

[a] Yields determined by NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard
[b]Isolated yield in parentheses

Table 4. Screening of the temperature.

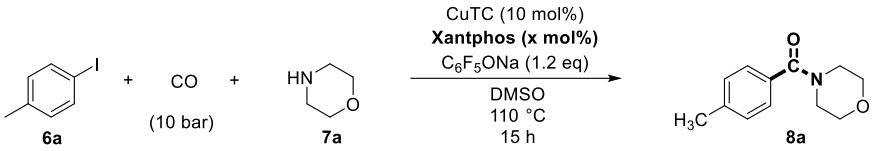


Scheme 93. Screening of the equivalent of $NaOC_6F_5$.

Entry	Equivalent of $NaOC_6F_5$	Yield (%)[a]
4	1.2 equiv.	71
5	2 equiv.	70

[a] Yields determined by NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard
[b]Isolated yield in parentheses

Table 5. Screening of the equivalent of $NaOC_6F_5$.



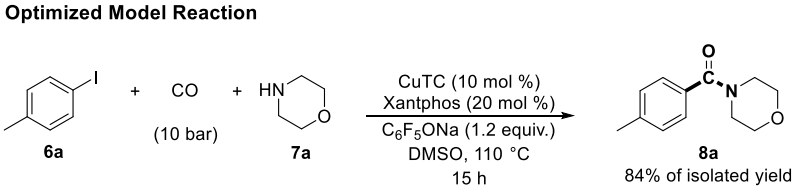
Scheme 94. Screening of the equivalent of Xantphos.

Entry	Catalytic loading of Xantphos	Yield (%)[a]
6	10 mol%	71
7	**20 mol%**	**86(84)**[b]

[a] Yields determined by NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard
[b]Isolated yield in parentheses

Table 6. Screening of the equivalent of Xantphos.

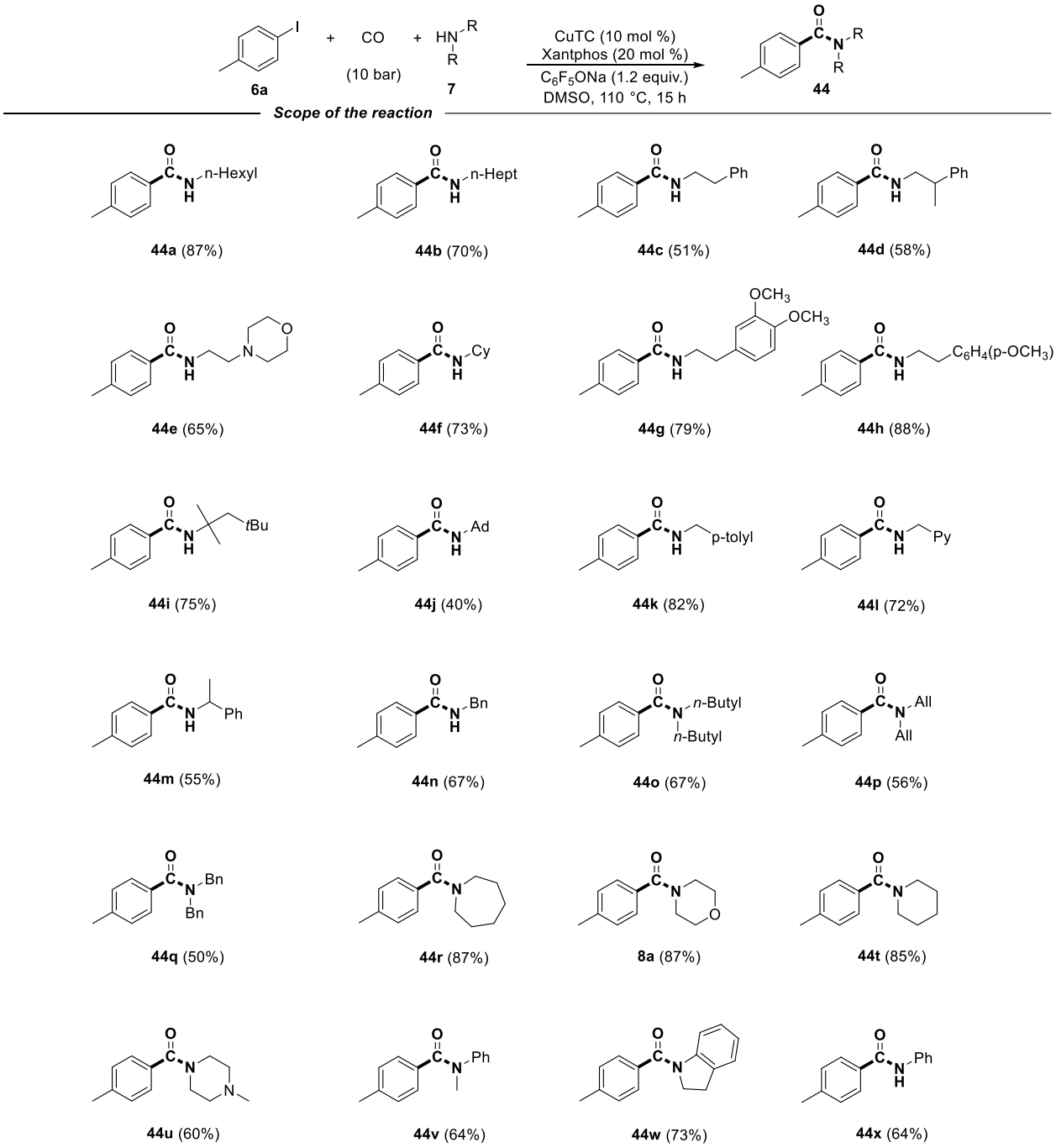
Under the optimized reaction conditions consisting of 10 mol% of Liebeskind's catalyst (CuTC), 20 mol% of Xantphos, 1.2 equiv. of sodium pentafluorophenoxide in DMSO at 110 °C and under 10 bar of carbon monoxide, *p*-tolyl-iodide **6a**, could be reproducibly and successfully aminocarbonylated with morpholine **7a** in an isolated yield of 84% (Scheme 95). At this point, after optimizing the reaction conditions, it was decided to investigate the scope of the reaction and carry out a systematic screening of amines and aryl iodides.



Scheme 95. Optimized model reaction for the aminocarbonylation of 4-iodotoluene.

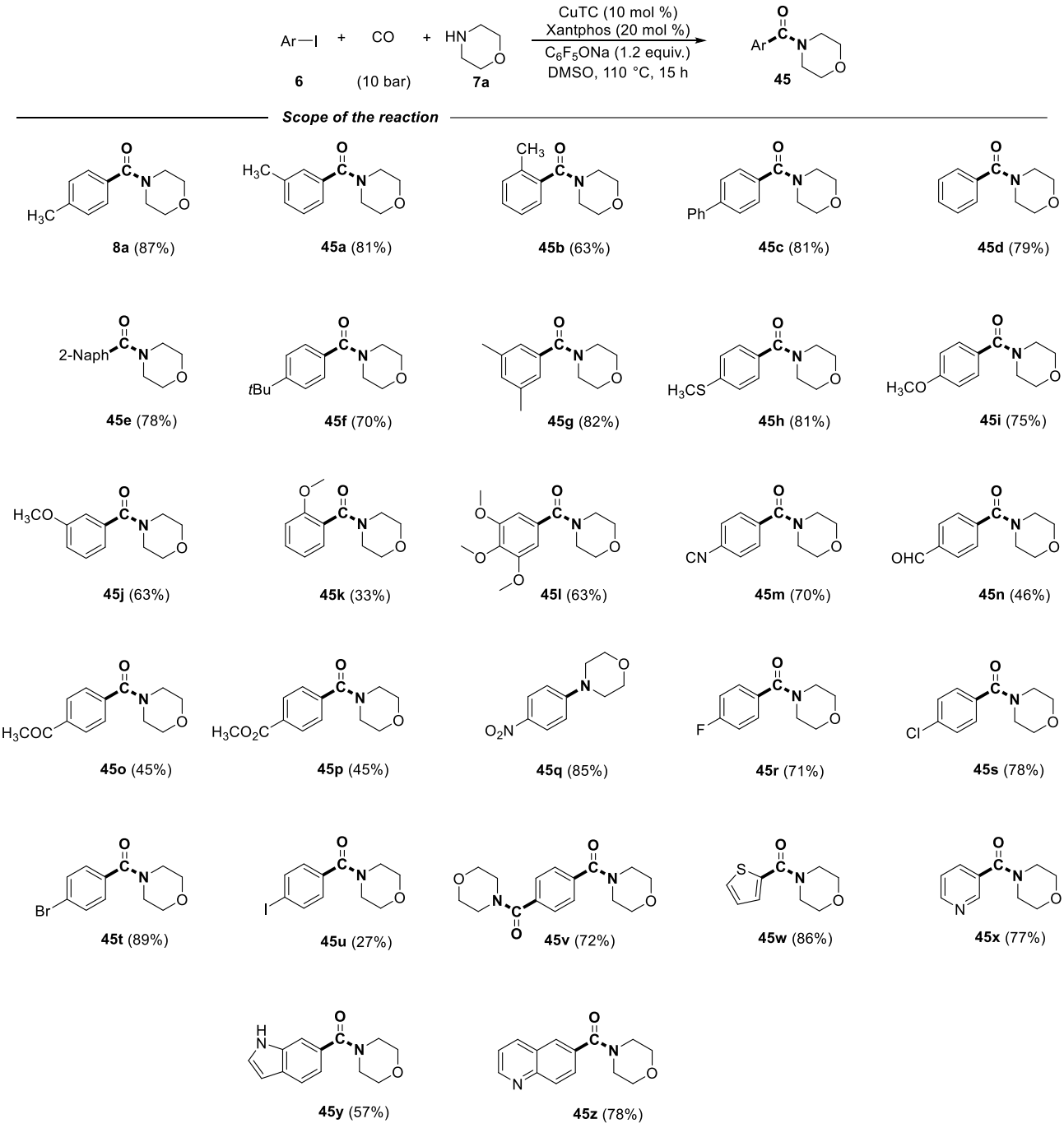
2.5. Study of the scope

Having in hand the optimized reaction conditions, the substrate scope was then investigated with various (hetero)aryl iodides and amines with the aim of delineating both the potential and limitations of our protocol. The scope was first studied with respect to the nature of the amine (**7**), using 4-iodo-toluene **6a** as the coupling partner (Scheme 96). A wide range of primary and secondary amines, cyclic and acyclic, were tested and afforded the desired products. The aminocarbonylation of primary amines with 4-iodotoluene led to good yields in a range of yields between 40 and 88%, **44a**-**44j**. To our surprise, even sterically hindered and conformationally rigid amines such as *tert*-octylamine and adamantylamine, still resulted in acceptable yields (75% and 40% for **44i** and **44j**, respectively) confirming the general applicability of the protocol developed towards more potentially unsuccessful substrates. When primary benzylic amines were tested, good yields were observed **44k**-**44l**, even in the instance of α-methylbenzylamine **44m**, where the methyl group close to the amino one lowered the yield to 55%. To our delight, sterically more hindered substrates as secondary amines, such as *n*-dibutylamine, *n*-diallylamine and dibenzylamine, still resulted in acceptable yields (67%, 56% and 50% for **44o**-**44q**, respectively). The ring size of cyclic amines as azepane **44r**, morpholine **8a**, piperidine **44t** and 1-methylpiperazine **44u** did not affect the success of the aminocarbonylation reaction and all of them led to the corresponding benzamides in a range of yields between 60 and 87%. Also less nucleophilic aromatic amines as *N*-methylaniline **44v**, indoline **44w** and aniline **44x** were successfully carbonylated, although with more moderate yields.



Scheme 96. Scope of the copper-catalyzed aminocarbonylation with representative amines.

Then, the substrate scope with various (hetero)aryl iodides was explored (Scheme 97). As shown next page, the procedure tolerates well diverse electronic and steric substituents onto the aromatic ring of the aryl iodides tested as well as (hetero)aryl iodides. A number of functional groups such as phenyl **45c**, methyl sulfide **45h** and methoxy **45i** were all well tolerated resulting in the formation of the reaction products in good to excellent isolated yields. Electron-rich and electron-poor substrates worked both well, although a general trend has been identified: electron-rich and electron-neutral aryl iodides are indeed able to provide higher yields than the ones obtained with electron-poor aryl iodides containing cyano **45m**, formyl **45n**, methyl ketone **45o**, and methyl ester **45p** as substituents. Surprisingly, when 1-iodo-4-nitrobenzene was used as substrate, only the Ullmann amination product **45q** was observed in 85% yield.

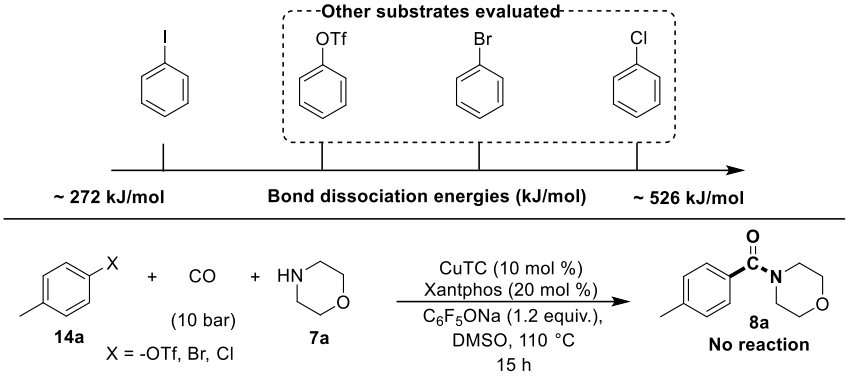


Scheme 97. Scope of the copper-catalyzed aminocarbonylation of morpholine with different (hetero-)aryl iodides.

Most probably, the strong electron-withdrawing character of the nitro group onto 1-iodo-4-nitrobenzene facilitates the oxidative addition of the catalyst onto the aryl iodide, the coordination of the amine and a quick reductive elimination which afford the formation of the product of Ullman amination. Interestingly, the reactions involving 4-haloiodobenzenes (halogen: F-, Cl-, Br-) proceeded chemoselectively at the aryl-iodine bond to give the corresponding fluorine-, chlorine-, bromine-containing products, respectively **45r**-**45u**. Notably, when 1,4-diodobenzene was used as a starting material, it was possible to obtain a mixture of mono-carbonylated **45u** and double-carbonylated **45v** products (D: 72% and M: 27%); however, doubling the equivalents of amine (8 eq), enabled a smooth double carbonylation in 89% of isolated yield. Furthermore, also more appealing iodinated aromatic heterocycles such as 2-iodothiophene **45w** 3-iodopyridine **45x**, 5-iodoindole **45y** and 6-iodoquinoline **45z**, could be successfully coupled to morpholine under our standard conditions to yield the corresponding amides in good yields.

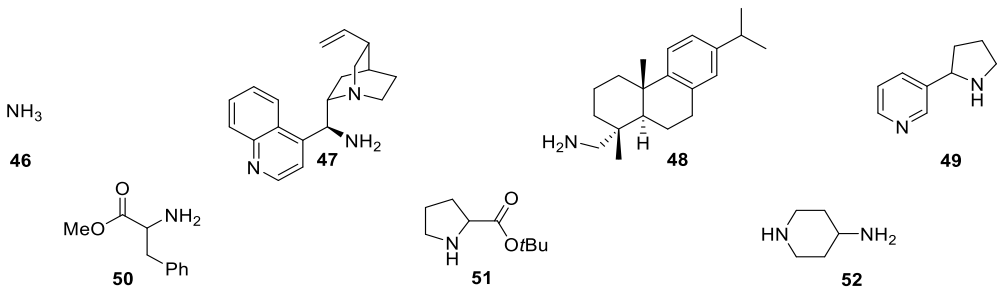
2.6. Limitations of the method

Additional research on the copper-catalyzed aminocarbonylative cross-coupling was next conducted using compounds with more complex structures or a lower reactivity. In order to illustrate the limitations of this procedure, we will try to summarize the substrates that have been tested but have yielded negative results in this section. In addition to aryl iodides, the reaction has also been tested on more challenging substrates such as aryl triflates, aryl bromides and aryl chlorides (Scheme 98). Because of their greater commercial abundance and lower prices, these substrates are frequently utilized as alternatives to the corresponding aryl iodides. These compounds have higher C–X bond dissociation energy than aryl iodides and are less susceptible to oxidative addition, which is often translated into a reduced reactivity in carbonylative cross-coupling reactions.



Scheme 98. Additional aryl halides and pseudo-halides tested.

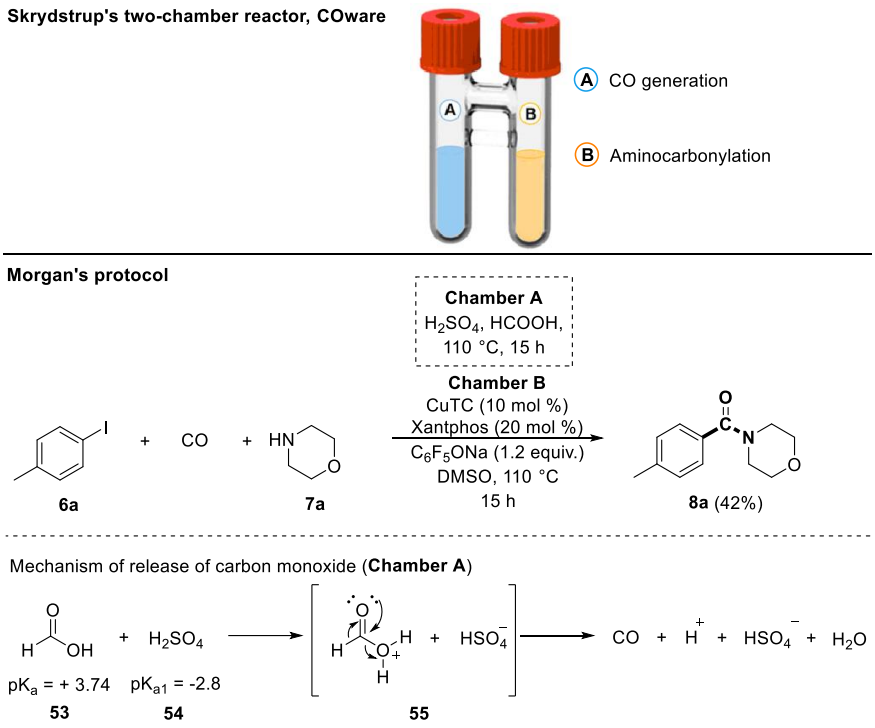
These substrates were examined throughout our investigation in an effort to expand the application of our catalytic system, but unfortunately, we were unable to obtain the aminocarbonylation product with these. Instead, only the presence of the starting material was detected, confirming both the low reactivity of the substrates selected and the inadequacy of the catalytic system. Furthermore, we also tested a series of amines with different structural complexity that unfortunately were not suitable for the carbonylative cross-coupling, since it was not possible to identify the formation of the products and isolate the desired amides from these substrates. Ammonia **46**, cinchonidine **47**, abietylamine **48**, nornicotine **49**, protected aminoacids **50-51**, and 4-aminopiperidine **52** were among the amines tested that did not result in the formation of the corresponding amides (Scheme 99). For what concern the protected amino acids, probably their ineffectiveness to be good nucleophiles in the copper-catalyzed aminocarbonylative cross-coupling is might be due to the fact that they are able to coordinate copper and poison the catalyst. As for, cinchonidine **47** and abietylamine **48**, they are probably too sterically hindered to be carbonylated and no product has been detected in crude reaction mixture either.



Scheme 99. Amines tested that have not led to the formation of the amicarbonylation products.

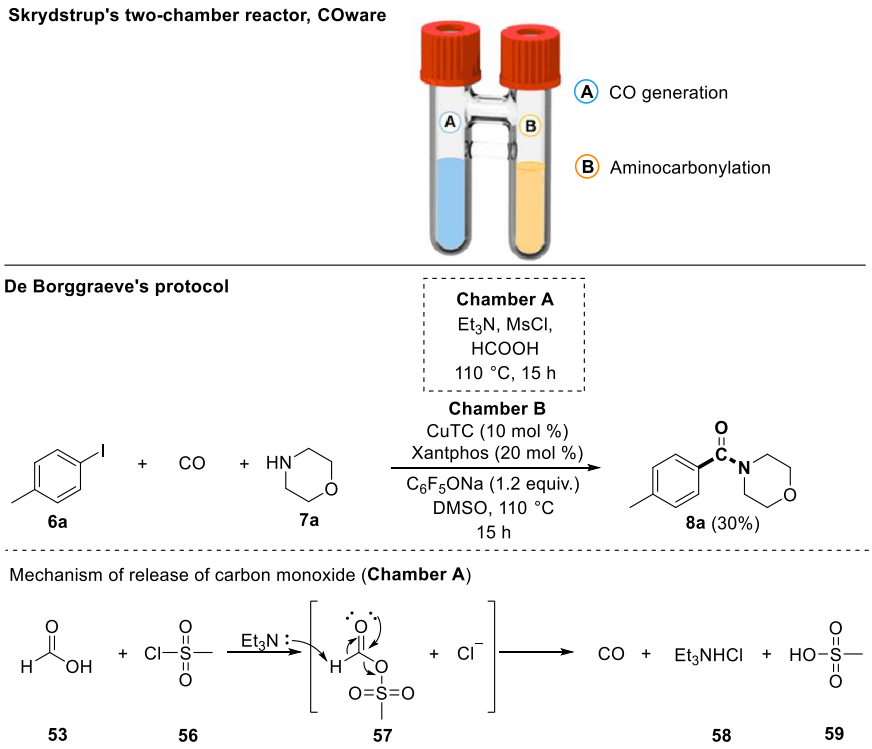
2.7. Aminocarbonylation with carbon monoxide generated *ex-situ* in a CO-ware

After delineating the scope and limitations of our procedure, we next considered the use of carbon monoxide surrogate in a two-chamber reactor, the main objective being to circumvent the use of high-pressure equipment and carbon monoxide cylinders. The use of stable precursors of carbon monoxide indeed offers an interesting option, particularly for small-scale reactions, in certain academic and industrial facilities that are either not equipped to handle carbon monoxide or reluctant to utilize it. To do so, we used Skrydstrup's two-chamber COware reactor, in which carbon monoxide is *ex-situ* generated in one chamber before reacting in the second one.[125] Among all the protocols known in literature to release carbon monoxide starting from carbon-monoxide surrogate, we tested two protocols that seemed the most appealing based on their simplicity and the reagents they are based on: the Morgan[126] and De Borggraeve[127] protocols. In the first case, carbon monoxide is successfully generated in the "two-chamber reactor" *ex-situ* by the Morgan reaction, in which formic acid **53** is dehydrated by sulfuric acid **54** (Scheme 100). In the second case, carbon monoxide is generated using the De Borggraeve protocols through the instant decomposition of formic acid **53** induced by the addition of mesyl chloride **56**, MsCl) and triethylamine (Scheme 101). In a two-chamber COware reactor of 20 mL, the first chamber (chamber A) was charged with the reagents required to generate carbon monoxide, while the second chamber (chamber B) was charged with the reagents required to perform the aminocarbonylation. The COware reactor was tightly closed and heated at 110 °C, and after 15 h at 110 °C, work up and column chromatography, the desired amide was obtained in 42% yield using the Morgan's protocol and in 30% yield using the De Borggraeve's protocol.



Scheme 100. Aminocarbonylation with carbon monoxide generated *ex-situ* in a two-chamber reactor using the Morgan's protocol.

[125] Friis, S. D.; Lindhardt, A. T.; Skrydstrup, T. *Acc. Chem. Res.* **2016**, *49*, 594–605.
[126] Brancour, C.; Fukuyama, T.; Mukai, Y.; Skrydstrup, T.; Ryu, I. *Org. Lett*. **2013**, *15*, 2794–2797.
[127] Veryser, C.; Van Mileghem, S.; Egle, B.; Gilles, P.; De Borggraeve, W. M. *React. Chem. Eng.* **2016**, *1*, 142–146.

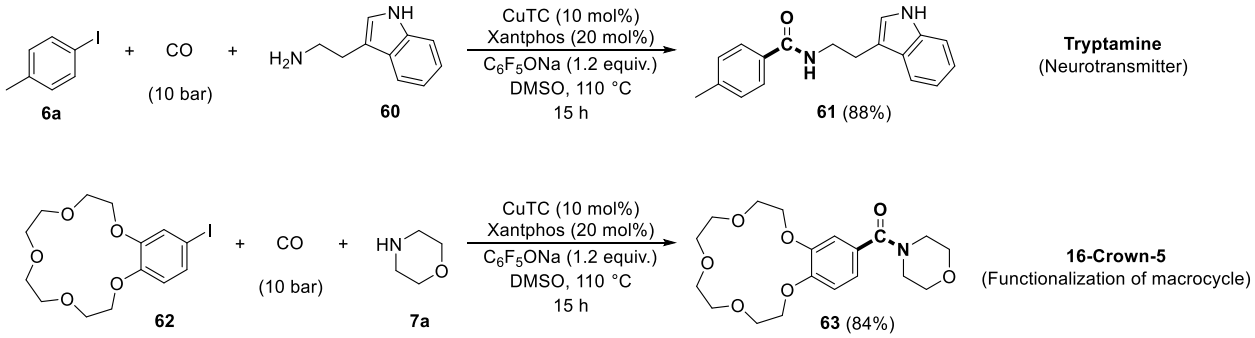


Scheme 101. Aminocarbonylation with carbon monoxide generated *ex-situ* in a two-chamber reactor using the Morgan's and the De Borggraeve's protocol.

These yields were not further optimized but demonstrate that the use of carbon monoxide and high pressure equipment is not strictly required for our carbonylative cross-coupling. The yields from the COware reactor are obviously lower than those from the autoclave, which might be attributed to the lower pressure of carbon monoxide used (4 bar). This value is the recommended maximum pressure to use with COware reactors.

2.8. Applications to the synthesis of complex substrates

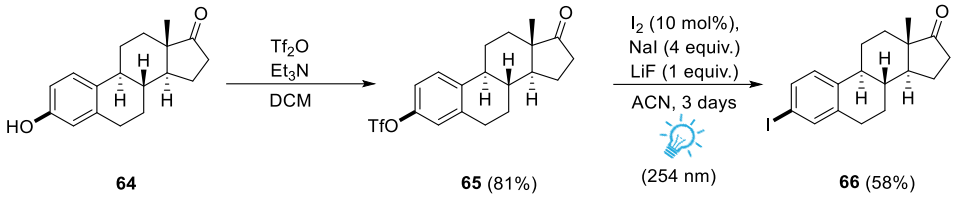
Additionally, we could perform the aminocarbonylation reaction onto the primary amine of tryptamine **60**, one of the most basic monoamine alkaloids, which is essential for many biological systems as a neurotransmitter.[128] It has also been possible to functionalize a more complex aryl iodide containing as side chain a 16-crown-5 ether **62**, an extremely common motif in supramolecular chemistry (Scheme 102).



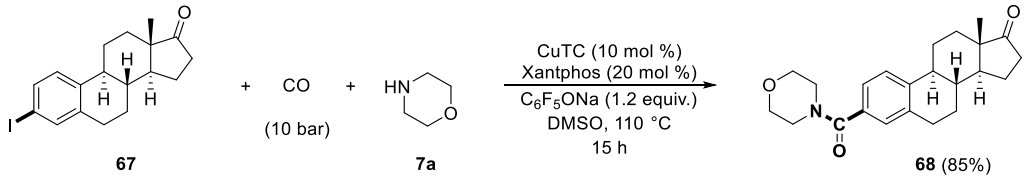
Scheme 102. Aminocarbonylation to the synthesis of complex substrates.

[128] Jones, R. S. G. *Prog. Neurobiol.* **1982**, *19*, 117–139.

Finally, in an effort to further demonstrate the generality of our protocol, we decided to perform the aminocarbonylation onto a molecule with a more complex architecture, our goal being to demonstrate the effectiveness of our protocol operating not only on simple structures but also on the most complicated ones. An iodinated-derivative of estrone was selected and prepared through functional group interconversion of the hydroxyl group onto the aromatic ring. Firstly, estrone **64** was treated with trifluoromethanesulfonic anhydride, which smoothly converted it into the corresponding aryl triflate **65** in 81% yield. Thereafter, the estrone-triflate **65** was converted in 58% yield into the estrone-iodide **66** using a simple and efficient photochemical reaction developed by the Li group in 2017, that converts successfully aryl triflates into the corresponding iodinated analogues (Scheme 103).[129] At this point, the iodinated steroid **67** was reacted under our standard conditions and to our delight the carbonyl product **68** was smoothly obtained in good yield, showing the ability of our protocol to be general and easily extendable even to substrates with greater complexity (Scheme 104).



Scheme 103. Conversion of an estrone-based aryl triflate into the corresponding iodide through a photochemical reaction under UV irradiation.

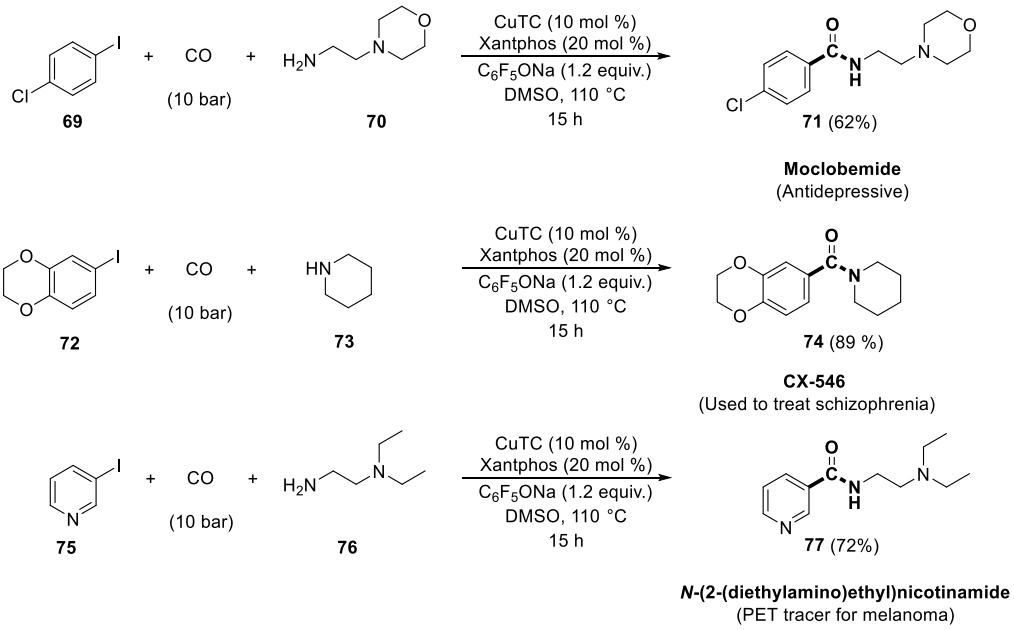


Scheme 104. Aminocarbonylation of estrone as model natural substrate.

2.9. Applications to the synthesis of molecules of biological interest

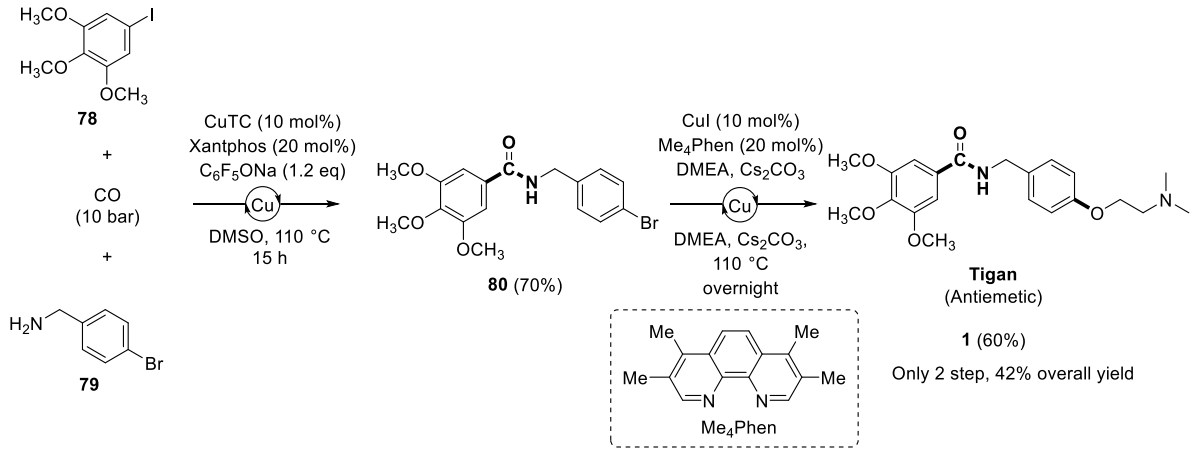
To further explore the potential application of our protocol, we next devoted our efforts to the synthesis of amides of biological interest. Therefore, we looked for benzamides that could be prepared by our copper-catalyzed aminocarbonylation. In this perspective, we successfully synthetized Moclobemide, a drug used to treat depression and social anxiety commercialized by Hoffmann–La Roche SA,[130] CX-546, an ampakine drug developed by Cortex Pharmaceuticals and used to treat schizophrenia,[131] and a pyridine derivative known to be an efficient PET tracer for melanoma in the clinical trial phase (Scheme 105).[132] To our delight, good yields were obtained even with the aryl iodides and the amines tested for the preparation of biologically active compounds. Indeed, Moclobemide and CX-546 were prepared in 62% and 89% of yield, confirming the general applicability of the protocol developed towards primary and secondary amines **71**-**74**. Furthermore, also more appealing iodinated aromatic heterocycles such as 3-iodopyridine have been successfully aminocarbonylated under our standard conditions to furnish the corresponding amide of the PET tracers for melanoma **77** in a 72% of yield.

[129] Liu, W.; Yang, X.; Gao, Y.; Li, C. *J. Am. Chem. Soc.* **2017**, *25*, 8621–8627.
[130] Jesse, D. M. *J. Chem. Educ.* **2008**, *85*, 1424–1425.
[131] Lipina, T.; Weiss, K.; Roder, J. *Neuropsychopharmacol.* **2007**, *32*, 745–756.
[132] Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc*. **2011**, *15*, 6061–6071.



Scheme 105. Aminocarbonylation of molecules of biological interest.

Additionally, we have also designed a synthesis of Tigan, an antiemetic drug developed by GlaxoSmithKline, using a new approach based on only two steps and a series of double copper-catalyzed cross-coupling reactions.[133] Firstly, the amidic moiety was installed using the commercially available reagents 5-iodo-1,2,3-trimethoxybenzene **78** and 4-bromo-benzylamine **79** as nucleophiles through the copper-catalyzed aminocarbonylative cross-coupling reaction. Thereafter, using 2-dimethylaminoethanol as solvent, we used a second copper-catalyzed protocol developed by the Buchwald group in 2008 for the easy O-arylation of the aryl-bromide intermediate **80**.[134] This protocol use 10 mol% of 3,4,7,8-tetramethyl-1,10-phenanthroline (Me_4-Phen) as a ligand in presence of 5 mol% of CuI and is particularly appealing for the reaction of aryl bromides with primary alcohols. This novel strategy is very attractive since it uses copper catalysts which enable the preparation of the target product **1**, in a sequence of only two steps, with an overall yield of 42% (Scheme 106).



Scheme 106. Double copper-catalyzed cross-coupling reactions for the synthesis of Tigan.

[133] Lescot, C.; Nielsen, D. U.; Makarov, I. S.; Lindhardt, A. T.; Daasbjerg, K.; Skrydstrup, T. *J. Am. Chem. Soc.* **2014**, *16*, 6142–6147.

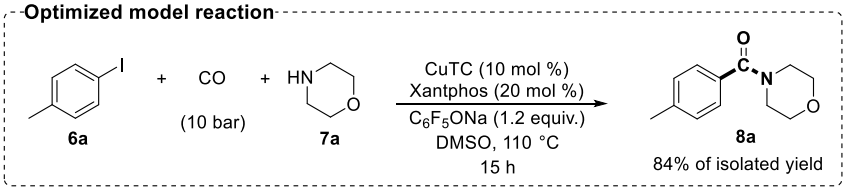
[134] Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *1*, 284–286.

As far as we know this is the most direct synthetic strategy for the preparation of Tigan. Clearly, even if other alternative methods are available in literature, this new synthetic strategy has the advantage to use very cheap and less-toxic copper catalysts affording the desired product in a sequence of only two-step, resulting tremendously attractive for industrial application.

At this point in the next section, after investigating the scope and the limitations of the reaction, we will devote our attention to illustrating the efforts made to investigate the reaction mechanism of our methodology and identify the key intermediates involved in the catalytic cycle.

2.10. Mechanism investigation

We next carried out a number of additional experiments with the aim to identify the possible key intermediates and understand the catalytic cycle. Firstly, we conducted a series of control experiments where each reagent was individually omitted from the reaction protocol devised. This allowed us to validate our protocol because the reactions failed to occur without the chosen ligand and copper salt. Moreover, we have realized that the role of C_6F_5ONa as additive is crucial for achieving higher reaction yields, since in its absence the desired product was isolated in only 47% **8a**, showing that C_6F_5ONa is able to boost the yield of our catalytic system (Table 7, entry 3).



Scheme 107. Optimized model reaction

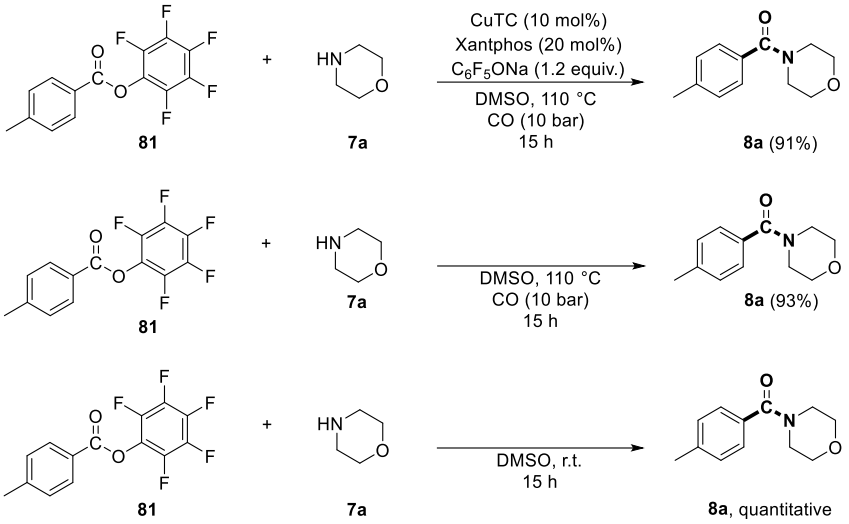
Entry	Chemical negative controls tests	Yield (%)[a]
1	No CuTC	-
2	No Xantphos	-
3	No C_6F_5ONa	47%
4	No morpholine	-
5	No CuTC and Xantphos	-
6	No CuTC, Xantphos and C_6F_5ONa	-

[a] Yields determined by NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

Table 7. Chemical negative controls experiment onto the model reaction.

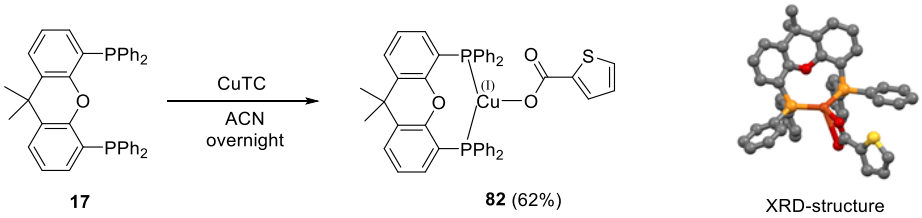
Having hypothesized the formation of an activated aryl ester intermediate **81**, we synthetized and tested this compound under different reaction conditions: (a) in the presence of morpholine with all other reagents and under our standard reaction conditions; (b) in the presence of morpholine without other reagents under the standard reaction conditions; (c) with morpholine in DMSO at room temperature and under atmospheric pressure (Scheme 108). Clearly, these results show that the activated ester does not decompose under the reaction condition at high temperature and pressure of carbon monoxide, and it is also very reactive toward morpholine to furnish the corresponding amide **8a** in excellent yields. Therefore, it is reasonable to believe that, under our conditions, the formation of an activated ester is highly probable before

the formation of the amide after aminolysis; nevertheless, its isolation or *in-situ* identification have not been possible to prove, most likely due to its rapid conversion to the amide.



Scheme 108. Reactivity tests of the activated phenyl ester.

Then, we turned our attention to the synthesis of a CuTC-Xantphos complex, the possible active catalyst. This was accomplished by dissolving an equimolar mixture of Xantphos **17** and CuTC in ACN in accordance with the method described by the Huang group in 2010,[135] from which a 1:1 complex was cleanly formed via precipitation (Scheme 109). The CuTC-Xantphos complex **82** has been crystallized for a single crystal XRD-analysis, that provided the desired structure with good resolution.

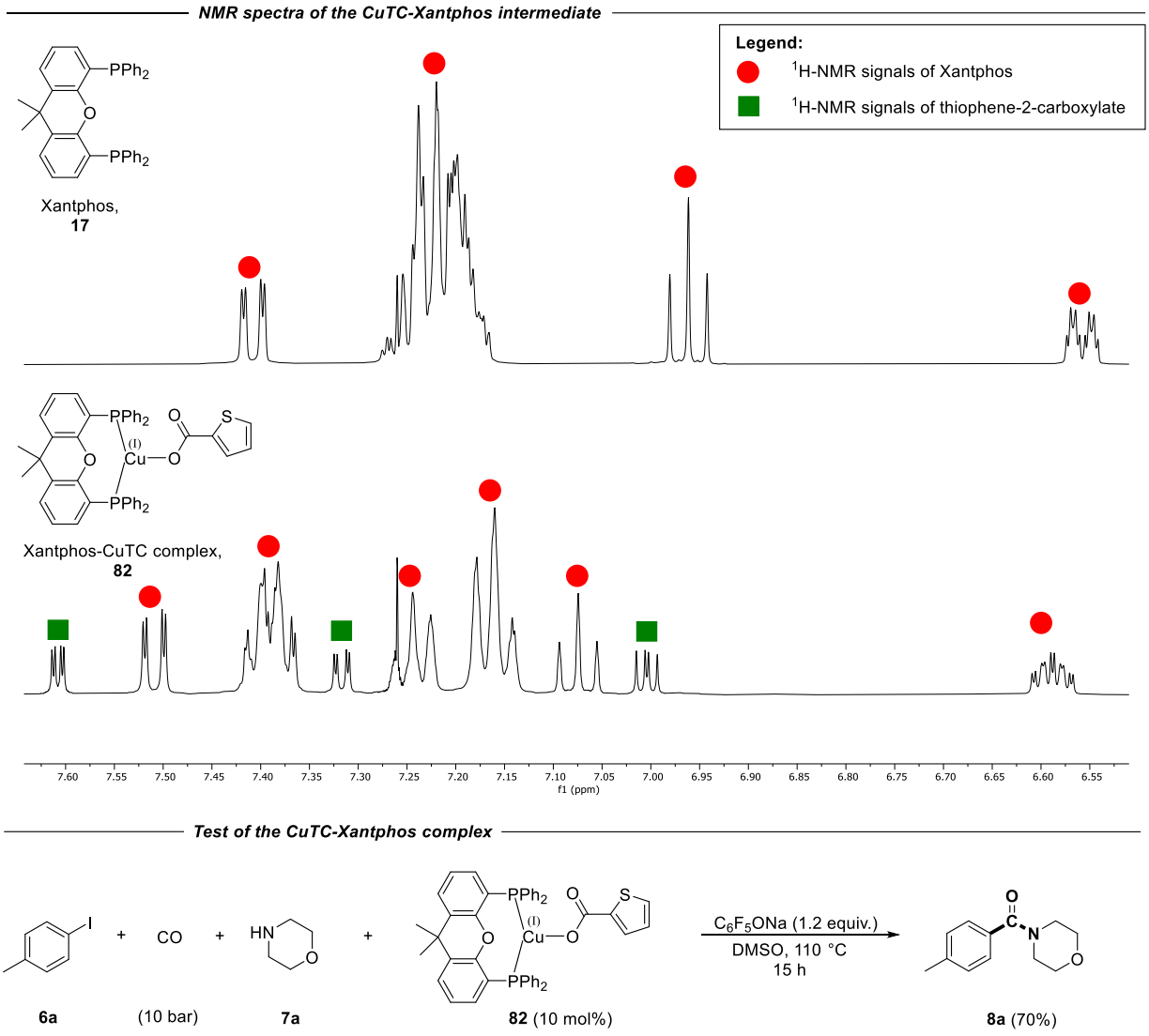


Scheme 109. Synthesis of the CuTC-Xantphos complex.

The formation of the CuTC-Xantphos complex has been confirmed by comparison of ^{1}H-NMR spectra between the CuTC-Xantphos complex **82** and the free Xantphos ligand where it is possible to highlight a clear shift of the chemical shift of the proton attached onto the aromatic ring of Xantphos and the appearance of the three proton signals of the thiophene-2-carboxylate at 7.6, 7.3 and 7.0 ppm (Scheme 110).

Then, we have tested the use of 10 mol% of the CuTC-Xantphos complex **82** on our model reaction, and we could identify and isolate the desired carbonylated product with a 70% of isolated yield. Therefore, it is possible to suppose that the CuTC-Xantphos complex, which is produced *in-situ*, may be the catalytically active species (Scheme 110).

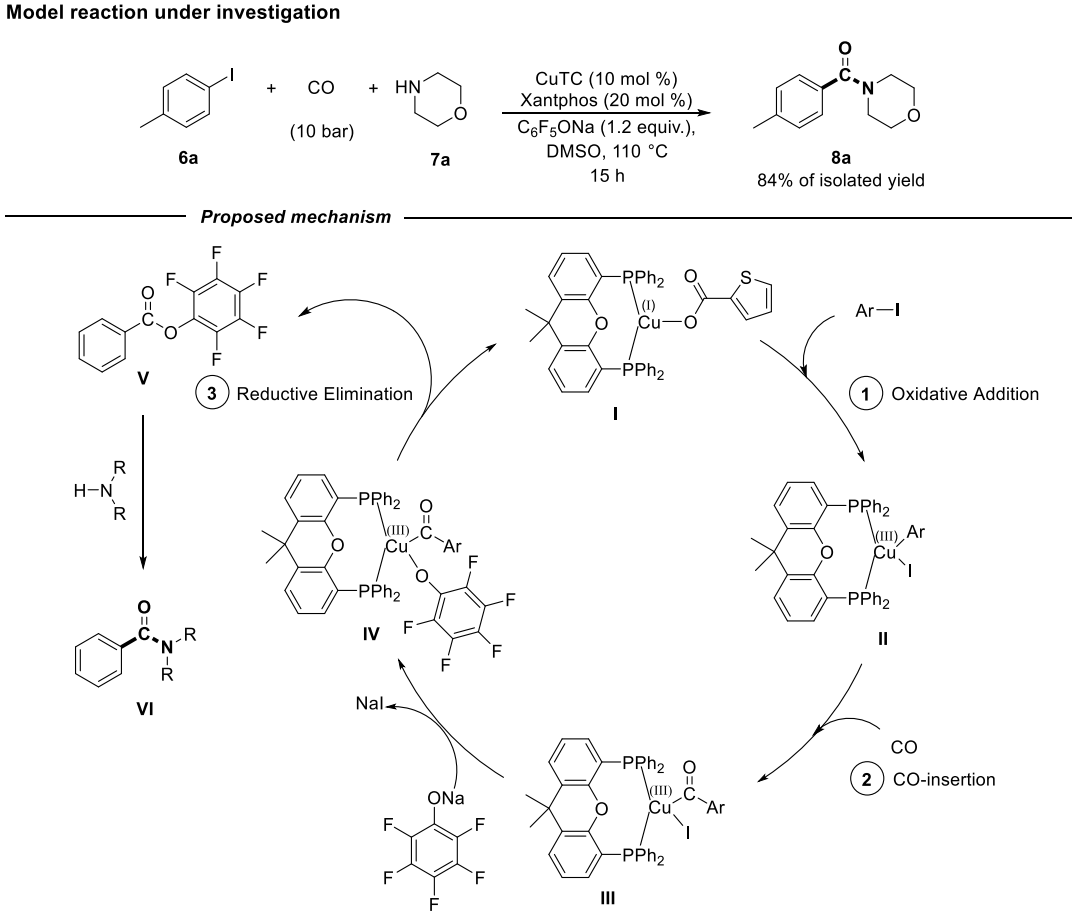
[135] Huang, J.; Chan, J.; Chen, Y.; Borths, C. J.; Larsen, R. D.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *132*, 3674–3675.



Scheme 110. Test of the CuTC-Xantphos complex with the model reaction.

2.11. Proposed reaction mechanism

Considering the experimental results obtained and the literature available in the field of carbonylative cross-coupling reaction, the most likely mechanism for the carbonylative cross-coupling investigated might involve a Cu(I)/Cu(III) catalytic cycle, in which the aryl halide would be activated by an oxidative addition at copper (I) to form an aryl-copper(III) intermediate **II**. Then, with the coordination of carbon monoxide to the metal center and the insertion in the Cu–Ar bond, a transient acyl-copper(III) intermediate **III** would be generated. At this stage sodium pentafluorophenoxide ($NaOC_6F_5$) would intercept the acyl copper species and lead to the formation, by ligand exchange and reductive elimination, of an activated ester **V** being quickly converted to the desired amide **VI** after aminolysis (Scheme 111).



Scheme 111. Proposed catalytic cycle for the copper-catalyzed aminocarbonylation.

2.12. ICP-MS analysis

During the investigation phase in which we tried to understand the reaction mechanism of the transformation developed, it was also decided to perform ICP-MS analysis in order to demonstrate the purity of the chemicals used and the absence of contaminants.

Inductively coupled plasma mass spectrometry (ICP-MS) is a type of mass spectrometry that uses an inductively coupled plasma to ionize the sample. This analytical technique has higher speed, accuracy, and sensitivity when compared to atomic absorption spectroscopy. For the ICP-MS analysis, we contacted a company named MEDAC to which we sent all the samples we used to be analysed.[136] The official document obtained is shown here below (Table 8).

MEDAC LTD
Analytical and chemical consultancy services

ANALYTICAL REPORT ICP-OES

MEDAC Ltd
Alpha 319
Chobham Business Centre
Chertsey Road
Chobham
Surrey
GU24 8JB
United Kingdom

www.medacltd.com
Tel: 01276 855410
Email: info@medacltd.com

Date 23rd December 2020

Company / Institution IMCN MOST

Sample Identification	Assay No.	Element	Results	Units
4 IODO TOLUENE	193260*	Pd	<10	ppm
MORPHPOLINE	192361	Pd	<0.1 <0.1	ppm
COPPER THIOPHENE	192362	Pd	37 35	ppm
SODIUM PENTAFLUOROPHENOLTATE	193263	Pd	<5 <5	ppm
XANTPHOS	193264	Pd	<5 <5	ppm
DIMETHYL SULFOXIDE	193265	Pd	0.2 0.4	ppm

Comments * Insufficient sample for duplicate analysis.

Analyst Stephen Goodall

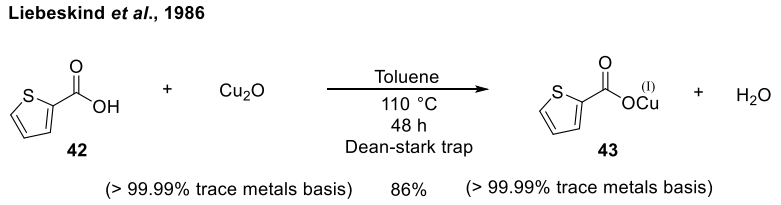
Table 8. ICP-MS results obtained by MEDAC.

From the analysis of the results obtained, we identified the presence of traces of palladium in the CuTC sample used for the reaction for a value between 35 and 37 ppm. This unexpected result immediately called into question all the results previously obtained, since the cross-coupling products could be no longer attributed to the copper catalyst used to catalyze the carbonylative cross-coupling but rather to the traces of palladium detected. It is indeed commonly acknowledged that palladium can be a contaminant of copper-

[136] Medac web site: https://www.medacltd.com.

catalyzed cross-coupling that is difficult to detect and capable of distorting and overestimating the experimental results due to its exceptional efficiency in catalysing carbonylative cross-coupling processes.[137]

Further control experiments were conducted at this stage in an effort to determine the cause of the contamination. Firstly, a new batch of CuTC using Cu_2O (>99.99%) and 2-thiophenecarboxylic acid as starting material was prepared following the Liebeskind's protocol (Scheme 112).[138] CuTC was prepared with high degree of purity (≥ 99.99% trace metals basis) using Cu_2O (≥ 99.99% trace metals basis) purchased from Sigma-Aldrich.[139]



Scheme 112. Synthesis of CuTC (99.99% purity) through the Liebeskind's protocol.

To compare the purity of the two batches of CuTC, the old batch utilized and the high-purity one newly prepared, and determine the presence of contaminants, both CuTC samples were sent to MEDAC for further ICP-MS analysis (Table 9). Unfortunately, we began to experience issues with experimental repeatability with ICP-MS analysis because we could no longer find any palladium traces in the old batch, as reported in the document obtained and shown here below. These analyses however revealed that no palladium contamination was detected in the new batch of CuTC.

This new batch of CuTC with high purity and no palladium contamination was evaluated in our copper-catalyzed aminocarbonylation but, unfortunately, we were not able to detect any traces of aminocarbonylated products anymore, pointing out that palladium species were the active catalysts. Most likely, it would have been necessary to test the purity of the Cu_2O as starting material in addition to the purity of the CuTC. Being unable to reproduce our results with another batch of catalyst, we decided it would be more reasonable and honest to stop this project, despite the lack of repeatability of ICP-MS analyses. It should be highlighted that this type of metal contamination is well documented in the literature; the cases that have been reported and are well-known relate to Suzuki and Sonogashira reaction. This is the first case in history of palladium contamination on aminocarbonylative cross-coupling, as far as we are aware.

[137] (a) Remmel, A. *Nature,* **2022**, *606*, 448–451. (b) Pentsak, E. O.; Eremin, D. B.; Gordeev, E. G.; Ananikov, V. P. *ACS Catal*. **2019**, *4*, 3070–3081.
[138] Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *11*, 2748–2749.
[139] https://www.sigmaaldrich.com/BE/en/product/sial/566284.

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A N A L Y T I C A L R E P O R T

Date 17th May 2021

Name Simone Grosso

Sample ID 1ST BATCH OLD

Formula $C_5H_3CuO_2S$

ELEMENT	C	H	N	S	Cu	Pd			
% Theory	31.49	1.59	-	16.81	33.33				
% Found 1	30.41	1.86	<0.10	16.60	31.74	<1ppm			
% Found 2	30.30	1.87	<0.10	16.60	31.99	<1ppm			

Comments:

Assay No: 195888-195891 Analyst: Richard Morris, Stephen Goodall

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Tel: 01276 855410
Email: info@medacltd.com

A N A L Y T I C A L R E P O R T

Date 17th May 2021

Name Simone Grosso

Sample ID 2nd BATCH NEW

Formula $C_5H_3CuO_2S$

ELEMENT	C	H	N	S	Cu	Pd			
% Theory	31.49	1.59	-	16.81	33.33				
% Found 1	31.29	1.83	<0.10	17.26	31.58	<1ppm			
% Found 2	31.40	1.82	<0.10	17.26	31.57	<1ppm			

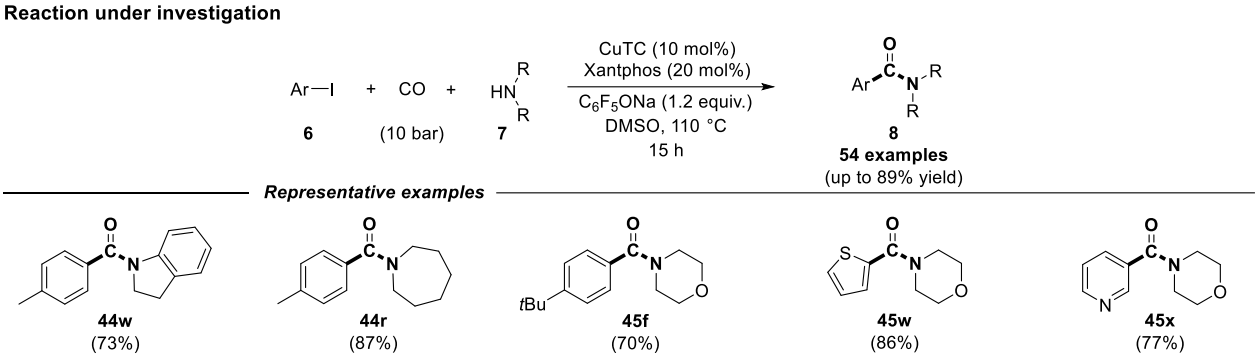
Comments:

Assay No: 195892-195895 Analyst: Richard Morris, Stephen Goodall

Table 9. Comparison of the ICP-MS results obtained on two different batches of CuTC prepared.

2.13. Conclusions and future perspectives

In conclusion, during the investigation that was carried out we have tried to develop a novel copper-catalyzed carbonylative cross-coupling of aryl iodides and amines. First of all, an extensive optimization was required when we initiated our studies, this optimization being based on iterative screenings of all reaction parameters. After numerous unsuccessful attempts, it was found out that 4-iodotoluene could be smoothly carbonylated with morpholine in a reproducible 84% of isolated yield when reacting with 10 mol% of Liebeskind's catalyst (CuTC), 20 mol% of Xantphos and a slightly excess of sodium pentafluorophenoxide in DMSO at 110 °C under a pressure of 10 bar. of carbon monoxide (Scheme 113).



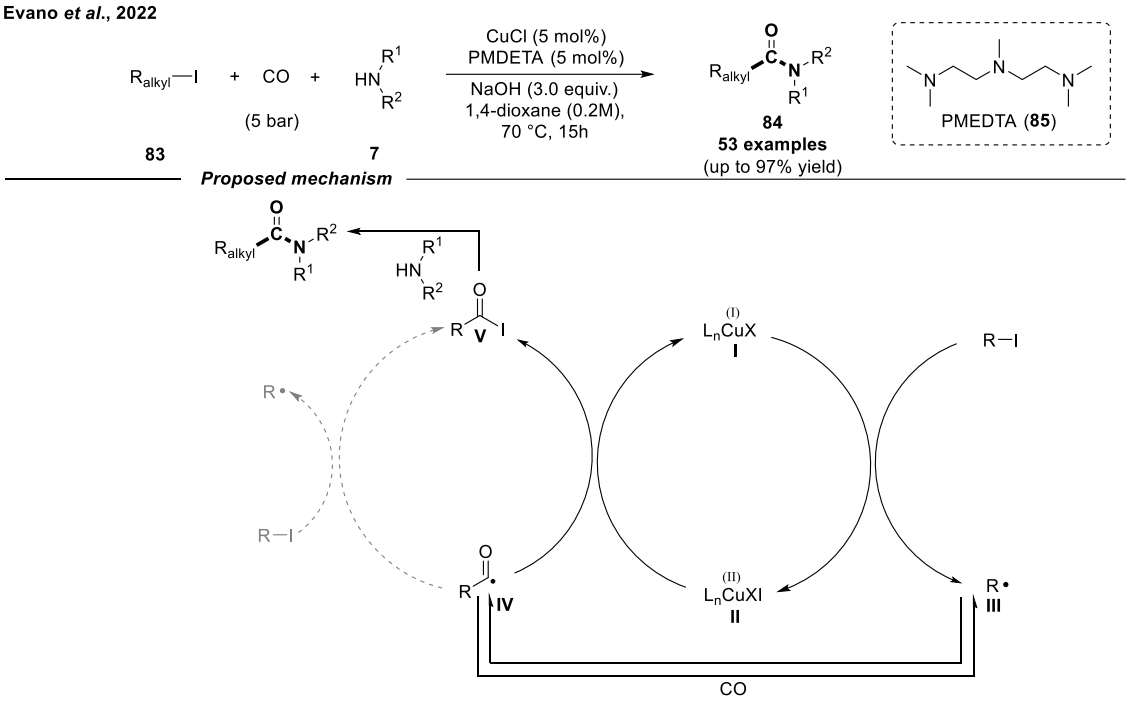
Scheme 113. Copper-catalyzed carbonylative cross-coupling of aryl iodides and amines.

Once we optimized the reaction conditions, we then assessed the scope and limitations of our system for the copper-catalyzed aminocarbonylation of a series of aryl iodides and amines. Therefore, a systematic variation of the aryl halide and amine natures was carried out.

Having identified the reaction conditions, a library of 54 examples of benzamides was prepared and all the compounds have been fully characterized through ^{1}H-NMR, ^{13}C-NMR, IR and HRMS. The protocol developed has been particularly effective for a wide range of primary, secondary, cyclic, acyclic and sterically hindered amines. Thereafter, the substrate scope with various (hetero)aryl iodides was explored. Electron-rich and electron-poor substrates worked both well.

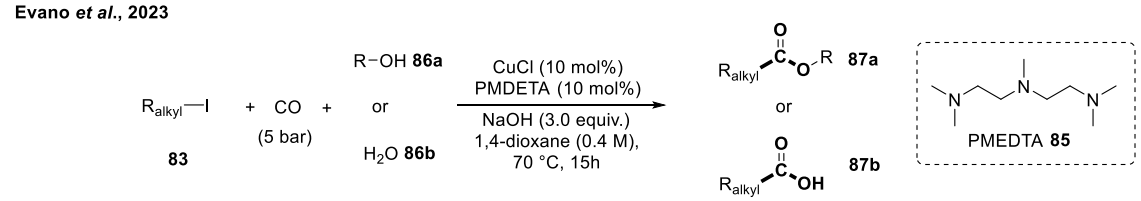
Unfortunately, at the end of this project traces of palladium were found inside the CuTC (copper(I) thiophene-2-carboxylate) batch used through ICP-MS analysis for a value between 35 and 37 ppm. This finding, together with the addition of reproducibility issues brought on by the use of a high purity CuTC (99.99%), caused the project to be discontinued. Under the reaction conditions of the described protocol, the palladium traces discovered in the CuTC batch most likely sufficed to catalyze the aminocarbonylation reaction with high yields.

Later, Dr. Johanne Ling, continued to investigate this research field with the development of a new copper-catalyzed carbonylative cross-coupling reaction between amines **7** and alkyl iodides **83** (Scheme 114).[140] By using a catalytic system composed of copper(I) chloride and PMDETA **85** in presence of sodium hydroxide under a pressure of 5 bar of carbon monoxide. With this protocol, a broad range of alkyl iodides and amines can be successfully coupled to form the corresponding amides **84**.



Scheme 114. Copper-catalyzed carbonylative cross-coupling of alkyl iodides and amines.

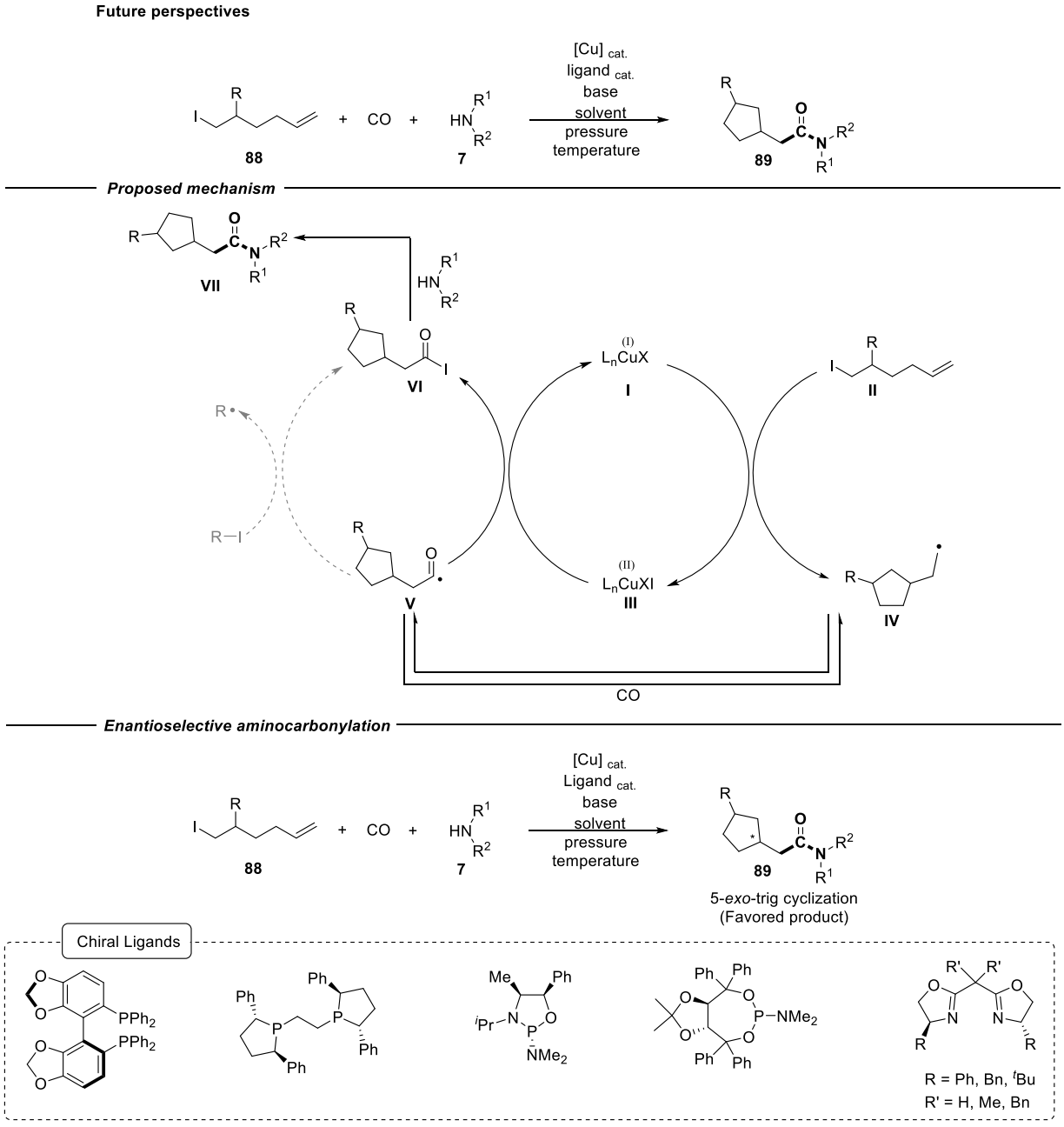
In parallel, in our research group, this synthetic strategy has been also applied to prepare a library of carbonyl derivatives such as esters **87a** and carboxylic acids **87b**. Specifically, the corresponding carbonylated compounds have been prepared through the reaction of the acyl iodide **V** that is formed during the reaction in presence of alcohols **86a** or water **86b** which were used as alternative nucleophiles to amines (Scheme 115).[141] In this way, simply adapting the identified reaction conditions and changing the nature of the nucleophiles was possible to obtain carbonyl derivatives of relevant interest using a novel copper-catalyzed carbonylative cross-coupling.



Scheme 115. Copper-catalyzed carbonylative cross-coupling of alkyl iodides with different nucleophiles.

[140] Ling, J.; Voisine, A. B.; Journot, G.; Evano, G. *Chem. Eur. J.* **2022**, *28*.
[141] Adaoudi, O.; Le Bescont, J.; Bruneau-Voisine, A.; Evano, G. *Synthesis,* **2023**, *55*, 2042–3417.

In the future, under the same reaction conditions, it can be envisioned to perform an intramolecular carbonylation of alkyl iodides **88** to prepare cyclic amides **89** (Scheme 116). Indeed, starting from a properly functionalized alkyl iodide **II** and operating under high dilution conditions it is possible to induce an intramolecular cyclization **IV** after the generation of the alkyl radical with an iodine atom abstraction step. Thereafter, the cyclized terminal alkyl radical **IV** can react with carbon monoxide to generate an acyl radical **V** which can easily evolve to the corresponding electrophilic acyl iodide **VI**. Finally, the acyl iodide in presence of the amine evolve to the target cyclic amide **VII**.



Scheme 116. Copper-catalyzed carbonylation for the preparation of cyclic amides.

Furthermore, it is also possible to envision an enantioselective intramolecular version of the aminocarbonylation cross-coupling developed in our laboratories (Scheme 116), in which an attempt will be made to promote asymmetric induction of the new stereocenter formed during the intramolecular radical cyclization with a 5-*exo*-trig pathway. Undoubtedly, for the successful development of an enantioselective aminocarbonylative cross-coupling will be required to identify the optimal copper source and a chiral ligand capable of promoting the reaction with good yields and a high level of enantioselection. In the literature, many examples of asymmetric reactions are already available suggesting the use of chiral ligands such as phosphines,[142] *N*-heterocyclic carbene,[143] bisoxazolines,[144] and phosphoramidites.[145] Among all the examples of asymmetric reactions documented in the literature, enantioselective carbonylative cross-coupling reactions are still uncommon and this field still remains unexplored. Therefore, all the ligands previously mentioned will be screened in order to develop an enantioselective version capable of inducing high levels of enantioselection. In this way it will be possible to develop an enantioselective intramolecular version of the aminocarbonylation reaction developed in our laboratories to prepare enantiomerically pure amides.

Alternatively, another future perspective is to use aryl iodides **6** with copper photoredox catalysis. Indeed, it is possible to envision a light-induced and exogenous photosensitizer-free copper-catalyzed radical aminocarbonylation of aryl iodide with under a pressure of carbon monoxide. Indeed,[146] we envisioned that this process could be an attractive opportunity and the copper complex might serve as both the photocatalyst and the carbonylation catalyst. Specifically, on the basis of the literature precedents, a light-driven $Cu^{I}/Cu^{II}/Cu^{III}$-based catalytic cycle might be envisioned for a copper-catalyzed radical aminocarbonylation of aryl iodide **6** with CO gas and amines **7** (Scheme 117). The first step of the proposed catalytic cycle might begin with the coordination of the base-deprotonated amine RNH_2 to $L_nCu(I)X$ **I** forming the intermediate $L_nCu(I)NHR$ **II**. Thereafter, a SET-mediated reduction of the aryl iodide by the photoexcited $L_nCu(I)$-NHR complex **III** (path a) or the ground state $L_nCu(I)$-NHR **II** species (path b), enable the formation of an aryl radical species **IV** and the oxidized $L_nCu(II)$-NHR **V**. Then, the aryl radical **IV** reacts with CO to furnish an acyl radical species **VI**.

At this point the acyl radical species can be intercepted by $L_nCu(II)$-NHR **V** complex to form high-valent Cu(III) complex **VII**. Subsequently, the acyl-Cu(III) intermediate **VII** undergoes to reductive elimination and furnishes the final product regenerating the active Cu(I) catalyst **I**.

Clearly, due to this transformation has never been reported, an extensive optimization based on iterative screening of all reactions parameters is required to deeply study this novel transformation.

---

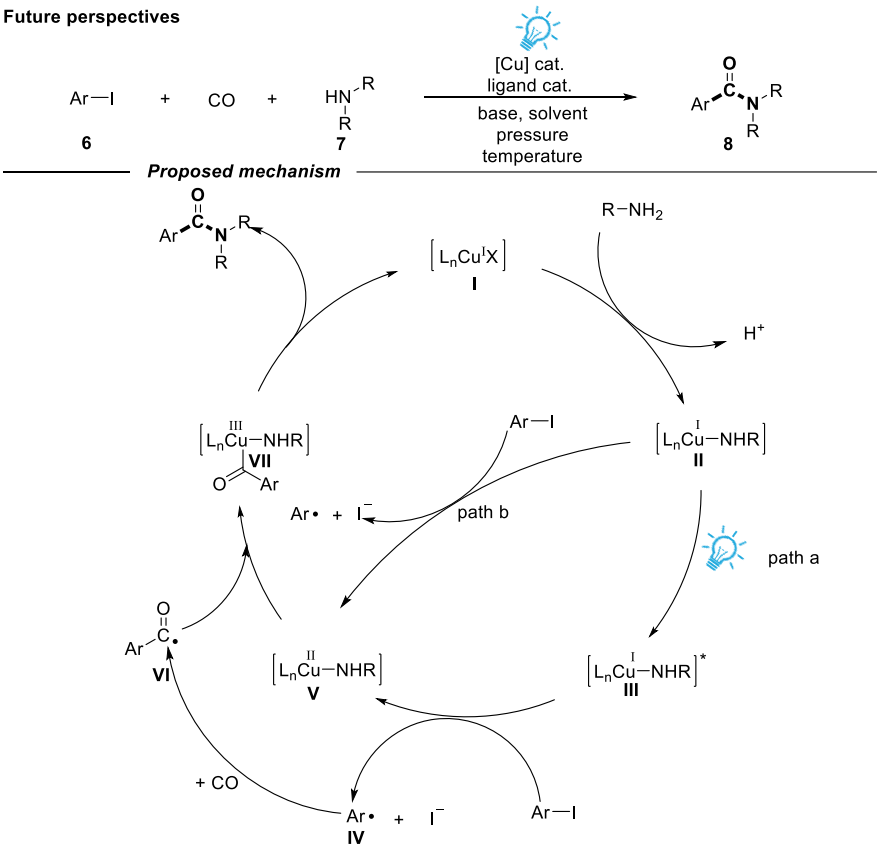
[142] a) Yuan, Y.; Zhao, F.; Wu, X. F. *Chem. Sci*. **2021**, *12*, 12676–12681. b) Yuan, Y.; Wu, F. P.; Schuenemann, C.; Holz, J.; Kamer, P. C.; Wu, X. F. *Angew. Chem. Int. Ed.* **2020**, *59*, 22441–22445.

[143] a) Liu, J.; Zhang, R.; Wang, S.; Sun, W.; Xia, C. *Org. Lett.* **2009**, *11*, 1321–1324. b) Egbert, J. D.; Cazin, C. S. J.; Nolan, S. P. *Catal. Sci. Technol.* **2013**, *3*, 912–926. c) Janssen-Müller, D.; Schlepphorst, C.; Glorius, F. *Chem. Soc. Rev*. **2017**,*46*, 4845–4854. d) Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 28, 8948–8964.

[144] a) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, 125, 12692–12693. b) Bigot, A.; Williamson, A. E.; Gaunt, M. *J. Am. Chem. Soc.* **2011**, *133*, 13778–13781. c) Harvey, J. S.; Simonovich, S. P.; Jamison, C. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *35*, 13782–13785.

[145] a) Bertozzi, F.; Pineschi, M.; Macchia, F.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2002**, *16*, 2703–2705. b) Piarulli, U.; Claverie, C.; Daubos, P.; Gennari, C.; Minnaard, A. J.; Feringa, B. L. *Org. Lett*. **2003**, *23*, 4493–4496. c) Šebesta, R; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Adv. Synth. Catal*. **2007**, *349*, 1931 – 1937.

[146] (a) Parasram, M.; Gevorgyan, V. *Chem. Soc. Rev*. **2017**, *46*, 6227–6240. (b) Hossain, A.; Bhattacharyya, A.; Reiser, O. *Science* **2019**, *364*, 450–461. (c) Kancherla, R.; Muralirajan, K.; Sagadevan, A.; Rueping, M. *Trends Chem.* **2019**, *1*, 510–523. (d) Lu, B.; Cheng, Y.; Chen, L. Y.; Chen, J. R.; Xiao, W. J. *ACS Catal.* **2019**, *9*, 8159–8164. (e) Kawamoto, T.; Sato, A.; Ryu, I. *Chem. Eur. J.* **2015**, *21*, 14764–14767.



Scheme 117. Copper-catalyzed aminocarbonylation of aryl iodides with photoredox catalysis.

First part: Carbonylative cross-coupling reactions

Chapter 3: Copper-catalyzed cross-coupling of acyl zirconium complexes and aryl iodonium salts

Chapter 3. Copper-catalyzed cross-coupling of acyl zirconium complexes and aryl iodonium salts

3.1. Introduction

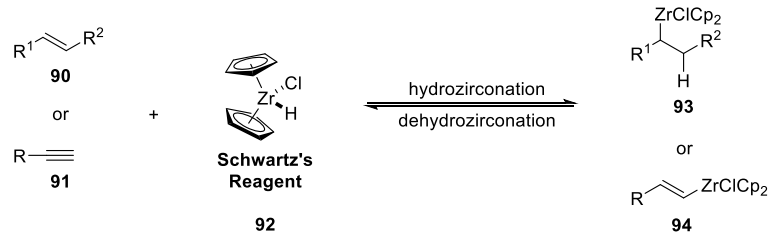
Built around the development of new copper-catalyzed carbonylative cross-coupling reactions, the first part of this manuscript will be devoted to the presentation of copper-catalyzed carbonylative cross-coupling reactions. In this third chapter, we will introduce the chemistry of acyl zirconium complexes, which are powerful synthetic equivalents of acyl anions, and then our main focus will be on showcasing the most cutting-edge copper-catalyzed catalytic systems that enable the cross-coupling between acyl zirconium complexes and electrophiles.

Among the many catalytic systems which have been developed in the last years for the construction of new carbon-carbon bonds, it turns out, quite surprisingly, that such literature is almost exempt from the description of copper-catalyzed cross-coupling reactions which imply the use of acyl zirconium complexes as carbon nucleophiles, despite the certain potential of these molecular bricks. Unfortunately, this area of copper-catalysis is still largely unexplored, despite a strong synthetic potential.

For these reasons, after presenting the general lines of the research area on which we conducted our investigation, we will outline the research done to develop a new methodology that enables the copper-catalyzed cross-coupling between acyl zirconium complexes and aryl iodonium salts. In this chapter, our focus will be on presenting the cross-coupling reaction that we have developed, the optimization phase and the investigation of the scope that has been accomplished. All the phases will be discussed in detail.

3.2. Hydrozirconation of alkenes and alkynes

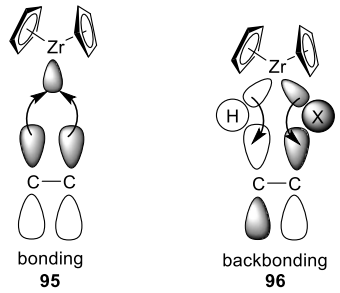
One of the most effective ways to prepare functionalized alkanes and functionalized stereodefined alkenes is through the hydrometalation of alkenes and alkynes via hydroboration, hydroalumination, and hydrozirconation.[147] The reaction of hydrometalation is the addition of H and M to alkenes **90** and alkynes **91** to yield metalated species, which can then be transformed into different functionalized compounds. Cp_2ZrHCl, commonly known with the name of Schwartz' reagent **92**, has been utilized in the instance of hydrozirconation. The hydrozirconation of unsaturated carbon-carbon double or triple bonds yields alkyl **93** or alkenylzirconium **94** complexes (Scheme 118), which can then be transmetalated to produce more reactive M–C bonds or react with electrophiles.



Scheme 118. Hydrozirconation of al alkenes/alkynes with the Schwartz reagent.

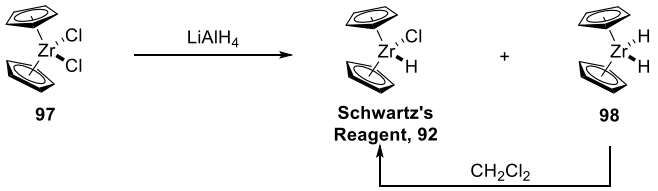
[147] Wipf, P.; Nunes, R. L. *Tetrahedron* **2004**, *60*, 1269–1279.

Generally, the addition of the Zr–H proceeds via *syn*-addition and with a concerted 4-centered process that typically places zirconium on the less-substituted carbon (*anti*-Markovnikov). The hydrozirconation is a spontaneous chemical process in which the zirconium has an empty d-orbital that interacts with p-orbitals of alkenes and alkynes **95** (Scheme 119). The Schwartz reagent and more in general zirconium complexes with the formula Cp_2ZrXY are 16-electron d^0 Zr (IV) complexes with one empty valence shell orbital available for coordination. Consequently, many reactions of these compounds are initiated by the molecular interaction of an electron donor such as the π-bond of an olefin/alkyne with the empty Zr orbital. The resulting unstable π-complex is quickly transformed into a σ-complex by hydrogen migration of H–Zr to the unsaturated C–C double or triple bonds. These alkyl or alkenyl σ-zirconium complexes can then be used to form a wide range of new bonds with electrophiles.[148] Similar to Grignard reagents, the C–Zr bond formed in alkyl or alkenyl -zirconium complexes is highly polarized, however, it is considerably shielded because of the steric crowding around the zirconium atom, and only small electrophiles directly attack the complex. Therefore, the chemistry of organozirconocenes has primarily focused on indirect reaction pathways where other metals participate in the formation of new carbon-carbon bonds. Indeed, combining hydrozirconation and transmetallation on other metals is possible to develop new reactions and exploit the potentiality of zirconium complexes.



Scheme 119. Molecular interactions of the π-bond of an olefin with the empty Zr orbital of Cp_2ZrHCl.

The Schwartz reagent **92** can be smoothly prepared by reduction of Cp_2ZrCl_2 **97** with various hydride sources such as $LiAlH_4$, $LiAlH(O^tBu)_3$ or $^iBu_2AlH$.[149] A possible by-product is the Cp_2ZrH_2 **98**, a zirconium(IV) dihydride, which can be converted into the desired product by a simple treatment with CH_2Cl_2 (Scheme 120).[150] Unfortunately, the Schwartz reagent slowly decomposes if exposed to air and light and because of its weak solubility in organic solvents, its purification is not easy. For these reasons, alternative methods have been developed in order to prepare freshly generated Cp_2ZrHCl, in this way the reagent immediately reacts with a substrate to give the hydrozirconation product.



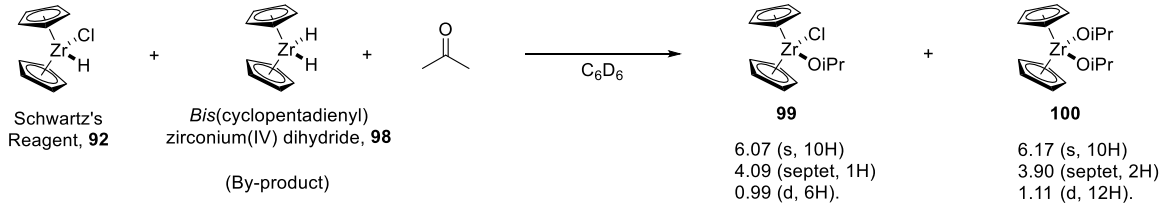
Scheme 120. Preparation of the Schwartz reagent with $LiAlH_4$.

[148] Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *40*, 12853–12910.

[149] (a) Wailes, P. C.; Weigold, H. *J. Organomet. Chem.* **1970**, *24*, 405–411. (b) Wailes, P. C.; Weigold, H.; Bell, A. P. J. *Organomet. Chem*. **1971**, *27*, 373–378. (c) Wailes, P. C.; Weigold, H.; Bell, A. P. *J. Organomet. Chem*. **1972**, *43*, C32–C34. (d) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett*. **1987**, *28*, 3895–3898.

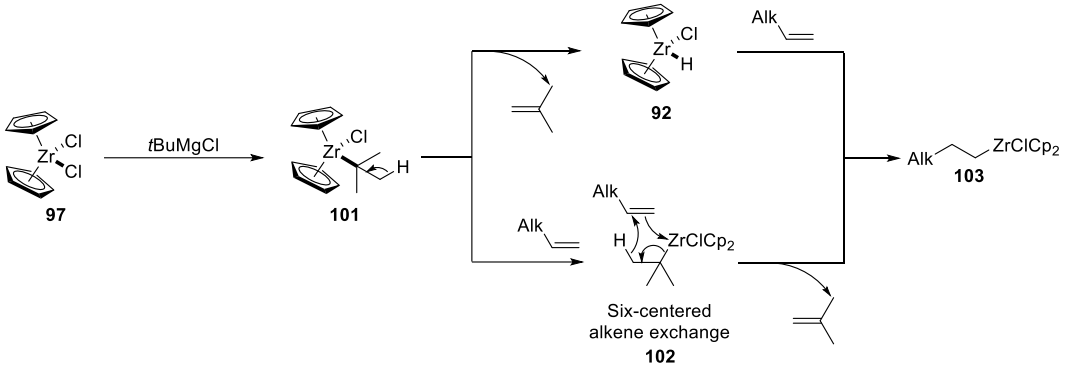
[150] Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Org. Synth.* **1993**, *71*, 77–81.

Noteworthy, the amount of by-product can be evaluated by ^{1}H-NMR by taking into account the relative areas of the signal of the monoisopropoxides **99** and diisopropoxides **100** formed after treating a sample of zirconium hydride with acetone (Scheme 121).



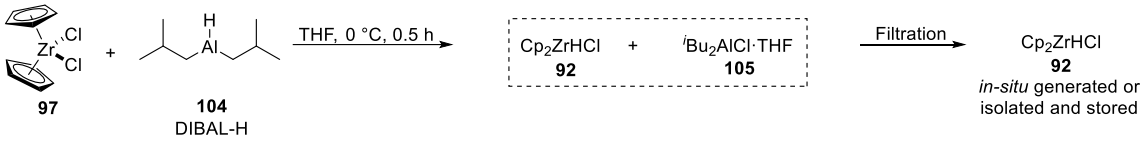
Scheme 121. ^{1}H-NMR of the mono- and diisopropoxides zirconium complexes.

With an easy elimination, which is the opposite of hydrozirconation, the Schwartz reagent can be produced *in-situ*. The interaction of Cp_2ZrCl_2 **97** with one equivalent of an alkyl metal reagent was studied by Negishi and co-workers.[151] Monoalkylzirconium derivatives were produced in excellent yields by simply combining monosubstituted alkenes with 1 equivalent of Cp_2ZrCl_2 and 1.1 equivalents of *t*BuMgCl in benzene-ether at room temperature. A transmetallation-elimination-hydrozirconation mechanism or a transmetallation and subsequently a six-centered alkene exchange mechanism **102** were both suggested as possible mechanisms for the reaction to proceed (Scheme 122).



Scheme 122. Preparation of the Schwartz reagent with *t*BuMgCl through the Negishi procedure.

Alternatively, a combination of Cp_2ZrCl_2 **97** and DIBAL-H **104** provides an efficient alternative to prepare *in-situ* the Schwartz reagent **92**. Indeed, it represents one of the most practical methods for the *in situ* formation of Cp_2ZrHCl. Negishi and colleagues extensively investigated the reaction of Cp_2ZrCl_2 with DIBAL-H. DIBAL-H is added into a solution of THF and Cp_2ZrCl_2 **97** at 0 °C to form a 1:1 mixture of Cp_2ZrHCl and ^{i}BuAlCl-THF **105**. Fresh Cp_2ZrHCl could be easily separated from the mixture after filtration (Scheme 123).[152]

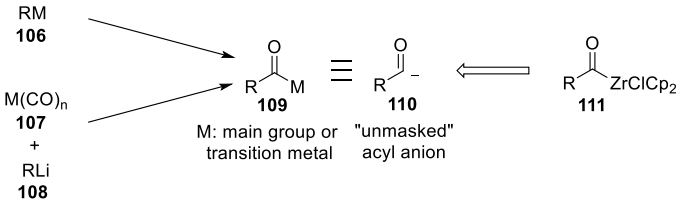


Scheme 123. Preparation of the Schwartz reagent with DIBAL-H through the Negishi procedure.

[151] (a) Negishi, E. I.; Miller, J. A.; Yoshida, T. *Tetrahedron Lett*. **1984**, *25*, 3407–3410. (b) Negishi, E. I.; Yoshida, T. *Tetrahedron Lett*. **1980**, *21*, 1501–1504.
[152] Huang, Z.; Negishi, E. *Org. Lett.* **2006**, *17*, 3675–3678.

3.3. Synthesis and reactivity of acylzirconocene complexes

Now that key concepts related to hydrozirconation reactions have been introduced, our focus will be on the acyl zirconium complexes that are the main subject of this chapter. In the past years, numerous research groups investigated the synthesis and reactivity of acyl-metal species **109** involving main group metals (M = Li, Zn, etc.).[153] These species are not well suited in organic synthesis due to their poor stability and/or the demanding reaction conditions required to prepare them. For instance, the acyl-lithium species production and reactions have been carried out in the presence of electrophiles at extremely low temperatures (around -110 °C). Along with the acyl-main group metal species, acyl-transition metal complexes have also long caught our interest since Ni, Fe, and Co acyl complexes are efficient "unmasked" acyl anion donors (Scheme 124).[154] Unfortunately, due to the significant toxicity of the metal carbonyl **107** required for the generation of the acyl-transition metal species **109**, their usage as reagents is a serious drawback. Consequently, only a small number of synthetic applications have been reported so far. Aside from the described acyl-transition metal complexes, compounds including acyl-Sm, Cr, and Sn exhibit appealing reactivity as acyl group donors.[155] Recently, in order to replace the aforementioned drawbacks of acyl-main group and acyl-transition metal complexes, the interest is increased towards acylzirconocene complexes **111** which are stable and easy-to-handle “unmasked” acyl anion donors **110**.



Scheme 124. Acylmetal as an “unmasked” acyl anion donor.

Over the past 20 years, organozirconocene compounds have been used as catalysts or stoichiometric reagents in a number of processes designed to form new carbon—carbon bonds. However, although being readily available from organozirconocene molecules, acylzirconocene complexes have not been frequently used in organic synthesis and very little synthetic use of the complexes to generate carbon–carbon bonds has been documented. The preparation of acylzirconocene chloride complexes can be easily accomplished in a one-pot procedure through the hydrozirconation of alkenes or alkynes with the Schwartz reagent, followed by the insertion of carbon monoxide (1 atm) into the alkyl- or alkenyl-zirconium bond under atmospheric pressure of carbon monoxide (Scheme 125).

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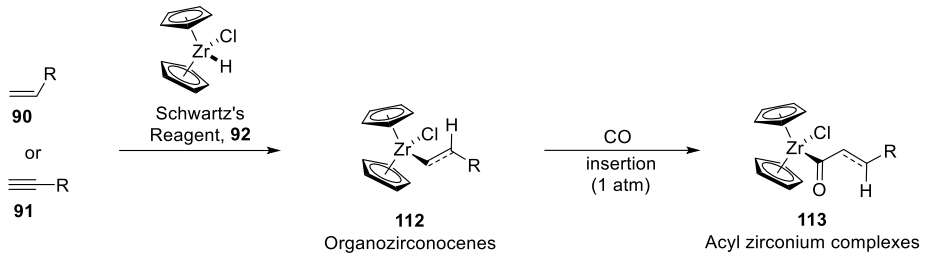
[153] a) Seyferth, D.; Hui, R. C.; Wang, W. L. *J. Org. Chem.* **1993**, *58*, 5843–5845. b) Seyferth, D.; Hui, R. C.; Wang, W. L.; Archer, C. M.; Weinstein, R. M. *J. Org. Chem.* **1992**, *57*, 5620–5629. c) Normant, J. F.; Chemla, F. *Tetrahedron*, **1997**, *53*, 17265–17274. d) Rathke, M. W.; Yu, H. *J. Org. Chem.* **1972**, *11*, 1732–1734.

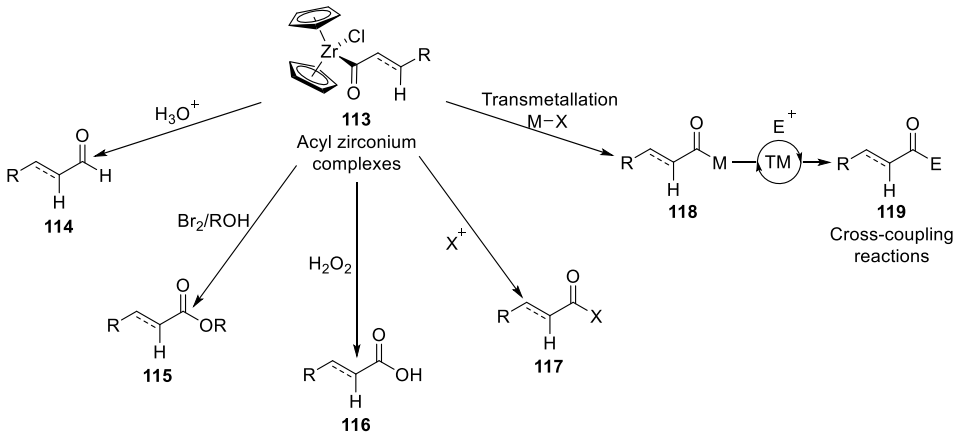
[154] Acyl-Ni: a) Hermanson, J. R.; Enginger, A. L.; Pinhas, A. R. *Organometallics* **2000**, *19*, 1609–1614. b) Hermanson, J. R.; Hershberger, J. W.; Pinhas, A. R. *Organometallics* **1995**, *11*, 5426–5437. c) Tamura, Rui; Hegedus, L. S. *Organometallics* **1982**, *1*, 1188–1194. Acyl-Fe: a) Collman, J. P.; Winter, S. R.; Clark, D. R. *J. Am. Chem. Soc.* **1972**, *5*, 1788–1789. b) Cooke, M. P.; Parlman, R. M. *J. Am. Chem. Soc.* **1977**, *15*, 5222–5224. c) McMurry, J. E.; Andrus, A. *Tetrahedron Lett.* **1980**, *21*, 4687–4690. Acyl-Co: a) Perry, R. J.; Hegedus, L. S. *J. Org. Chem.* **1985**, *50*, 4955–4960. b) Hegedus, L. S.; Inoue, Y. *J. Am. Chem. Soc.* **1982**, *18*, 4917–4921.

[155] Acyl-Cr: a) Sakurai, H.; Tanabe, K.; Narasaka, K. *Chem. Lett*. **1999**, *28*, 309–310. b) Sakurai, H.; Tanabe, K.; Narasaka, K. *Chem. Lett*. **2000**, *9*, 168–169. Acyl-Sn: a) Shirakawa, E.; Nakao, Y.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc*. **2000**, *122*, 9030–9031. b) Verlhac, J. B.; Chanson, E.; Jousseaume, B.; Quintard, J. P. *Tetrahedron Lett*. **1985**, *49*, 6075–6078. c) Kosugi, M.; Naka, H.; Harada, S.; Sano, H.; Migita, T. *Chem. Lett.* **1987***, 16,* 1371–1372. Acyl-Sm: a) Namy, J. L.; Colomb, M.; Kagan, H. B. *Tetrahedron Lett*. **1994**, *35*, 1723–1726. b) Collin, J.; Dallemer, F.; Namy, J. L.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 3118–3122. c) Collin, J.; Kagan, H. B. *Tetrahedron Lett*. **1988**, *29*, 6097–6100.



Scheme 125. Formation of acylzirconocenes chlorides.

Acyl zirconium complexes **113** are versatile intermediates as "unmasked" acyl anion equivalents which can be smoothly converted, depending on subsequent procedures, into aldehydes **114**, esters **115**, carboxylic acids **116** and acyl halides **117** (Scheme 126).[156] These transformation were the first practical applications of acylzirconocene chlorides to organic synthesis. The transmetallation reaction on metals **118** is undoubtedly the most significant of all the reactions that acyl zirconium complexes may carry out because it allows the acyl group to be transferred easily as a nucleophile in cross-reaction coupling. This makes it obvious that the transmetallation of acylzirconocene chlorides onto transition metals **118** is the point of divergence that enables the development of new catalytic systems through coupling with new electrophiles.



Scheme 126. Traditional reactions of acylzirconocene complexes.

In addition to the traditional reactions, acylzirconocene complexes have been also employed to develop new carbon-carbon bond reactions with carbon electrophiles. For instance, acyl zirconium complexes **113** add to aldehydes/enones **120**/**124**,[157] and imines **122**,[158] to furnish α-hydroxy ketones **121**, 1,4-diketones **125** and α-aminoketones **123**, respectively (Scheme 127). Over the past years the transmetallation of acylzirconocene complexes to various transition metals has been well studied in cross-coupling reactions since the direct introduction of an acyl group in a nucleophilic manner can be tremendously attractive when carried out without using the so-called "umpolung" procedures.

Since the development of these methods, palladium catalyzed cross-coupling reactions have received great attention in the past decades. Palladium catalysis has expanded the reactivity of acyl zirconium complexes towards a much broader range of electrophiles.[159] Although these catalytic systems have advantages in reactivity, their high costs and toxicity still limit tremendously their applications on a large scale.

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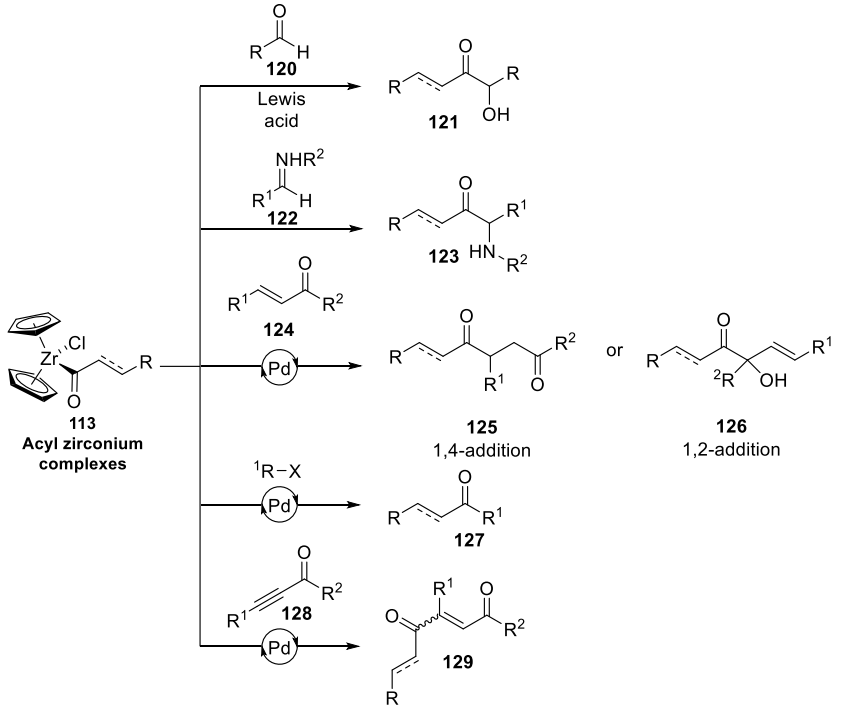
[156] Bertelo, A.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 228–230.
[157] Hanzawa, Y.; Tabuchi, N.; Taguchi, T. *Tetrahedron Lett*. **1998**, *39*, 8141–8144.
[158] Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett*. **2001**, *42*, 1547–1549.
[159] (a) Hanzawa, Y.; Tabuchi, N.; Taguchi, T. *Tetrahedron Lett.* **1998**, *39*, 6249–6252. (b) Hanzawa, Y.; Kakuuchi, A.; Yabe, M.; Narita, K.; Tabuchi, N.;Taguchi, T. *Tetrahedron Lett.* **2001**, *42*, 1737–1739.

For these reasons, the development of economic and environmentally benign synthetic methods has recently become an important but challenging goal in transition metal catalysis. Moreover, the exploration of non-noble catalysts in organic synthesis has proved to be one of the ideal choices, due to their advantages such as abundance, low price and low toxicity. Therefore, in the next section we will dedicate our attention to introduce the latest advances that have been achieved by copper catalysis using acyl zircononium complexes. Indeed, in the last years new efficient cross-coupling reactions of acylzirconocene chloride with electrophiles have been developed simply by utilizing a catalytic amount of Cu(I) salts. In this way, the reactivity of "unmasked" acyl anion is exploited, without the use of noble metals.



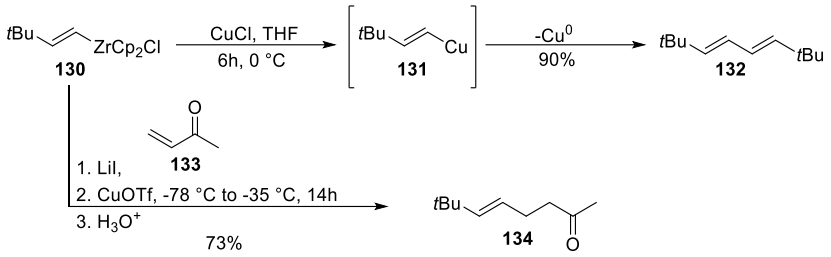
Scheme 127. Reactions of acylzirconocene complexes with carbon electrophiles and Pd-catalysis.

3.4. Cu-catalyzed cross-coupling reactions of acylzirconocene complexes

Because organocopper reagents are so widely used in synthetic organic chemistry,[160] the transmetallation of organic ligands from zirconium to copper has attracted the attention of many research groups in the past years. In 1977, Schwartz reported the first instance of a successful transfer of vinyl groups from zirconocene to copper(I) salts. CuCl added to the alkenyl zirconocene **130** resulted in the formation of yellow-green copper complexes that underwent thermal decomposition to produce the (*E*, *E*)-diene **132** in good yield and a copper mirror. Moreover, the *in-situ* conversion of the alkenyl copper species **131** into the corresponding ate complexes with LiI allowed the conjugate addition reaction to enones **133** (Scheme 128). Unfortunately, using these procedures, stoichiometric amounts of copper(I) salts were required, and alkyl groups did not transmetalate at a synthetically useful rate, longer time were needed.[161] Following the ground-breaking study on Zr-Cu transmetallation numerous reactions between organozirconium species and copper(I) salts have been reported.[162]

[160] Krause, N. *Modern Organocopper Chemistry*, 1th ed.; Vol. 1; Wiley-VCH: Weinheim, Germany, **2002**.
[161] Yoshifuji, M.; Loots, M. J.; Schwartz, J. *Tetrahedron Lett*. **1977**, *15*, 1303–1306.
[162] Wipf, P. *Synthesis* **1993**, *6*, 537–557.

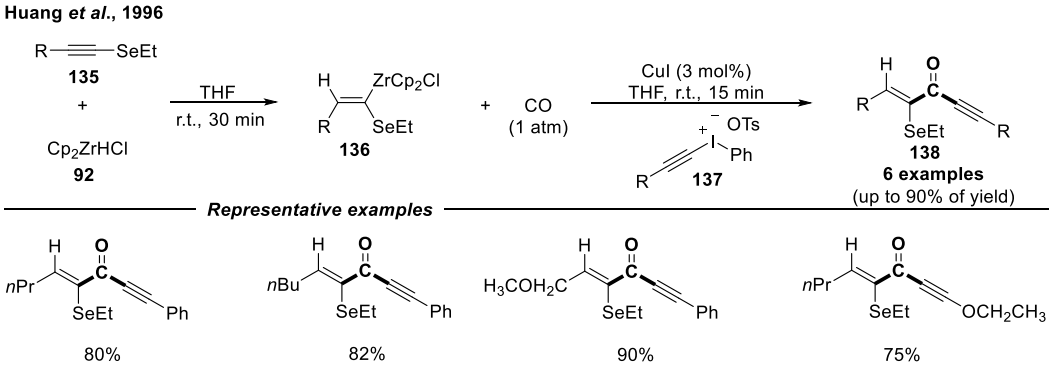
The first example of conjugate addition catalyzed by catalytic amount of copper(I) salts in presence of alkenyl zirconocenes **130** was described by Wipf and Smitrovich in 1991.[163]



Scheme 128. First report of transmetallation from Zr to Cu(I) salts.

Since then, many copper-catalyzed cross-coupling have been developed, although only a limited numbers of innovations have been published to address the utility of acylzirconocene chlorides reagents under copper catalysis.[164] Indeed, the use of acylzirconocene chlorides reagents under copper catalysis, despite of the great potentials, is still an unexplored area of chemistry and only a limited numbers of innovations have been described in literature to address their utility. In these examples, cross-coupling reactions of acylzirconocene complexes were promoted by the use of catalytic amounts of Cu(I) salts in presence of electrophiles such as alkynyliodonium tosylates[165], allylic and propargylic halides,[166] α,β-enones and allenyl ketones,[167] and isoquinolinium derivatives[168].

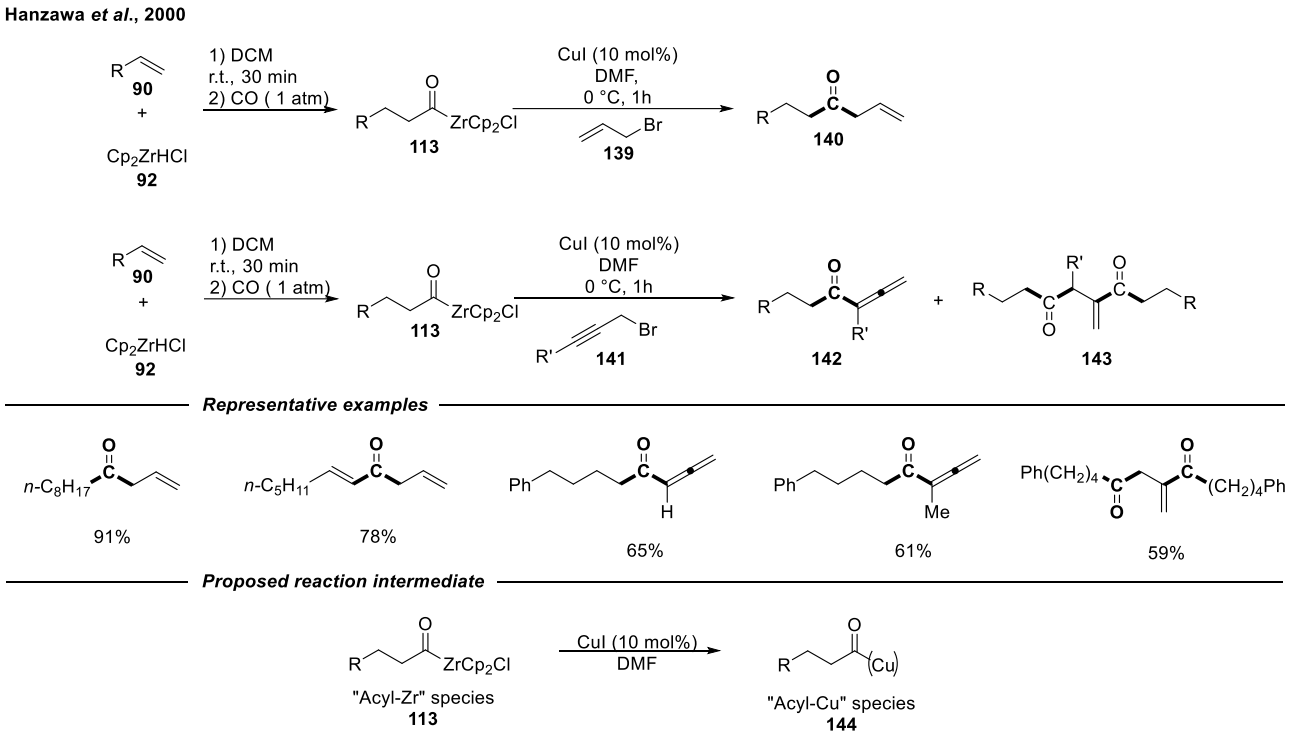
One of the first reports in which acyl zirconocenes chlorides were employed with copper catalysis appeared in 1996 when Huang described a novel cross-coupling of (*E*)-α-selanylvinylzircononiums **136** with alkynyliodonium tosylates **137** under extremely mild conditions (Scheme 129). This protocol starts with the hydrozirconation of alkynyl selenides **135** followed with the insertion of carbon monoxide to generate a (*E*)-α-selanylenoylzirconium complex, which are highly reactive with alkynyliodonium salts **137** as electrophilic partner in presence of 3 mol% of CuI. With this method was possible to prepare a small library of six unsymmetrical vinyl alkynyl ketones **138** in good yields.



Scheme 129. Copper-catalyzed carbonylative cross-coupling of (*E*)-α-selanylvinylzirconiums with alkynyliodonium tosylates.

[163] Wipf, P.; Smitrovich, J. H. *J. Org. Chem*. **1991**, *56*, 8494.
[164] Marek, I. *Titanium and Zirconium in Organic Synthesis*, 1th ed.; Vol. 1; Wiley-VCH, Verlag GmbH & Co. KGaA, **2002**.
[165] Sun, A. M.; Huang, X. *Tetrahedron,* **1999**, *55*, 13201–13204.
[166] Hanzawa, Y.; Narita, K.; Taguchi, T. *Tetrahedron Lett*. **2000**, *41*, 109–112.
[167] Hanzawa, Y.; Narita, K.; Taguchi, T.; Yabe, M. *Tetrahedron Lett*. **2002**, *52*, 10429–10435.
[168] Saito, A.; Sakurai, H.; Sudo, K.; Murai, K.; Hanzawa, Y. *Eur. J. Org. Chem*. **2013**, *32*, 7295–7299.

In 2000, the Hanzawa group developed a successful cross-coupling reaction of acylzirconocene chloride with carbon electrophiles such as allylic **139** and/or propargylic halides **141** by utilizing a catalytic amount of a CuI (10 mol%) to furnish allylic and/or allenyl ketones in good yields and under mild reaction conditions (Scheme 130).[169] The reactions were performed in DMF or THF as solvents, and were completed within one hour to give the corresponding acyl-allyl **140** or acyl-allenyl **142** coupled products without in good to excellent yields. Noteworthy, using an excess (2 equiv.) of propargyl bromide, the formation of an allenyl ketone is the sole product of the reaction which can be achieved. Instead, when an increased amount (3 equiv.) of acylzirconocene chlorides is used the only product formed is a 1,4-dicarbonyl compound derived from Michael-type addition of the acylzirconocene chloride to the previously formed allenyl ketone. Although the exact role of the copper catalyst is still unclear, the authors proposed that most probably the transmetallation of the acyl group from zirconium to copper occurs to generate a transient "acyl-Cu" species, **144** which is highly nucleophilic and capable to reacts with the allylic **139** and/or propargylic halides **141**.

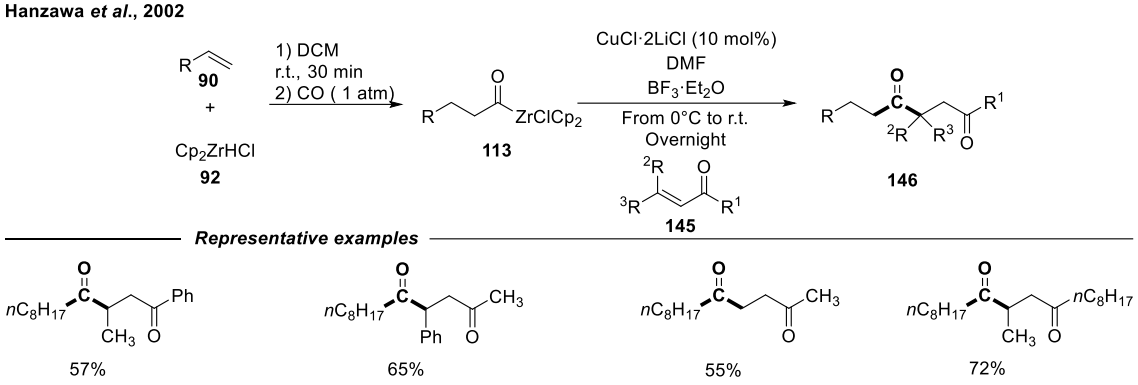


Scheme 130. Copper-catalyzed cross-coupling reaction of acylzirconocene with allylic/propargylic halides and enones.

Two years later, the Hanzawa group have also reported and additional study in which was described a novel reaction of acylzirconocenes chloride **113** in presence of catalytic amount of copper salt and enones **145** (Scheme 131). The copper catalyst has been employed to promote the conjugate addition reaction of acylzirconocene chlorides onto the enone to yield 1,4-diketone compounds **146**. In this way, it has been possible to smoothly introduce an acyl anion to the β-carbon of the α, β-unsaturated carbonyl compounds **145**. The authors reported that with the addition of CuCl·2LiCl (10 mol%) and $BF_3{\cdot}OEt_2$ (2 equiv.) to the reaction mixture containing the enone and the acyl zirconium complex the 1,4-conjugate addition proceeded efficiently to furnish the target 1,4-diketone in good to excellent yields. Noteworthy, using a soft-nucleophile such as the acyl-copper formed *in-situ* through the Zr-Cu transmetallation, the only isolated product was the 1,4-addition product. Indeed, in all the cases examined no traces of the 1,2-addition product have been

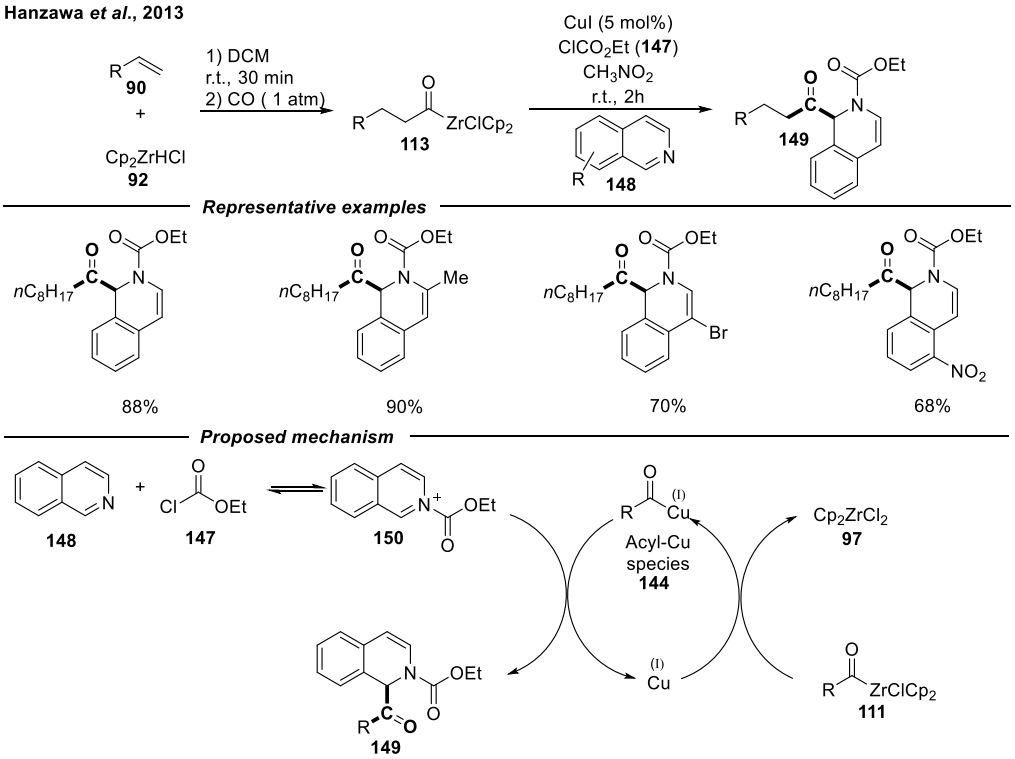
[169] Hanzawa, Y.; Narita, K.; Taguchi, T. *Tetrahedron Lett*. **2000**, *41*, 109–112.

identified. The current Cu(I)-catalyzed 1,4-addition is limited to α,β-enones as substrate. Indeed, no conjugate addition reaction took place when α, β-ester, -amide and -nitrile compounds were used.



Scheme 131. Copper-catalyzed conjugate addition reactions of acylzirconocene chloride.

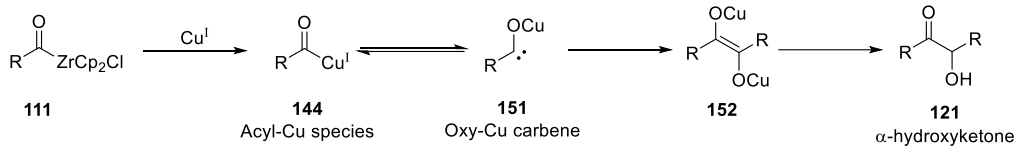
More recently, the Hanzawa research group reported in 2013 a novel copper-catalyzed Reissert-type acylation of isoquinoline derivatives **150** using acylzirconocene chlorides as nucleophile **113** (Scheme 132).[170] Using CuI (5 mol %) in nitromethane in the presence of ethyl chloroformate **147**, isoquinoline derivatives **150** were efficiently acylated in good yields at the C_1 of the pyridine ring. Ethyl chloroformate is used as electrophile to generate *in-situ* the *N*-acyl isoquinolinium intermediates **150**. The authors proposed that the reaction mechanism starts with the formation of an acyl-copper species **113** after the Zr-Cu transmetallation. Thereafter, the acyl-copper **144** adds onto the electrophilic *N*-acyl isoquinolinium intermediates to furnish the product of the Reissert-type acylation reaction.



Scheme 132. Copper-catalyzed Reissert-type acylation with acylzirconocene chloride complexes.

[170] Saito, A.; Sakurai, H.; Sudo, K.; Murai, K.; Hanzawa, Y. *Eur. J. Org. Chem*. **2013**, *13*, 7295–7299.

The formation of the acyl-Cu species **144** is confirmed by the presence of traces of α-ketols **121** as by-products. The α-ketols are formed in traces by the homocoupling reaction of oxy-copper carbenes **151** derived from the acyl-copper species **144** (Scheme 132).[171]



Scheme 132. Homocoupling reaction of oxy-copper carbenes derived from the acyl-copper species.

Despite of the high synthetic potential, as it is possible to note through the protocols previously described, the use of acyl zirconium complexes in combination with copper catalysis has still very limited applications. As a matter of fact, it has only been in recent years that new methodologies have made it possible for us to think about the disconnections of acyl groups within molecules in a novel way, taking advantage of the "umpolung" that synthetic chemists have for long time underestimated. For these reasons, there is a growing interest to investigate an unexplored area of copper catalysis involving acylzirconocene complexes. Furthermore, the use of copper as non-noble catalyst to catalyze carbonylative cross-coupling reactions is proving to be one of the best alternative because of its benefits that include availability, low cost and toxicity. Meeting this challenge would be of significance in a field of zirconium and copper chemistry that has been little explored in the past.

Based on our ongoing research interests and considering all the advantages of non-noble metals, we became interested to investigate an unexplored area of copper catalysis to develop a novel carbonylative copper-catalyzed cross-coupling reaction of acyl-zirconocene complexes with electrophiles. In the next paragraphs we will introduce the objectives of our experimental research which will be used as starting point to present our investigation and the results collected.

3.5. Objectives

Since the first report of Zr-Cu transmetallation reaction by Schwartz in 1977,[172] only a limited numbers of innovations have been published to address the utility of acylzirconocene chlorides **113** reagents under copper catalysis.[173] Therefore, there is a strong need to investigate an unexplored area of copper-catalysis involving acyl-zirconocene complexes for fully exploit its synthetic potential. Meeting this challenge would be of significance in a field of zirconium chemistry that has received too little attention in the past. Additionally, bearing in mind the toxicity of carbon monoxide, it would be beneficial from a safety standpoint to develop new synthetic routes that circumvent the use of pressurized gas cylinders, as well as reaction conditions necessitating high CO pressures. Inspired by the work of the Skrydstrup group to develop new carbonylative transformations using the two-chamber system, we envisioned that also acylzirconocene complexes **113** could be prepared for the first time with this new type of apparatus.[174] Indeed, to the best of our knowledge, acylzirconocene complexes have never been prepared with a two-chamber system, a competent tool for conducting safe reactions with carbon monoxide.

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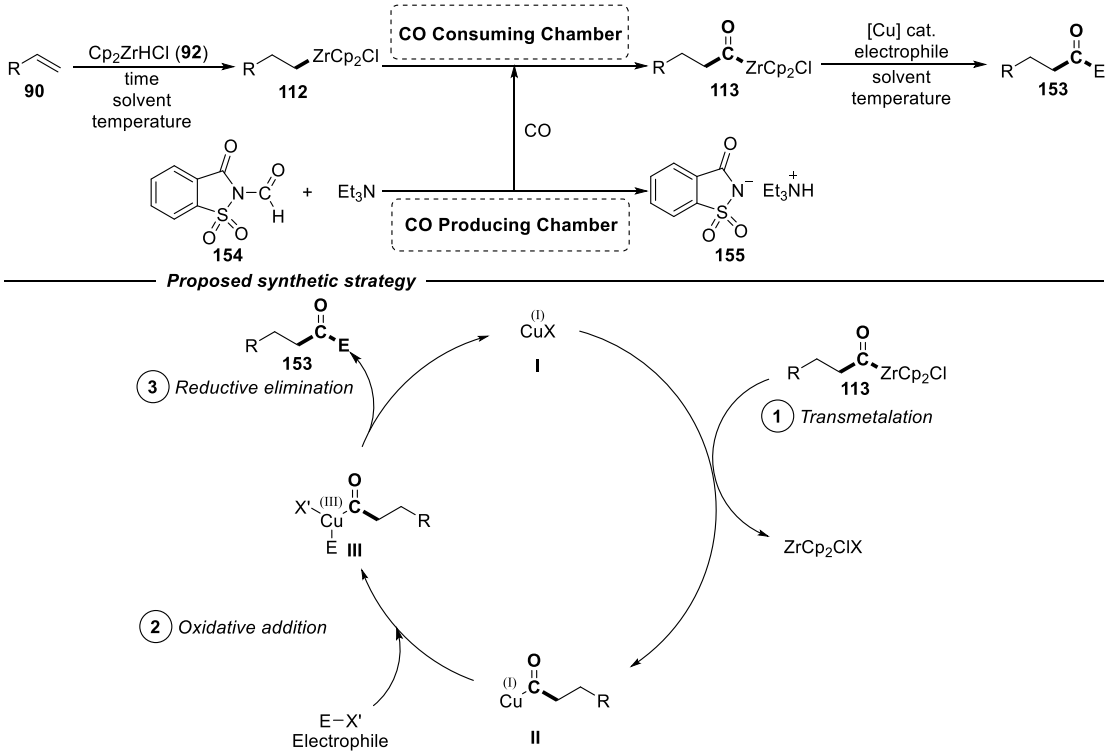
[171] Hanzawa, Y.**;** Narita, K.**;** Yabe, M.; Taguchi, T. *Tetrahedron*, **2002**, *58*, 10429–10435.
[172] Yoshifuji, M.; Loots, M. J.; Schwartz, J. *Tetrahedron Lett*. **1977**, *18*, 1303–1306.
[173] (a) Marek, I. *Titanium and Zirconium in Organic Synthesis*, 1th ed.; Vol. 1; Wiley-VCH, Verlag GmbH & Co. KGaA, **2002**. (b) Hanzawa, Y.; Narita, K.; Taguchi, T. *Tetrahedron Lett*. **2000**, *41*, 109–112. (c) Hanzawa, Y.; Narita, K.; Taguchi, T.; Yabe, M. *Tetrahedron Lett*. **2002**, *52*, 10429–10435. (d) Saito, A.; Sakurai, H.; Sudo, K.; Murai, K.; Hanzawa, Y. *Eur. J. Org. Chem*. **2013**, *32*, 7295–7299. (e) Sun, A. M.; Huang, X. *Tetrahedron,* **1999**, *55*, 13201–13204.
[174] Friis, S. D.; Lindhardt, A. T.; Skrydstrup, T. *Acc. Chem. Res.* **2016**, *49*, 594–605.

Motivated by the interest to explore an understudied area of copper catalysis, the main goal of this research project has been focused on the development of a new copper-catalyzed carbonylative cross-coupling by using acylzirconocenes complexes as "unmasked" acyl anion equivalents. The acylzirconocenes **113** were generated *in-situ* via regioselective addition of Schwartz's reagent on alkenes **90** under a low pressure atmosphere of carbon monoxide. The methodology is designed using an easy to handle two-chamber reactor where carbon monoxide is generated *ex-situ* from *N*-formylsaccharin **154**, a carbon monoxide surrogate. By using a simple protocol, a series of alkyl aryl ketones were successfully synthetized in moderate to good yields from readily available starting material.

Specifically, we envisaged a strategy based on the *in-situ* generation and reactivity of acylzirconocene complexes, $RCOZrCp_2Cl$ **113**. Then, we assumed that the transmetallation of acylzirconocene chloride **113** to the copper catalyst **I** could yield a transitory acyl-Cu species **II** able to undergo oxidative addition with an electrophile to form a transitory copper(III) complex **III**. Finally, reductive elimination of product closes the catalytic cycle. Therefore, in this chapter will be summarized the work done to develop a new copper-catalyzed carbonylative cross-coupling using acylzirconocenes complexes as carbon nucleophile (Scheme 133).

The model system used for our investigation will be discussed first, after which the optimization for the set-up of the copper-catalyzed carbonylative cross-coupling by a systematic variation of all crucial parameters (nature of the copper salt, solvent, temperature, carbon monoxide surrogate, CO pressure) will be presented. Furthermore, in order to ascertain the scope of this chemical transformation and highlight its uses and limitations, a methodical variation of the nature of both reaction partners will be described.



Scheme 133. Proposed synthetic strategy for the development of a new copper-catalyzed carbonylative cross-coupling of acylzirconocene complexes.

3.6. Preliminary considerations

We began our investigation through the set-up of a model reaction using the two chamber reactor (COware) developed by Skrydstrup and co-workers (Scheme 134).[175] The CO-ware is a system that makes it possible to avoid handling carbon monoxide directly. This system requires a solid carbon monoxide surrogate that is stable and easy to handle. The CO-ware is a reactor with two chambers one chamber for the release of carbon monoxide and the other chamber for the reaction that consumes carbon monoxide. Thus, carbon monoxide can diffuse between the two reactor chambers via the headspace due to their spatial separation. For the use of this system the ideal gas law is frequently used to reveal the maximum theoretical pressure expected in the vessel. Despite the fact that the ideal gas law ignores solvent vapour pressure and gas dissolution, it is a useful tool for estimating and calculating the internal pressure of a two-chamber system when high-boiling solvents are used. The volume of the headspace (V_H) is determined by knowing the total internal volume of the reactor (V_T), as well as the solvent volumes of the left ($V_{S,L}$) and right chamber ($V_{S,R}$).

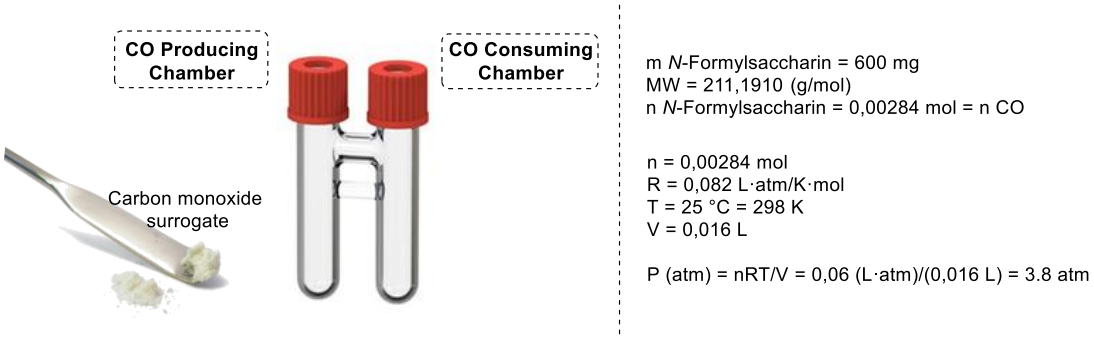
$$V_H = V_T - V_{S,L} - V_{S,R}$$

When the two-chamber reactor is closed at atmospheric pressure the amount of "atmosphere particles" such as carbon monoxide, nitrogen or hydrogen (n_{atm}) is calculated using the inverse formula of ideal gases.

$$n_{atm} = \frac{pV}{RT}$$

At a fixed reaction temperature T_R, the internal pressure is calculated by the ideal gas law considering that the total amount of gas particles is given by the sum of the amount of gaseous reagent generated (n_R)
$n_T = n_R$.

Despite the fact that COware is made of pyrex glass, stress testing has shown that these reactors can withstand pressures of up to 15 bar without failing,[176] even though all of the reactions discussed in this account were typically carried out at pressures no higher than 5 bar.

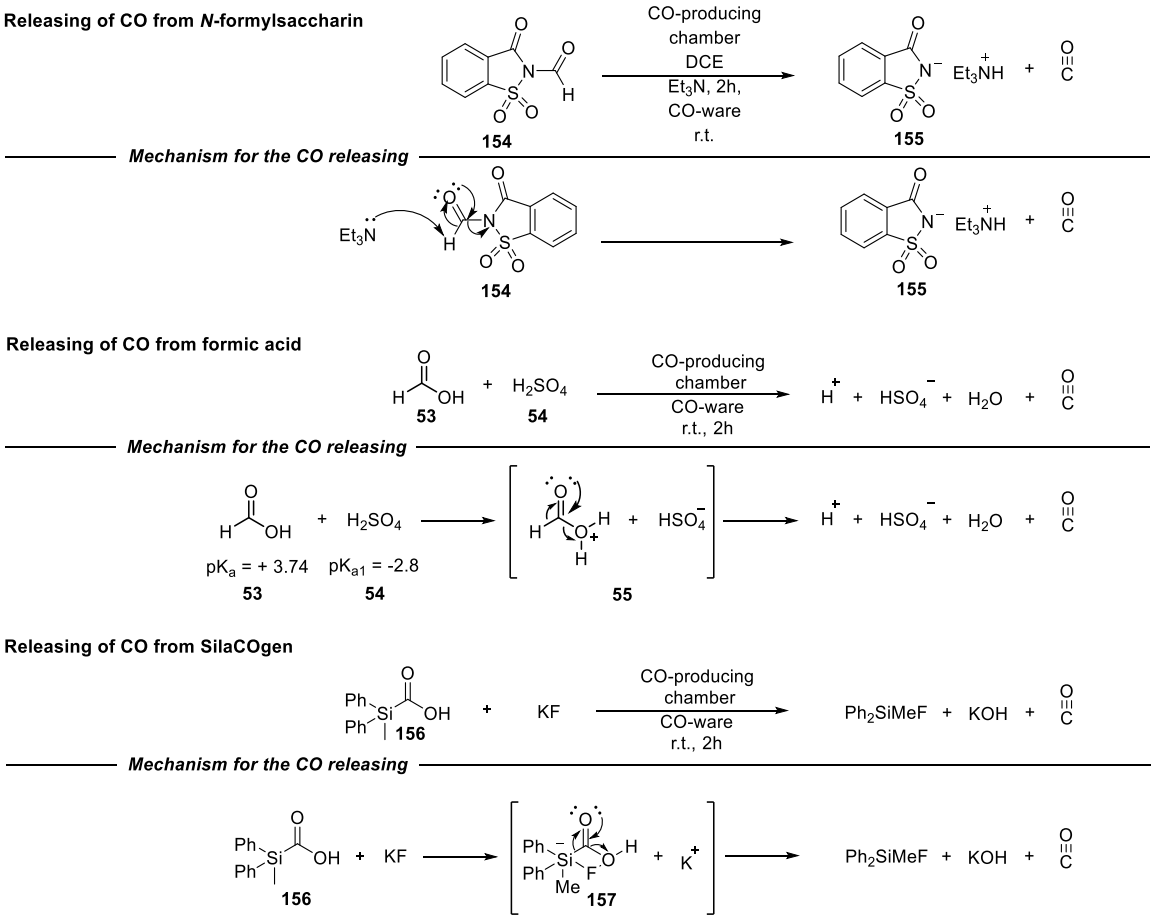


Scheme 134. COware gas reactor.

In order to promote the formation of the acylzirconocene complexes with the two-chamber reactor, it was important to identify the carbon monoxide surrogate at the beginning of our study to put in the CO producing chamber. An ideal surrogate of carbon monoxide to be considered effective must have the following properties: it must be a stable crystalline solid at room temperature, economic, capable to rapidly decomposes to inert reaction by-products and release carbon monoxide in a controlled manner.

[175] Demaerel, J.; Veryser, C.; De Borggraeve, W. M. *React. Chem. Eng.* **2020**, *5*, 615–631.
[176] Korsager, S.; Nielsen, D. U.; Taaning, R. H.; Skrydstrup, T. *Angew. Chem. Int. Ed*. **2013**, *52*, 9763–9766.

During the set-up of our model system, the identification of the best carbon monoxide surrogate to be used in the two-chamber reactor, we selected three different surrogates available in our laboratory to release CO: (a) a mixture of sulphuric acid **53** and formic acid **54** (Morgan's mixture), (b) *N*-formylsaccharin **154**, (c) and methyldiphenylsilanecarboxylic acid **156** (commercially named SilaCOgen). In the following Scheme 135 for each of the carbon monoxide surrogates we tested, both the reagents used and the reaction mechanism necessary to induce the release of carbon monoxide are presented.

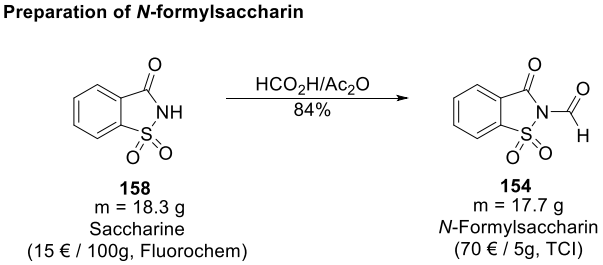


Scheme 135. Carbon monoxide surrogate selected to generate carbon monoxide.

During our first trials we tried to generate carbon monoxide using the Morgan's mixture which is composed of sulphuric acid **53** and formic acid **54**. However, the choice to generate carbon monoxide through the Morgan's mixture was quickly abandoned. Indeed, the reaction is strongly exothermic and produces water as by-product, which can quickly form moisture in the two-chamber system and inhibit moisture-sensitive reactions. Then, SilaCOgen **156** was tested as carbon monoxide surrogate in order to evaluate the release of carbon monoxide. This carbon monoxide surrogate is widely used in the literature and extremely effective, however as it has high commercial prices (265€ for 5g, SyTracks), we chose to discard SilaCOgen **156** as its daily use was unsustainable.[177]

[177] https://www.sytracks.com/product/st407

Finally, *N*-formylsaccharin **154** has been chosen as the best candidate to form carbon monoxide because it allows a controlled release of CO and the starting material to prepare it is commercially available and very economical (Saccharine: 15 € / 100g, Fluorochem). *N*-formylsaccharin can be easily prepared in the laboratory according to general procedure reported by the Cossy[178] and Fleischer[179] group (Scheme 136). *N*-formylsaccharin can be easily prepared using formic acid and acetic anhydride to form *in-situ* acetic formic anhydride which reacts with saccharin **158** to produce the desired carbon monoxide surrogate in good yield. Using this CO surrogate, the release of carbon monoxide is smoothly induced through the dropwise addition of triethylamine in the CO-producing chamber containing *N*-formylsaccharin.[180]



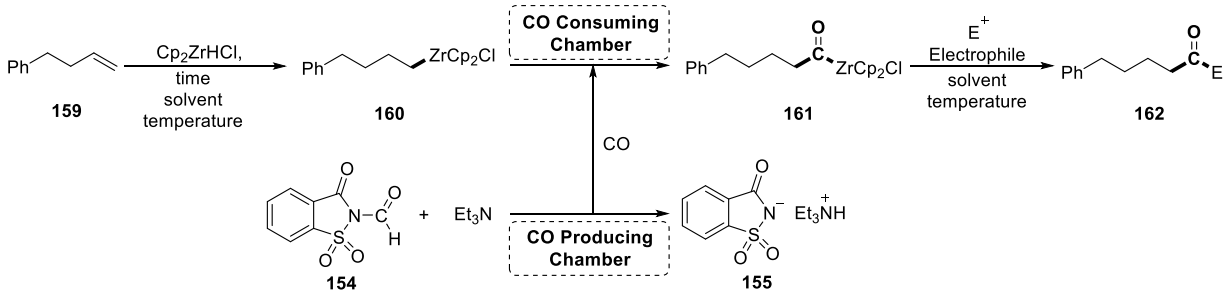
Scheme 136. Carbon monoxide surrogate selected to generate carbon monoxide.

After a brief optimization of the reaction set up, our attention has been devoted on the preparation of acyl zirconium complexes in order to develop a new copper-catalyzed cross-coupling. In the following sections we will describe the optimization required for the preparation of acyl zirconium complexes and the development of a new copper-catalyzed carbonylative cross-coupling.

3.7. Optimization of the reaction conditions

3.7.1. Preparation of the acylzirconocene complex

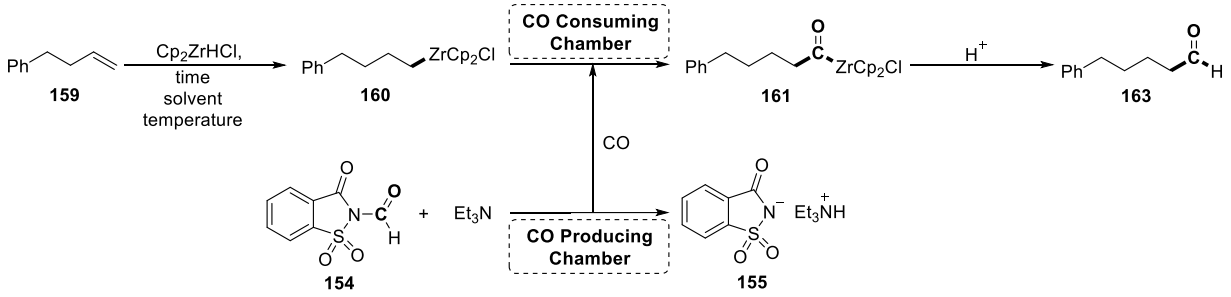
The preparation of the acylzirconocene chloride complex has been accomplished with a one-pot procedure through the hydrozirconation of alkenes with the Schwartz reagent **92**, followed by the insertion of carbon monoxide into the alkyl-zirconium bond under a pressure of carbon monoxide. To test the feasibility of our strategy and then to optimize it, we chose a simple commercially available model substrate named 4-phenyl-1-butene **159** (Scheme 137).



Scheme 137. Model reaction under investigation.

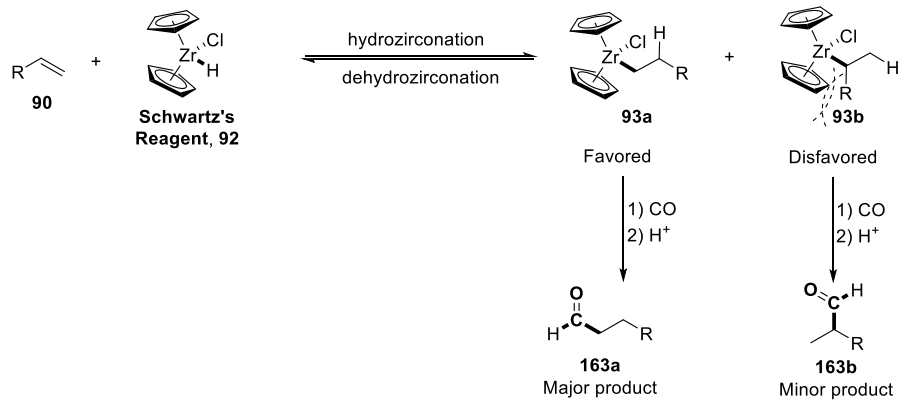
[178] Cochet, T.; Bellosta, V.; Greiner, A.; Roche, D.; Cossy, J. *Synlett*, **2011**, *13*, 1920–1922.
[179] Gehrtz, P. H.; Hirschbeck, V.; Fleischer, I. *Chem. Commun*. **2015**, *51*, 12574–12577.
[180] Tan, Y.; Lang, J.; Tang, M.; Li, J.; Mi, P.; Zheng, X. *ChemistrySelect*, **2021**, *6*, 2343–2349.

Aside from the simplicity of the model substrates, 4-phenyl-1-butene **159** was chosen for the optimization phase because of its favourable spectroscopic properties, which will make it easier to analyse the reaction crude and assess the ^{1}H-NMR yield. Specifically, the ^{1}H-NMR spectra (in $CDCl_3$ at 25 °C - room temperature) of 4-phenyl-1-butene **159** and of its carbonylated derivatives have characteristic sharp signals which allow to easily evaluate the percentage yield and the identity of the starting material and the target product. To test this strategy, the CO-producing chamber was charged with *N*-Formylsaccharin **154**, and the CO-consuming chamber was charged with the Schwartz's reagent **92** in DCM. This solvent has been used as first choice in both the chambers due to is inert and with a higher boiling point. Considering the experimental procedures available in the literature, for both hydrozirconation and the insertion of carbon monoxide, a reaction time of two hours each has been fixed. Here, the CO insertion into the carbon-zirconononium bond has been evaluated by using acid hydrolysis to form the homologated aldehyde **163** of the acylzirconocene complex **161** (Scheme 138). In order to analyse the various preliminary tests, it was agreed to avoid systematic isolation of the homologated aldehyde formed during the acid hydrolysis. With this in mind, it was decided to determine the ^{1}H-NMR yield NMR using 1,3,5-trimethoxybenzene as internal standard.



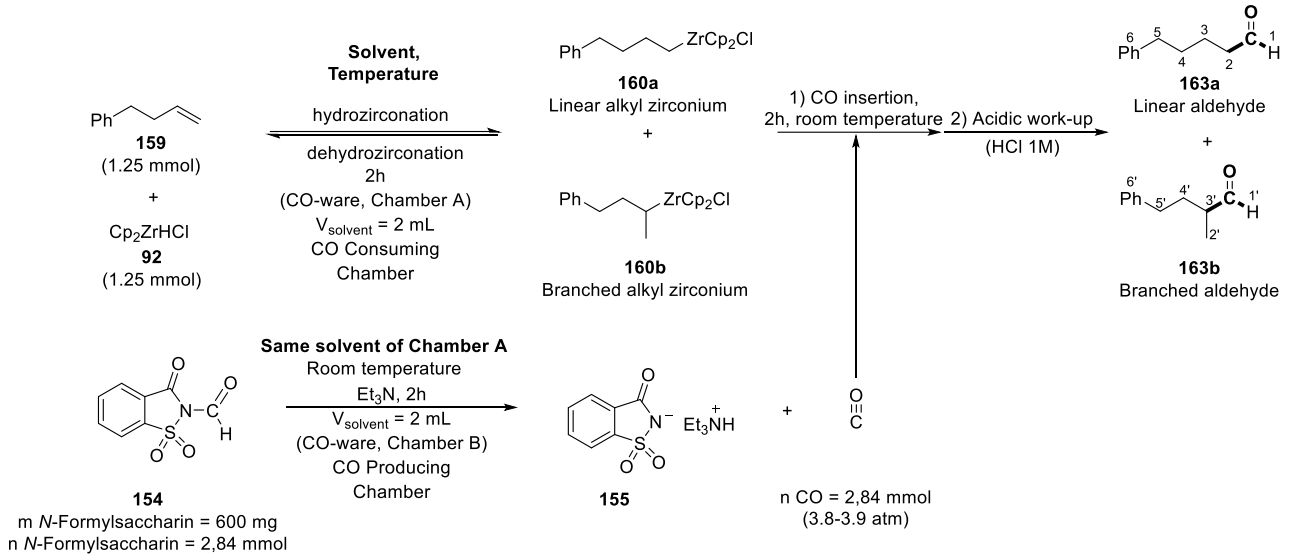
Scheme 138. Acid hydrolysis to form the homologated aldehyde of the acylzirconocene complex.

For the preparation of the acylzirconocene chloride complexes **161**, temperature and solvent were the first two parameters which have been optimized. Indeed, these two key parameters can lead to the formation of either a single product or a mixture of structural isomer, impossible to separate. Indeed, when an alkene and the Schwartz reagent Cp_2ZrHCl **92** are combined, an alkyl zirconocene σ-complex is quantitatively formed. Considering the position of the double bond onto the olefin, the alkylzirconocene complex can be rapidly isomerized to afford only the primary alkylzirconocene complex **93a**. The isomerization is due to the combination of β-hydride elimination and hydrozirconation. The regioselectivity is related to the steric hindrance of the bulky "Cp_2Zr" moiety and the least sterically hindered terminal alkylzirconocene complex is typically the main product **93a** (Scheme 139).



Scheme 139. Steric hindrance effect of the Schwartz reagent and a monosubstituted olefin.

For instance, using the *anti*-Markovnikov and *cis*-addition rules, the monosubstituted alkene follows an hydrozirconation to yield a linear alkyl zirconocene complex **93a** (Scheme 139) with high selectivity. Due to the strong steric repulsion between the Cp and the substituent attached to the alkene, the branched regioisomer is not preferred in this process. In order to evaluate the best reaction conditions that would only produce the linear product while preventing the branched one, the hydrozirconation reaction with the model substrate has been tested under various reaction conditions using a two-chamber reactor of 20 mL (Scheme 140). The hydrozirconation was conducted using the Schwartz reagent **92** purchased by Sigma-Aldrich. Then, the hydrozirconation reaction is carried out at room temperature using different solvents (DCE, DCM, and THF), the desired homologated aldehyde is quantitatively formed. Unfortunately, the linear homologated aldehyde **163a** was obtained with the presence of traces of branched aldehyde **163b** in 10% yield as a by-product of the reaction. In contrast, when the reaction is conducted in THF (b.p. 66 °C) and/or 1,2-dichloroethane (b.p. 83 °C) for two hours at a higher temperature (60 °C) only the linear aldehyde **163a** is formed as it is depicted below in the Table 10. The yields were calculated using 1,3,5-trimethoxybenzene as an internal standard.



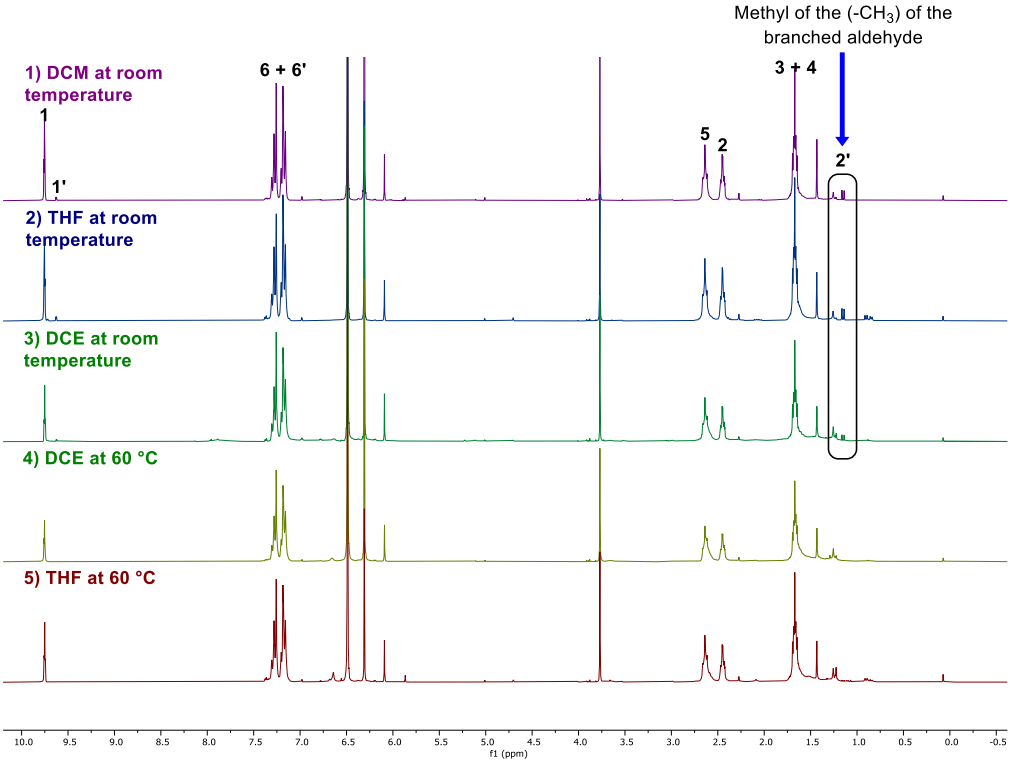
Scheme 140. Reaction conditions tested for the generation of the acyl-zirconium complex.

Entry	Solvent	Temperature	^{1}H-NMR yield of the Linear aldehyde	^{1}H-NMR yield of the Branched aldehyde
1	DCM	Room temperature	90%	10%
2	DCE	Room temperature	77%	10%
3	THF	Room temperature	90%	10%
4	DCE	60 °C	76%	-
5	THF	60 °C	76%	-

Table 10. Table of the reaction conditions tested for the generation of the acyl-zirconium complex.

These results are very clear by comparing the NMR spectra of the reaction crude collected testing the reaction under different conditions as it is depicted in the Scheme 141 below. Indeed, a sharp doublet signal at 1.15 ppm has been identified in the reaction crude corresponding to the methyl group of the branched aldehyde **163b** when the hydrozirconation reaction is carried out at room temperature using

different solvents (DCE, DCM and THF). Additionally, it is also possible to identify the signal of the proton of the branched aldehyde **163b** at 9.62 ppm with a very low intensity. When the hydrozirconation reaction is carried out at 60 °C these signals are totally suppressed, and only the linear aldehyde **163a** is obtained.



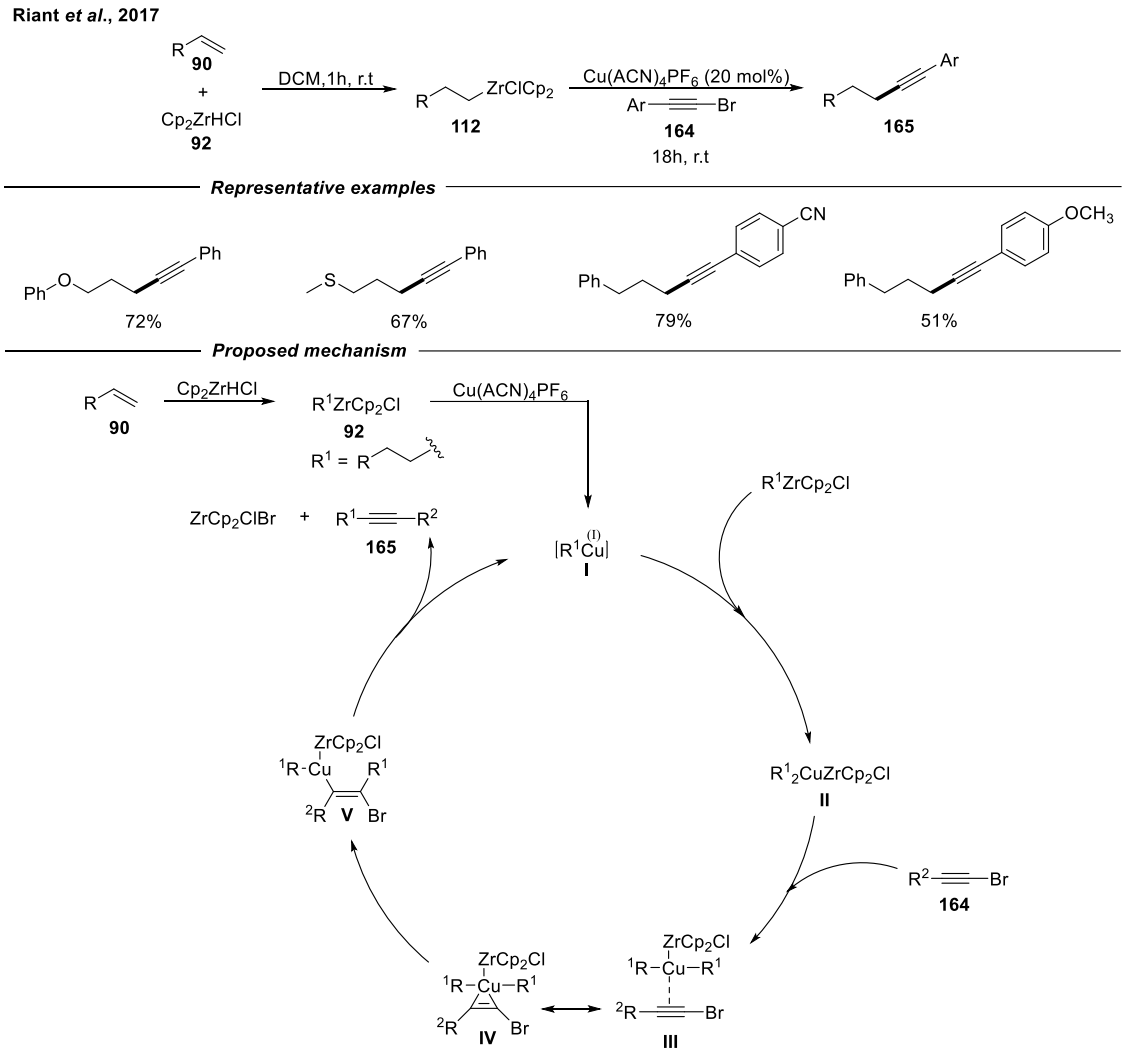
Scheme 141. Overlap of the ^{1}H-NMR spectra of the reaction crudes collected under different reactions conditions.

This result is due to the effect of the higher temperature, indeed when the hydrozirconation reaction is carried out at 60 °C the internal alkylzirconocene complex **160b** which is formed can be rapidly isomerized to the corresponding primary alkylzirconocene complex **160a**, which is the product of hydrozirconation less sterically hindered, more stable and thermodynamic. The high temperature can easily speed up the isomerization due to the combination of a β-hydride elimination and an additional hydrozirconation at the terminal position of the alkene. However, it is important to note that since acyl-zirconium complexes are not very stable at high temperatures, it is best to avoid exceeding 60 °C as higher temperatures can easily cause their decomposition. This explains the slightly lowered reaction yields at 60 °C. Therefore, taking into account the results obtained, DCE at 60 °C for two hours were chosen as the best reaction conditions to carry out the hydrozirconation reaction because no branched aldehyde **163b** formation was observed. Instead for what concerns the insertion of carbon monoxide into the Zr–alkyl bond, two hours at room temperature in DCE were sufficient to finally furnish the desired acyl-zirconium complex.

3.7.2. Nature of the electrophiles

After a brief optimization of the reaction set up, we focused on identifying the best electrophile capable of reacting with acyl zirconium and allowing the development of a new cross-coupling. At the beginning of our investigation, taking into account the previous and available experience in our laboratory, we started to test haloalkynes as a possible electrophilic candidate. Indeed, haloalkynes proved to be an excellent candidate to be used in the development of new copper-catalyzed cross-coupling with alkylzirconocenes. Riant and Indukuri in 2017 reported a novel copper-catalyzed cross-coupling by the

reaction between alkynyl bromides **164** and alkylzirconocenes **112** (Scheme 142).[181] The alkylzirconocenes complexes **112** were formed *in-situ* via the regioselective reaction of Cp_2ZrHCl **92** and alkenes **90**. Thereafter, the alkylzirconocenes reacted with bromoalkynes **164** in presence of only 20 mol% of $Cu(ACN)_4PF_6$ to furnish in good yields the corresponding internal alkynes **165**. This protocol is based on a direct hydrozirconation/transmetallation/cross-coupling sequence of alkenes to easily prepare dialkylated alkynes, which are not easy to prepare using alternative methods. The most interesting aspect of this transformation is its "ligand-less" and "base-free" conditions which make this protocol very attractive from the standpoints of cost, atom economy and ease of purification.

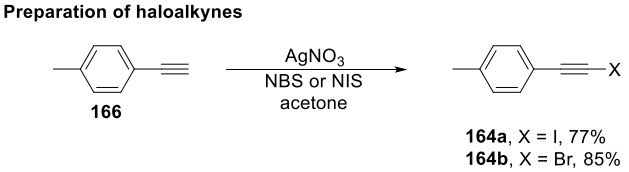


Scheme 142. Transmetalation of alkylzirconocenes in copper-catalyzed alkyl–alkynyl cross-coupling reactions.

Therefore, taking into account the research conducted by Riant and co-workers, our initial investigation was focused on determining the best reaction conditions using as electrophile a bromo-alkyne named 1-(bromoethynyl)-4-methylbenzene **164b**. Indeed, these substrates had already demonstrated to be a good electrophilic partner for copper-catalyzed cross-coupling with alkynyl zirconocenes complexes. Haloalkynes were smoothly prepared employing a mild and efficient method based on the electrophilic bromination/iodination of terminal alkynes with *N*-bromosuccinimide (NBS)/ *N*-iodosuccinimide in presence

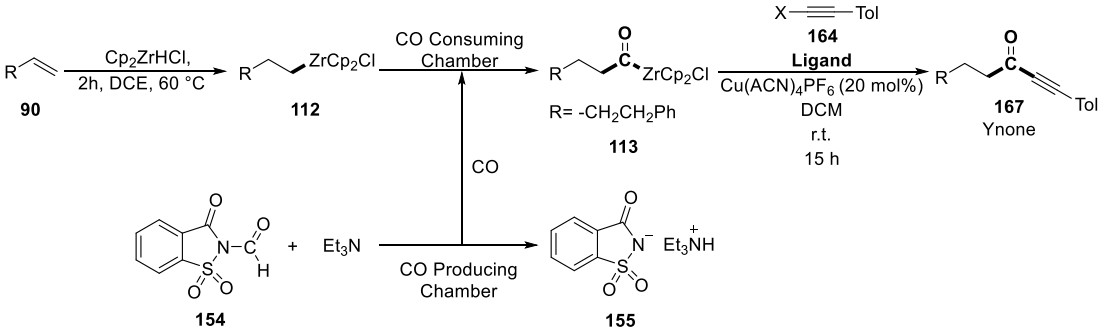
[181] Indukuri, K.; Riant, Olivier. *Adv. Synth. Catal*. **2017**, *6*, 1–8.

of $AgNO_3$ as catalyst (Scheme 143).[182] This protocol is widely used due to the mild reaction conditions, high efficiency and simple manipulation.



Scheme 143. Preparation of haloalkynes with NBS/NIS and $AgNO_3$.

After preparing the starting material, we began evaluating the influence of the ligand's nature on the selected model system as depicted in the Scheme 144 below. The nature of ligand is one of the most important parameters because it forms a stable copper-ligand complex, which aids in the solubility of the copper catalyst. Additionally, the ligand may be also crucial in stabilizing the reaction intermediates. Therefore, by making the complex that is generated in solution more soluble and/or stabilizing the reaction intermediates, the best ligand can increase the yield of the reaction product. For these reasons we carried out a screening of a library of ligands commonly used in copper-catalysis with the intention of identifying the most suitable candidate. Specifically, we focused our attention on ligands such as N,P ligands, O,P ligands, phenanthroline derivatives,[183] diamines[184] and diphosphine[185]. The efficacy of these ligands was evaluated for the reaction of cross-coupling of acylzirconocenes **113** with bromoalkynes **164** in presence of 20 mol% of $Cu(ACN)_4PF_6$. Notably, in this initial trials we considered a ratio copper/ligand which was kept equal, 1:1 respectively. The results obtained with respect of the nature of the ligands are collected in the Table 11 below. Most initial attempts were regrettably unsuccessful since in most cases only traces of the product were found in the crude mixture. In most cases, only traces of the reaction product have been identified, either using bromo-alkynes or using iodo-alkynes. Unfortunately, also using iodo-alkynes as model substrate the target product **167** was not formed, even if it should be easier to activate the C–I bond due to the lower bond dissociation energy.



Scheme 144. Screening of ligands onto the model reaction with halo-alkynes.

Following these results, we began to believe that the nature of the electrophile was not suitable for reacting with acyl-zirconium complexes **113**. In fact, by highlighting the formation of degradation by-products unidentified in the presence of traces of the desired product **167**, we were able to recover the halo-alkyne **164** as starting material.

[182] Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett.* **1994**, *7*, 485–486.

[183] (a) Buchwald, S. L.; Koval, E. D.; Altman, R. A. *J. Org. Chem*. **2007**, *16*, 6190–6199. (b) Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657–2660.

[184] Surry, D. S.; Buchwald, S. L. *Chem. Sci*. **2010**, *1*, 13–31.

[185] van Leeuwen, P. W.N.M.; Kamer, P. *Catal. Sci. Technol*. **2018**, *8*, 26–113.

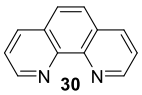
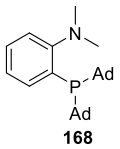
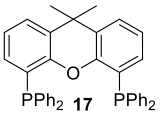
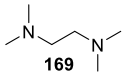
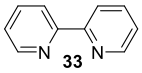
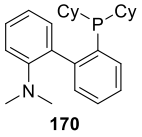
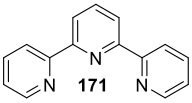
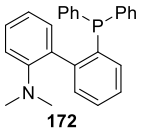
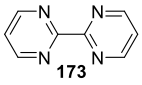
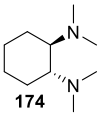
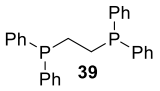
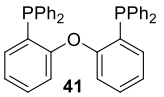
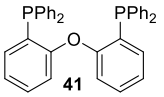
Entry	X	Ligand	Yield (%)[a]
1	Br	1,10-Phenanthroline  **30**	-
2	Br	MeDalphos  **168**	15%
3	Br	Xantphos  **17**	15%
4	Br	TMEDA  **169**	-
5	Br	Bipy  **33**	-
6	Br	DavePhos  **170**	20%
7	Br	Terpyridine  **171**	15%
8	Br	PhDavePhos  **172**	-
9	Br	2,2'-Dipyrimidyl  **173**	22%
10	Br	*trans-N*, *N*'-Dimethyl cyclohexane-1,2-diamine  **174**	-

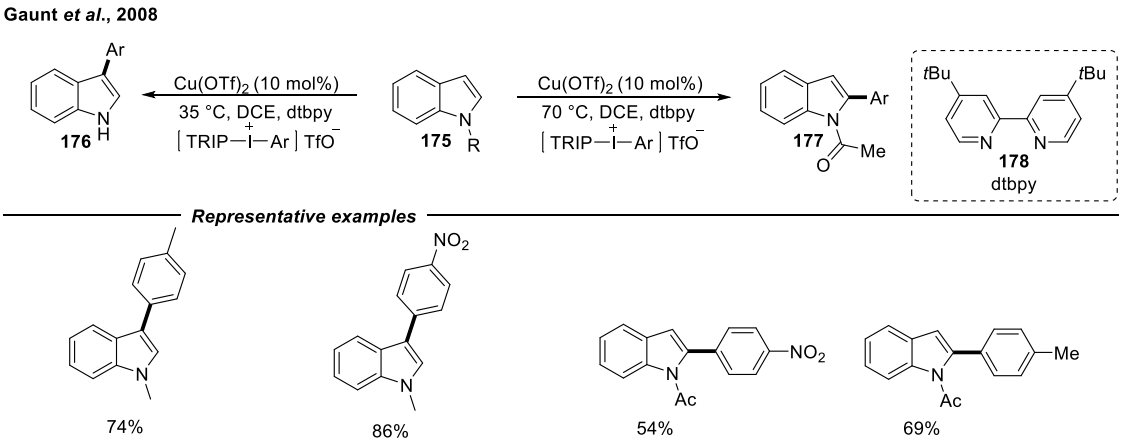
Table 11. Screening of ligands onto the model reaction.

Entry	X	Ligand	Yield (%)[a]
11	Br	Dppe  **39**	-
12	Br	DPEPhos  **41**	33%
13	I	DPEPhos  **41**	35%

[a] Yields determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

Table 11. Screening of ligands onto the model reaction.

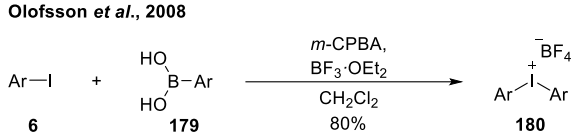
Due to the lack of reactivity and the low yields obtained, we have focused our attention on finding electrophiles that are more effective. At this point, we have been inspired by the report of Gaunt and co-workers which developed in 2008 a novel copper-catalyzed protocol for the C–H bond functionalization of indoles **175**. Indeed, this process can selectively promote the arylation of indoles at either the C_3 or C_2 position under mild reaction conditions.[186] Indeed, we imagined that it was interesting to test the aryl-iodonium salt as electrophilic partner for our cross-coupling as it has been done by the Gaunt group (Scheme 145). In light of the poor results obtained with halo-alkynes, most probably for a lack of reactivity, we thought it was interesting to change the nature of the electrophile and looking for something more reactive.



Scheme 145. Cu-catalyzed direct and site-selective arylation of indoles.

[186] Grimster, N. P.; Gaunt, M. J.; Phipps, R. J. *J. Am. Chem. Soc.* **2008**, *26*, 8172–8174.

Specifically, we envisioned that by increasing the electrophilic character of the electrophile replacing the halo-alkynes with the aryl iodonium salts, it was easier to promote the formation of the target product by increasing the reaction yield. Therefore, using the Olofsson's protocol, which was developed in 2008, a symmetrical diphenyliodonium tetrafluoroborate salt **180** was prepared in order to test the model reaction with this new electrophile.[187] By using boronic acid **179** and iodobenzene **6** as commercially available starting reagents, this procedure has been used to prepare the starting material we wanted to test. The diphenyl iodonium tetrafluoroborates was prepared without the need of an additional anion-exchange step, the protocol uses boron trifluoride etherate and mCPBA (Scheme 146). Noteworthy, at the beginning of our investigation we voluntarily chose to use symmetrical aryl iodonium salts in order to avoid the formation of a mixture of arylated products. In addition, as anion of the diaryl iodonium salt was chosen the tetrafluoroborate as result of its inert nature. Consequently, we started to test the aryl iodonium salts **180** in the presence of different copper sources.



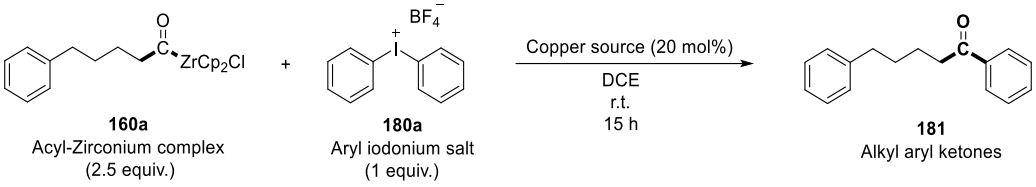
Scheme 146. Preparation of diphenyliodonium tetrafluoroborate salt using the Olofsson's protocol.

3.7.3. Nature of the copper sources

At this point, using diphenyliodonium tetrafluoroborate **180a** as model substrate we carried out a screening of several copper sources in presence of the acyl zirconocene complex **160a** prepared using the two chamber reactor as depicted in the Scheme 147. In this way has been evaluated the efficiency of a set of representative copper sources using diphenyliodonium tetrafluoroborate as electrophile, Table 12. The source of copper is a significant factor in the development of new reactions because depending on its nature depends on its chemical reactivity, solubility in organic solvents and stability of reaction intermediates. By changing the nature of the electrophile and of the copper salts, more interesting results have been obtained. Most likely the nature of the copper catalyst has an important role in promoting the cross-coupling by facilitating the formation of the target product.

Our first attempts were made using catalytic amounts of copper catalyst 20 mol% under standard reaction conditions. Disappointingly, the use of $Cu(ACN)_4PF_6$ gave the desired ketone in low yield 15%. Other copper salts such as CuBr·DMS, $CuBr(PPh_3)_3$, $Cu(ACN)_4BF_4$ were tested as well and the carbonylated product was obtained with a yield of 17%, 25% and 20%, respectively. Moreover, we found a little increment in the yields (30% and 35%) when CuTC and CuOAc were tested. A more encouraging result was obtained when switching to Cu_2O and CuSCN, with these copper sources although a full conversion was not reached, the product was obtained as the major product in 48% and 54% yields. The yield of the coupling product was enhanced to 64% upon switching the copper catalyst to CuI. Higher yields and cleaner reactions were obtained when switching to CuCN, to our surprise the coupling product **181** was obtained in 84%. This slight increase in reaction yield is most likely due to an increase in the reaction solubility of the copper source, which may encourage the formation of the target product. As a result, by changing the nature of the electrophile and the nature of the copper source we have highlighted the formation of the expected carbonyl product **181**. This result can be attributed to a higher electrophilicity of the starting material and the identification of the most suitable copper source.

[187] Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem*. **2008**, *73*, 4602–4607.



Scheme 147. Screening of copper sources.

Entry	Copper source	Yield (%)[a]
1	CuTC	30
2	CuBr·DMS	17
3	$Cu(ACN)_4BF_4$	20
4	**CuCN**	**84**
5	$Cu(ACN)_4PF_6$	15
6	CuOAc	35
7	$CuBr(PPh_3)_3$	25
8	CuSCN	54
9	CuI	64
10	Cu_2O	48

[a] Yields determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

Table 12. Screening of copper sources.

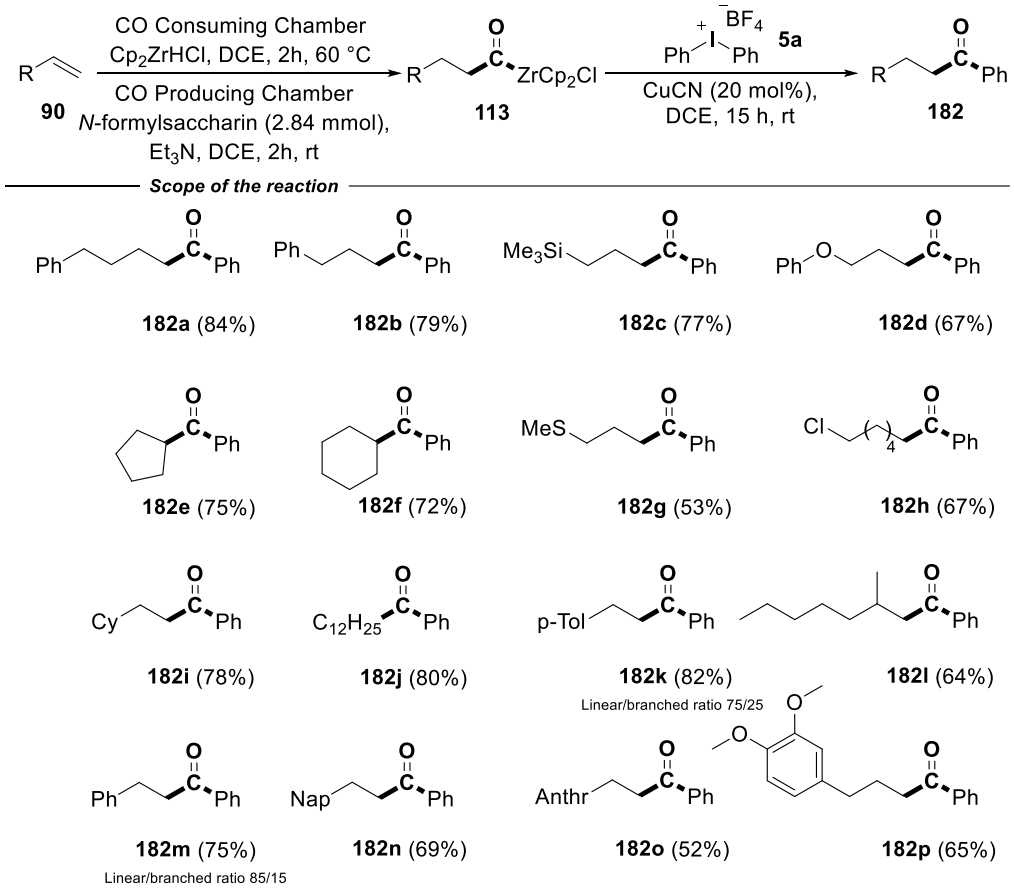
At this point, after optimizing the reaction conditions, it was decided to investigate the scope of the reaction and carry out a systematic screening of alkenes and aryl iodonium salts in order to prepare a library of aromatic ketones.

3.8. Investigation of the scope

3.8.1. Scope of the reaction with various alkenes

With the optimized reaction conditions in hand, we then explored the substrate scope of the reaction with various alkyl acyl-zirconocene chlorides, generated *in-situ* from alkenes and coupled with diphenyliodonium tetrafluoroborate (Scheme 148). In all cases, aryl ketones **182a-182p** were prepared in moderate to good yields. Primary alkenes functionalized with heteroatoms (Si, O, S), furnished the desired aryl ketones **182c**, **182d**, and **182g** in 77%, 67% and 53% yields, respectively. Notably, the carbonylative cross-coupling of 6-chloro-1-hexene, with a potentially leaving group, also afforded the desired ketone **182h** in 67% yield. Simple acylzirconocenes derived from terminal alkenes such as, vinylcyclohexane and 1-dodecene were also coupled with the aryl iodonium salt, to give the unsymmetrical ketones **182i** and **182j** in 78% and 80% yields, respectively. This method has been also effective for the synthesis of cyclic aryl ketones with different ring size, indeed starting from cyclopentene and cyclohexene as starting material it has been possible obtain the compounds **182e** and **182f** in 75% and 72% yields. Gratifyingly, the reaction was still found to be operative, although with less efficiency, when geminal di-substituted alkene 2-methylhept-1-ene was used, although the product **182l** was obtained with a lowered yield of only 64%. Noteworthy, when 4-vinyltoluene and styrene were used with our protocol the corresponding di-arylketones **182k** and **182m** were prepared in

82% and 75% of yields, although a mixture of inseparable structural isomer was obtained with a linear/branched ratio of 75/25 for compound **182k** and of 85/15 for compound **182m** after purification.



Scheme 148. Scope of the reaction with various alkenes.

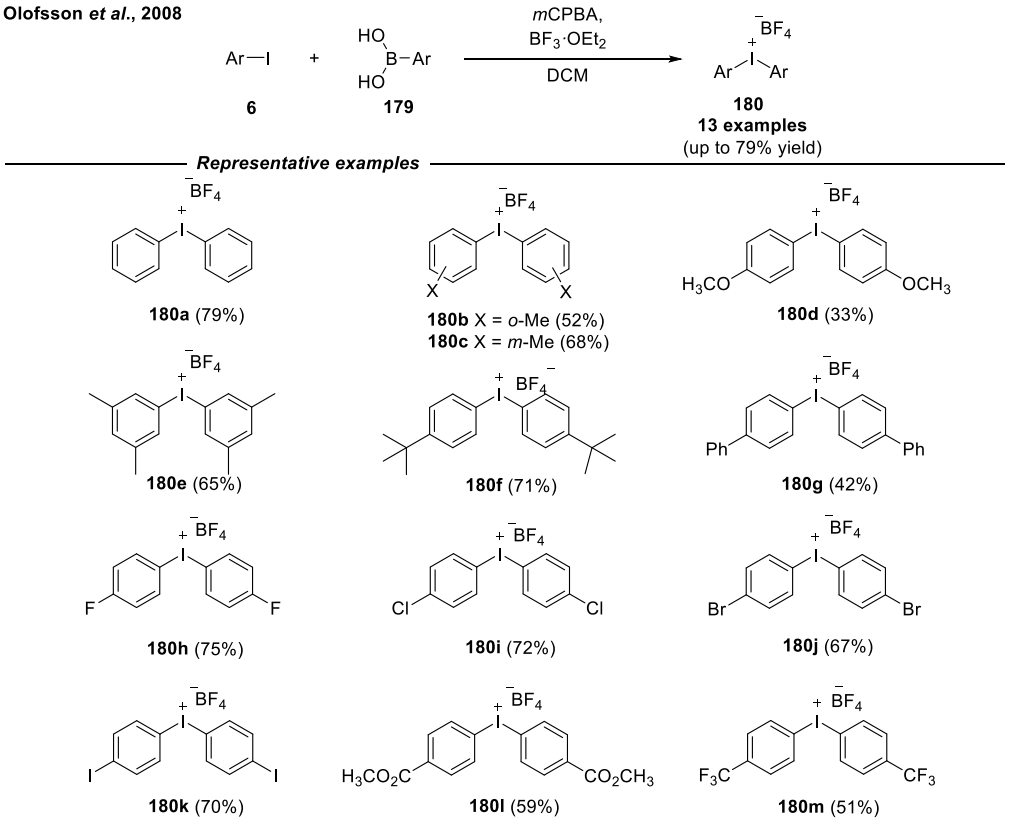
In the case of styrenes **182k**-**182m**, the aryl ring appears to favor the isomerization of the terminal alkyl zirconocenes at the benzylic position.[188] Finally, we investigated the reactivity of more sterically hindered substrates as vinyl polycyclic aromatic hydrocarbon. We were pleased to find that functionalization of 1-vinylnaphthalene **182n** and 9-vinylanthracene **182o** took place at the terminal position of the vinyl moiety, without the formation of a mixture of structural isomers. However, the increased steric hindrance on the vinyl moiety resulted in a significantly lower yield of the desired ketone **182n** and **182o** in 69% and 52% yields, respectively.

[188] Wipf, P.; Jahn, H. *Tetrahedron,* **1996**, *52*, 12853–12910.

3.8.2. Preparation of a library of diaryliodonium tetrafluoroborates

After varying the nature of the alkene to examine the scope of the reaction, our attention has been oriented toward varying the nature of the aryl iodonium salts **180** (Scheme 149). Using the Olofsson's protocol, which was developed in 2008, a small library of aryl iodonium salts **180** has been prepared in order to test the model reaction.[189] By using boronic acids **179** and iodobenzenes **6** as commercially available starting reagents, this procedure has been used to prepare a library of symmetrical diaryliodonium tetrafluoroborate salts in good yields. As it produces diaryliodonium tetrafluoroborates without the need for an additional anion-exchange step, the protocol uses boron trifluoride etherate and mCPBA, which has recently been reported in a number of iodine oxidations.[190]

Both electron-deficient **180l**-**180m** (-CO_2CH_3, -CF_3) and electron-neutral **180e**-**180f** (CH_3, *t*Bu-) symmetrical salts can be synthesized with this protocol and the substitution pattern can be easily changed. In addition, also the halogenated iodoarenes **180h**-**180k** (-F, -Cl, -Br, -I) were smoothly oxidized and coupled with the corresponding boronic acids, respectively, yielding symmetric salts. Unfortunately, low yields have been observed using electron-rich substrates, such as *p*-methoxy- **180d** and *p*-phenyl- **180g** starting material.



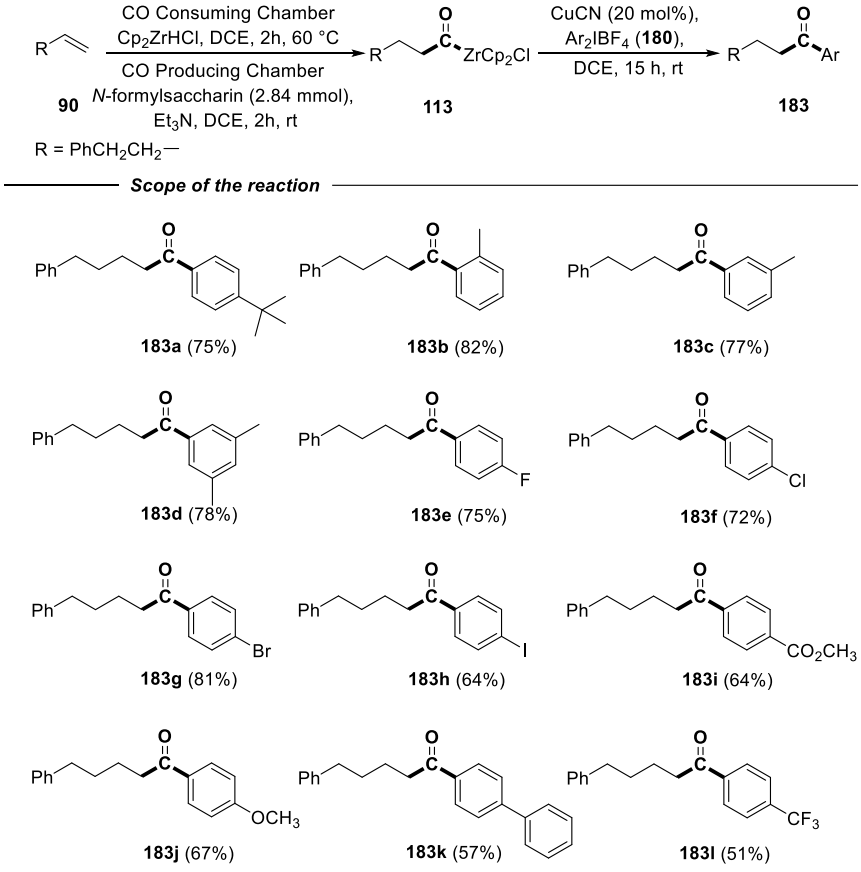
Scheme 149. Library of diaryliodonium tetrafluoroborates prepared.

[189] Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem*. **2008**, *73*, 4602–4607.

[190] (a) Dohi, T.; Maruyama, A.; Yoshimura, M.; Morimoto, K.; Tohma, H.; Kita, Y. *Angew. Chem. Int. Ed*. **2005**, *44*, 6193–6196. (b) Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc*. **2005**, *127*, 12244–12245. (c) Yamamoto, Y.; Togo, H. *Synlett.* **2006**, *5*, 798–800. (d) Togo, H.; Yamamoto, Y. *Synlett.* **2005**, *16*, 2486–2488. (d) Tohma, H.; Maruyama, A.; Dohi, T.; Shiro, M.; Morita, T.; Kita, Y. *Angew. Chem. Int. Ed.* **2004**, *43*, 3595–3598.

3.8.3. Scope of the reaction with various diaryliodonium tetrafluoroborates

Having demonstrated the applicability of the optimized conditions on various alkenes, we then turned our attention to the scope of various substituted symmetrical diaryl iodonium salts (Scheme 150). Gratifyingly, as evidenced by results depicted below, the aryl iodonium salts tested could be smoothly coupled to furnish the desired products in moderate to good yields. The protocol well tolerates diverse electronic and steric substituents onto the aromatic ring of the diaryliodonium salts. In general, under our reaction conditions aryl iodonium salt tetrafluoroborate bearing neutral substituents such as methyl and *ter*-butyl **183a-183d** could be easily transferred to give the expected products in yields ranging from 75-82%. Similar reactivity was observed when the series of 4-halogen diphenyl iodonium salts (-F, -Cl, -Br, -I) were tested to give the envisaged products **183e-183h** in fair to good yields 64-81%. These halogenated products are particularly appealing since in one step not only a carbonylative arylation take place onto the parent molecule, but also a halogen is inserted, which could be further exploited for subsequent functionalization. Symmetrical iodonium salts with electron donating group such as methoxy and phenyl all produced the desired products **183j** and **183k**, although with a slight decrease in reaction yields 67% and 57%, respectively. Finally, no significant different in yield were observed when aryl iodonium salts bearing electron-withdrawing groups were examined. The formation of the carbonylated product has been easily achievable, although resulted in a significantly lower yield of the ketone **183i** and **183l** in 64% and 51% yields, respectively.



Scheme 150. Scope of the reaction with various aryl iodonium tetrafluoroborates.

3.9. Limitations of the methodology

Empirically, the rate of hydrozirconation tends to decrease in the following order of reactivity: terminal alkyne **184** > terminal monosubstituted alkene **185** ≈ internal alkyne **186** > internal disubstituted alkene **187** ≈ 2,2-disubstituted terminal alkene **188** > trisubstituted alkene **189** (Scheme 151). For instance, an unsymmetrical diyne preferentially reacts at the less substituted triple bond,[191] while an enyne follows selectively the hydrozirconation at the alkyne moiety.[192] The rate of hydrozirconation for cyclic alkenes is highly influenced by ring size and ring strain. Cycloheptene and cyclooctene are very resistant substrates, whereas bicyclic alkenes, for instance, react quite quickly. Tetrasubstituted alkenes don't typically react. Even with internal alkenes, zirconium migration along the carbon chain results in terminal organometallics because of the rapid β-elimination of secondary alkylchlorozirconocene species.

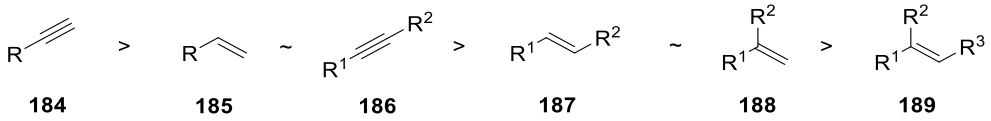


Figure 151. Relative rates of hydrozirconation for different substrates.

In attempt to further broaden the scope of our methodology, also the reactivity of trisubstituted alkenes **191**-**193** and cyclic alkenes **194**-**195** was briefly evaluated (Scheme 152). Unfortunately, no formation of the desired products was observed. Most probably, the low rate of hydrozirconation of the tri-substituted alkenes has suppressed the process and prevented the formation of the carbonylated products.

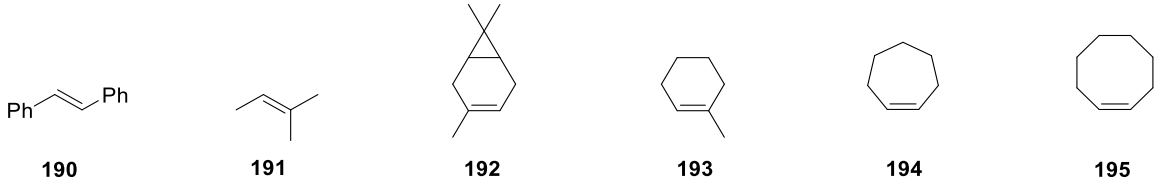


Figure 152. Failed tested substrates that did not lead to the product formation.

In an effort to extend the potential of our copper-catalyzed carbonylative cross-coupling of alkenes and evaluate its efficiency in "real life" situations, the reaction with a complex substrate was next envisioned. Unfortunately, it was impossible to isolate the aryl-ketone of the (±)-α-tocopherol derivate **196** (Scheme 153). The crude of the reaction was found to be a mixture of starting material with traces of reaction product. Furthermore, because there was an unidentified by-product with the same retention factor of the product, it was impossible to purify, isolate, and characterize the traces of the target compound. In fact, even after several sequential purifications we could not get the clean isolated compound.

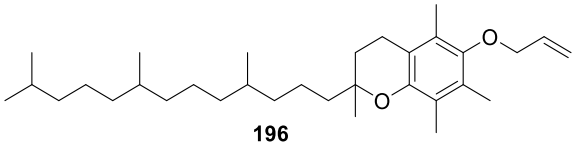


Figure 153. Scope of the reaction with various alkenes.

[191] Fryzuk, M. D.; Bates, G. S.; Stone, C. *J. Org. Chem.* **1991**, *56*, 7201–7211.
[192] Crombie, L.; Hobbs, A. J. W.; Horsham, M. A.; Blade, R. J. *Tetrahedron Lett*. **1987**, *28*, 4875–4878.

3.10. Applications to the synthesis of molecules of biological interest

Lastly, in a further effort to demonstrate the synthetic value of this transformation and inspired by the seminal work of the Szymoniak group on the synthesis of 2,6-*cis*-disubstituted piperidines **200** via a sequential hydrozirconation/acylation followed by an intramolecular reductive amination (Scheme 154),[193] we sought to target this biologically relevant structure through the use of a revised strategy based on the use of acyl zirconium complexes and the protocol developed in our laboratories.

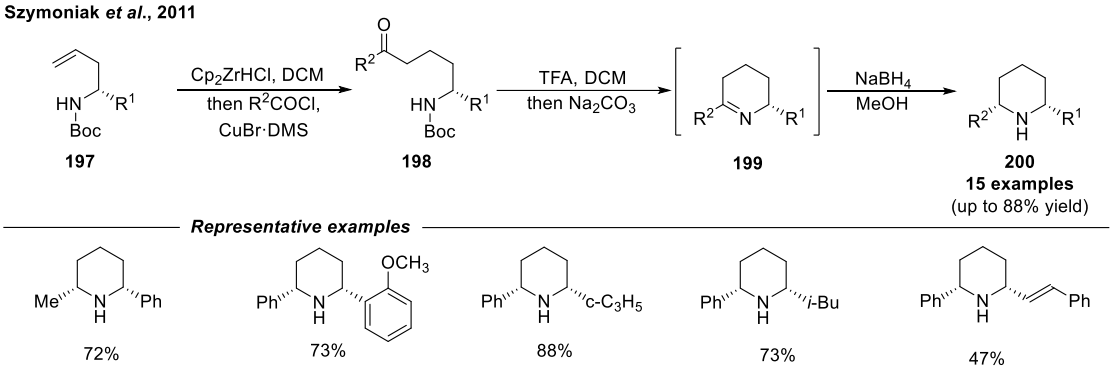


Figure 154. Szymoniak's procedure for the diastereoselective access to 2,6-cis-disubstituted piperidines.

Indeed, 2,6-disubstituted piperidines are important alkaloid's structure can be found in a wide variety of living organisms in nature, including plants, insects, marine invertebrates and microorganisms as can be seen from the many examples **201**-**206** reported in Scheme 155. However, their biological activity and the wide range of therapeutic uses that are possible are what have garnered the most interest.[194] Moreover, many new medicinally important drugs have been developed by changing the structures of known alkaloids and taking inspiration from their mode of action.

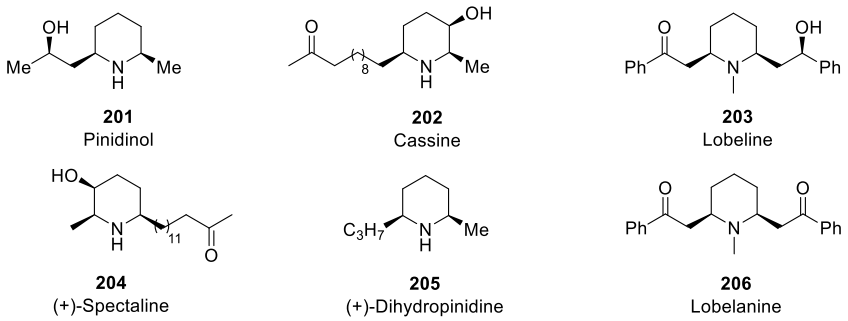


Figure 155. Examples of 2,6-disubstituted piperidine alkaloids found in nature.

For these reasons, despite the many synthetic pathways available to prepare these molecules, [195] we decided to target 2,6-disubstituted piperidine **213** through a sequence of three steps based on the use of acylzirconocene chlorides complexes (Scheme 156). Notably, this part of the project was conducted in collaboration with Marcelina Mlynczak, a bachelor's student in chemistry of the University of Dublin (Erasmus Programme). First of all, we have performed a mild and highly efficient three-component reaction in the presence of 5 mol % of $Cu(OTf)_2$ as Lewis acid and 3-phenylpropionaldehyde **207**, carbamate **209** and

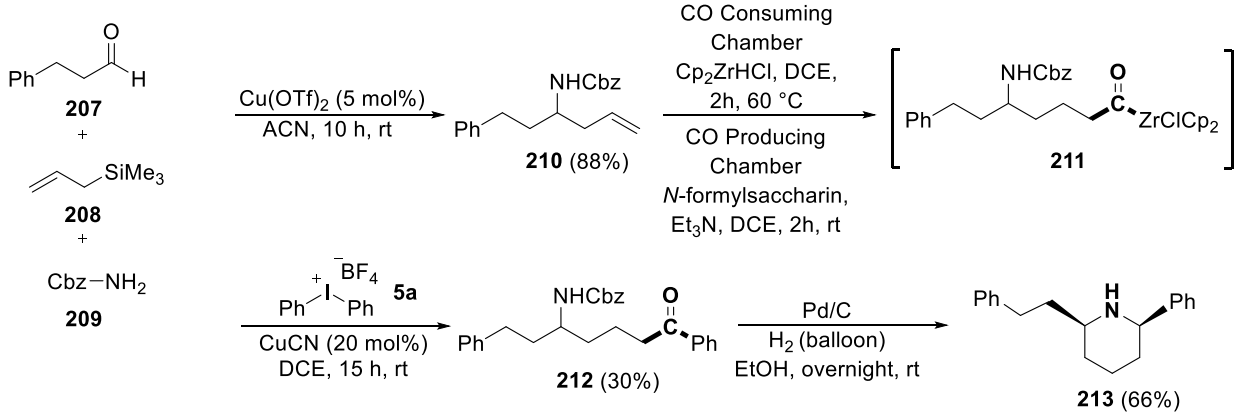
[193] Coia, N.; Mokhtari, N.; Vasse, J. L.; Szymoniak, J. *Org. Lett.* **2011**, *23*, 6292–6295.

[194] a) Fodor, G. B.; Colasanti, B. *In Alkaloids: Chemical and Biological Perspectives*, 1th ed.; Vol. 3; Pelletier, S. W. Ed. Wiley: New York, **1985**. (b) Jones, T. H.; Blum, M. S. *In Alkaloids: Chemical and Biological Perspectives*, 1th ed.; Vol. 1; Pelletier, S. W. Ed. Wiley: New York, **1983**.

[195] Ha, H. J.; Macha, L.; Srivastava, N. *Org. Biomol. Chem.* **2020**, *18*, 5493–5512.

allyltrimethylsilane **208**.[196] Using this protocol the desired homoallylamines **210** has been prepared with 72% of isolated yield. In the first step of our reaction sequence, the electrophilic Cbz-imine reacts with allyltrimethylsilane **208** in the presence of $Cu(OTf)_2$, in a manner similar to the Sakurai reaction.[197] The Lewis acid is required to promote the transformation which is a type of electrophilic allyl shift. The driving force of this transformation is the formation of an intermediate of β-silyl carbocation stabilized by the β-silicon effect. This procedure is highly efficient for the synthesis of homoallylamines and offers several advantages including the mild reaction conditions, low catalytic loading and no formation of by-products.

Once the desired Cbz-protected homoallylamine **210** was prepared, we have performed our protocol for the synthesis of the desired aryl ketone **212** in 30% yield, this yield is lower compared to our previous results and most probably it is due to the low compatibility of the benzyl carbamate group in the presence of the Schwartz's reagent. Most likely, the Schwartz' reagent reacts with the carbonyl moiety of the starting material and cause a decreasing of the reaction yield. One possible alternative could be to employ the benzyl protective group due to is easy to remove under hydrogenolysis and is inert when the Schwartz' reagent is used. This result was not further optimized and has been sufficient to continue our synthetic strategy. Indeed, after a Pd-catalyzed Cbz-deprotection, it was triggered a spontaneous intramolecular cyclization, which led firstly to the synthesis of the imine intermediate and then through an *in-situ* reduction to the corresponding 2,6-disubstituted piperidine **213** in 66% yield. Lastly, the ^{1}H-NMR and ^{13}C-NMR spectra of the piperidine synthesized in the lab were compared to an identical one published in the literature and with a known configuration. The chemical shift of the NMR analysis are identical, thus it is possible to assert that the molecule synthesized during the course of this project has the same structure as the one reported in the literature by the Helmchen's research group.[198] The stereochemical configuration of the product was ascertained by means of a comparative analysis with an identical compound that has been previously documented in the literature.

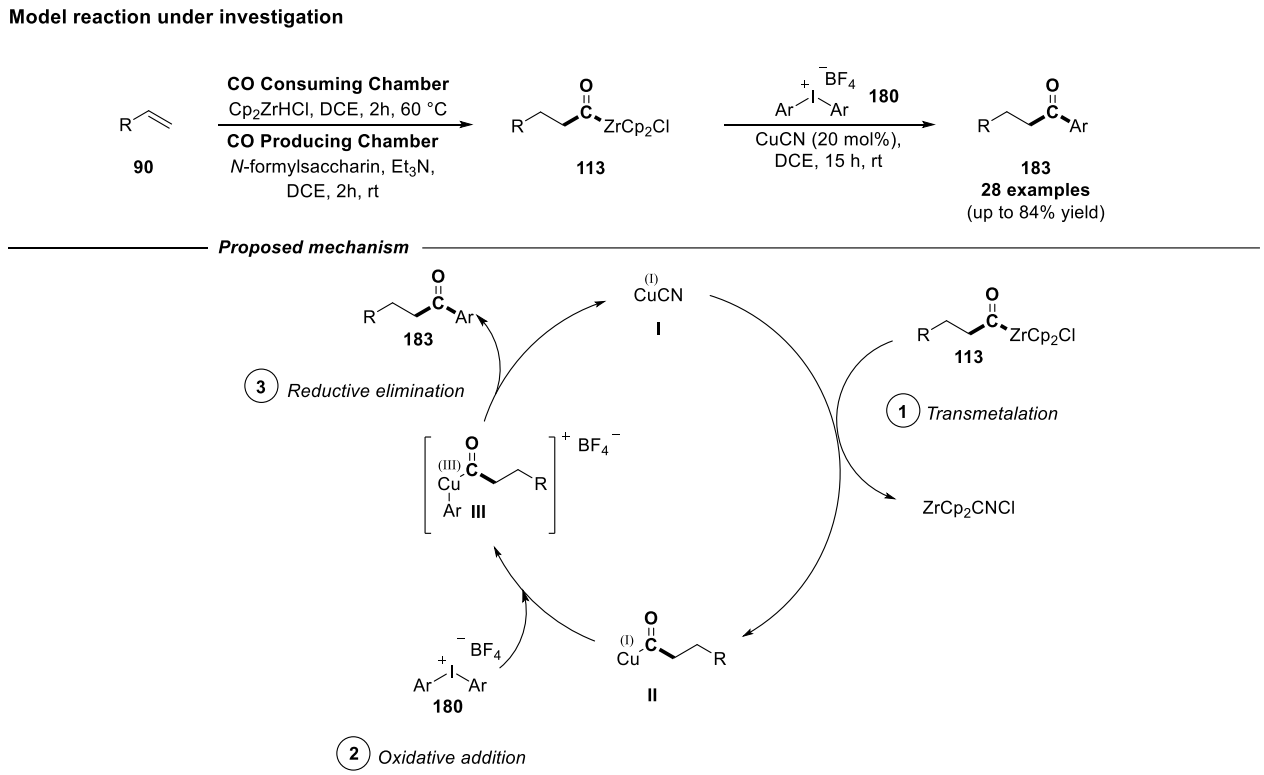


Scheme 156. Applications of the copper catalyzed carbonylative cross-coupling: synthesis of a 2,6-disubstituted piperidine.

[196] Pasunooti, K. K.; Leow, M. L.; Vedachalam, S.; Gorityala, B. K.; Liu, X. W. *Tetrahedron Lett.* **2009**, *50*, 2979–2981.
[197] (a) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Letters*. **1976**, 941–942. (b) Hosomi, A.; Sakurai, H. *Tetrahedron Lett*. **1976**, 1295–1298.
[198] Jäkel, M.; Qu, J.; Schnitzer, T.; Helmchen, G. *Chem. Eur. J*. **2013**, *19*, 16746–16755.

3.11. Proposed reaction mechanism

Considering the experimental results obtained and the literature available in the field of carbonylative cross-coupling reaction, the most invoked mechanism for the carbonylative cross-coupling investigated might be a Cu(I)/Cu(III) catalytic cycle based on two electrons redox process (Scheme 157). Firstly, the acylzirconocene chloride complex **113** is prepared through the hydrozirconation of alkenes **90** with the Schwartz's reagent and consequent insertion of carbon monoxide into the alkyl-zirconium bond. The pressure of carbon monoxide is easily triggered by the addition of triethylamine to *N*-formylsaccharin. Then, the acyl-copper species **II** is generated by the acyl-group transfer of acylzirconocene chloride to CuCN **I**. Meanwhile, the acyl-copper species can undergo oxidative addition into hypervalent iodonium salt **180** forming copper complex **III**. Finally, reductive elimination of product closes the catalytic cycle.



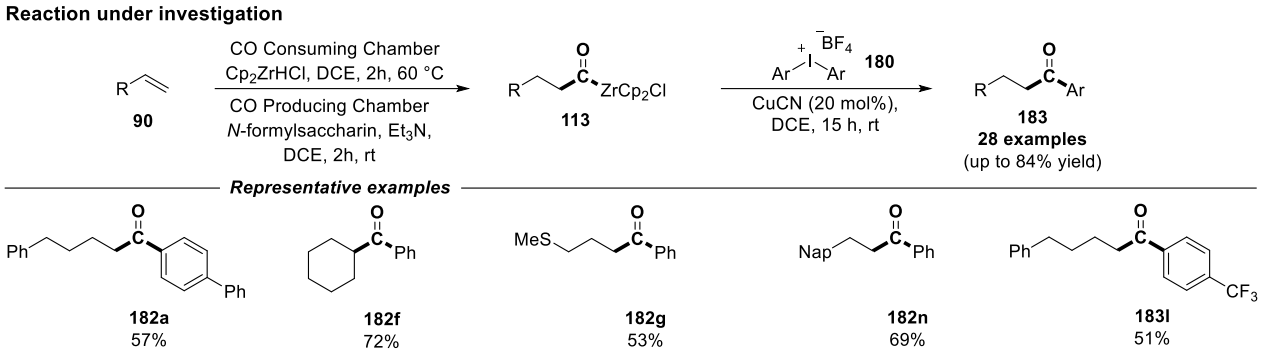
Scheme 157. Copper-catalyzed carbonylative arylation of alkenes with aryl iodonium salts.

It is important to highlight that by using copper cyanide as a copper source, it is also possible to hypothesize the formation of an anionic acyl-cuprate, $[Cu(CN)COR]^-$ as a reaction intermediate. Indeed, in literature higher order cyanocuprates are known to be excellent nucleophiles able to smoothly react with electrophiles.[199] However, its formation may be hypothesized, but has not been experimentally proven.

[199] (a) Lipshutz, B. H. *Synthesis*, **1987**, *4*, 4325–341. (b) Lipshutz, B. H. *Synlett*. **1990**, *3*, 119–128. (c) Lipshutz, B. H. *Synthesis*, **1987**, *4*, 325–341.

3.12. Conclusions and future perspectives

In conclusion, during the investigation that was carried out we have tried to develop a novel copper-catalyzed carbonylative cross-coupling by the reaction between aryl iodonium salts **180** and acylzirconocenes complexes **113** (Scheme 158). First of all, an extensive optimization was required when we initiated our studies, this optimization being based on iterative screenings of all reaction parameters. After numerous attempts, it was found out that 4-phenyl-1-butene could be smoothly converted in the corresponding acyl zirconium complex by the treatment with Schwartz's reagent and keeping the reaction mixture under a CO pressure. Subsequently, the acyl-zirconocene was coupled with diphenyliodonium tetrafluoroborate in 80% of isolated yield when reacting with 20 mol% of copper cyanide in DCE at room temperature. Interestingly, this transformation has been developed using carbon monoxide generated *ex-situ* from *N*-formylsaccharin in a two chambers reactor.



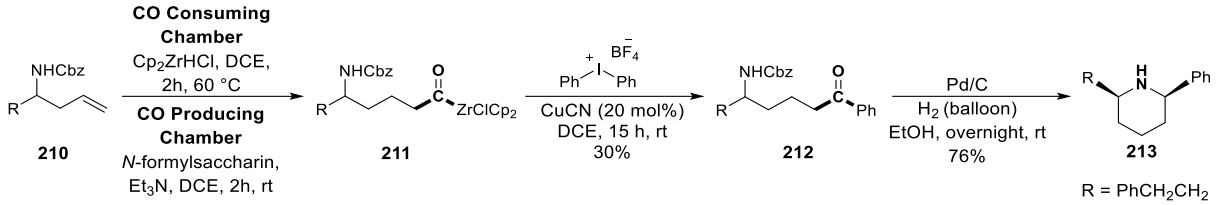
Scheme 158. Copper-catalyzed carbonylative arylation of alkenes with aryl iodonium salts.

Once we optimized the reaction conditions, we then assessed the scope and limitations of our system for the copper-catalyzed carbonylative arylation of a series of alkenes and aryl iodonium salts. Therefore, a systematic variation of the aryl iodonium salts and alkenes natures was carried out. Having identified the reaction conditions, a library of 28 examples of alkyl aryl ketones was prepared and all the compounds have been fully characterized through ^{1}H-NMR, ^{13}C-NMR, IR and HRMS.

The substrate scope of the reaction was explored with various alkyl acyl-zirconocene chlorides, generated *in-situ* from alkenes and coupled with diphenyliodonium tetrafluoroborate. Primary alkenes functionalized with heteroatoms furnished in good yields the desired aryl ketones. This method has been effective for the synthesis of linear and cyclic aryl ketones with different ring size. Noteworthy, when styrenes were used a mixture of inseparable structural isomer was obtained (linear and branched ketone). Finally, we investigated the reactivity of more sterically hindered substrates as vinyl polycyclic aromatic hydrocarbon.

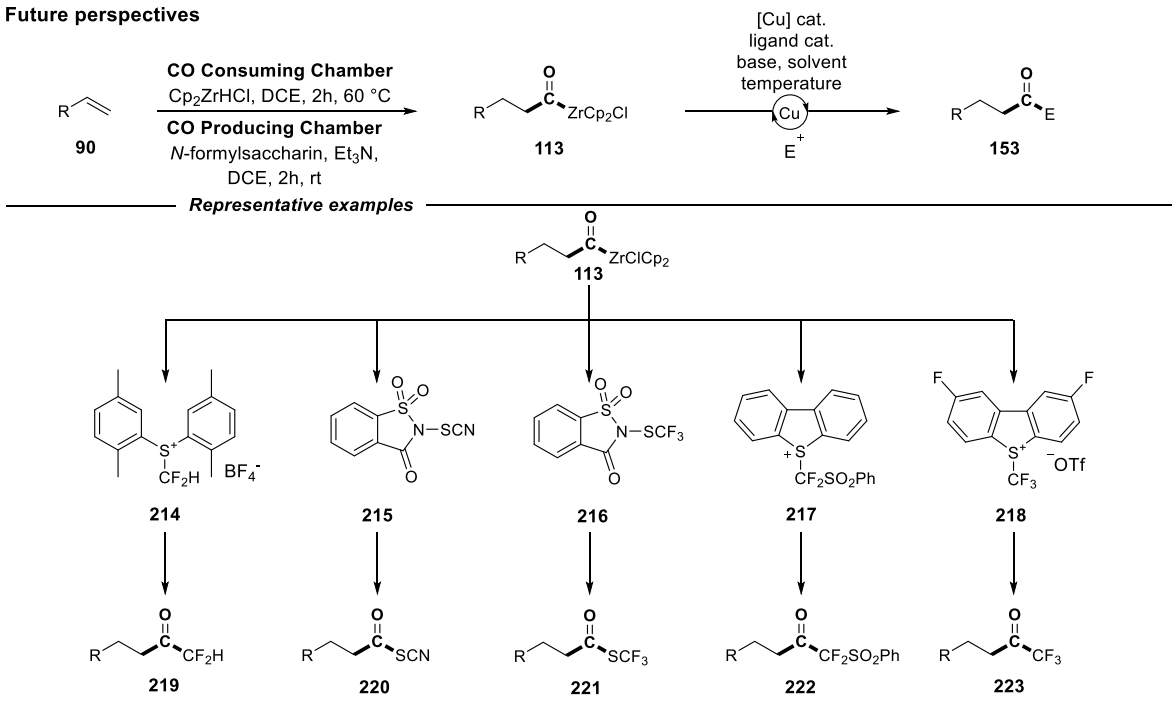
After varying the nature of the alkene, our attention has been oriented toward varying the nature of substituted symmetrical diaryl iodonium salts. Gratifyingly, the protocol well tolerates diverse electronic and steric substituents onto the aromatic ring of the diaryliodonium salts. In general, aryl iodonium salt tetrafluoroborate bearing neutral substituents could be easily coupled to give the carbonyl products. Symmetrical iodonium salts with electron donating group provided the desired products, although with a lower reaction yields. When aryl iodonium salts bearing electron-withdrawing groups were examined, the formation of the carbonylated product has been easily achievable, although resulted in a significantly lower yield of the ketone.

Lastly, in a further effort to demonstrate the synthetic value of this transformation the synthesis of the 2,6-disubstituted piperidine **213** has been performed in three steps based on the use of acylzirconocene chlorides complexes **211** (Scheme 159).



Scheme 159. Application of the copper-catalyzed carbonylative cross-coupling to the synthesis of 2,6-disubstituted piperidine.

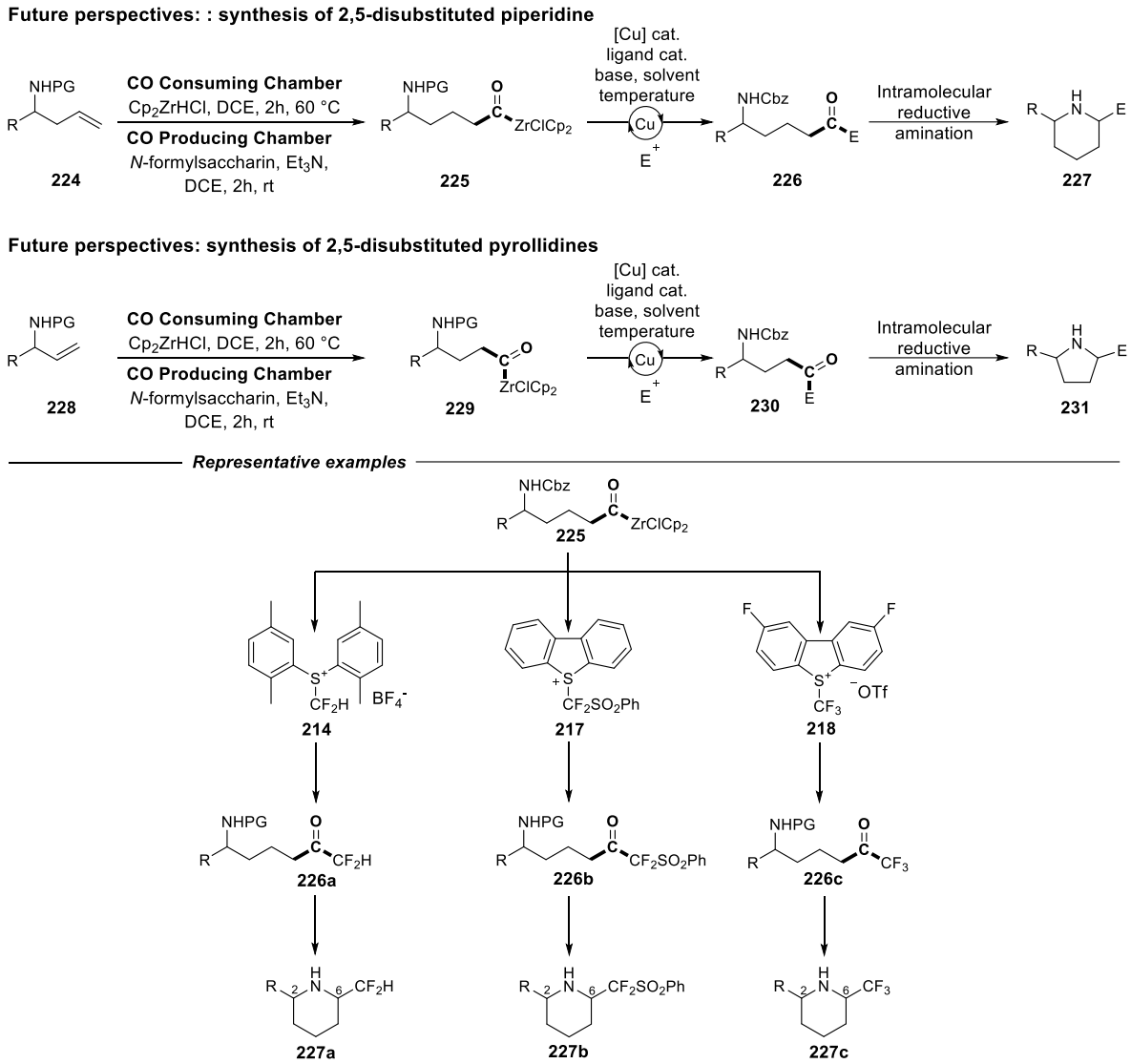
In the future, under similar reaction conditions, it can be envisioned to exploit the reactivity of acyl-zirconocene complexes **113**, readily prepared from alkenes and carbon monoxide, to prepare additional carbonyl compounds of high synthetic value which are not easy to prepare with the classical methods. In fact, by reacting acylzirconocene chlorides complexes with electrophilic compounds like those described in the scheme below, new copper-catalyzed carbonylative cross-coupling reactions could be developed. For this purpose, -CF_2H **214**,[200] -SCN **220**,[201] -SCF_3 **221**,[202] -CF_2SO_2Ph **222**, [203] -CF_3 **223**,[204] moieties may be particularly appealing and might be smoothly incorporated using various electrophilic agents reported in the literature (Scheme 160).



Scheme 160. Copper-catalyzed carbonylative functionalization of alkenes with electrophiles.

[200] Noto, N.; Koike, T.; Akita, M. *Chem. Sci*. **2017**, *8*, 6375–6379.
[201] Wu, D.; Qiu, J.; Karmaker, P. G.; Yin, H.; Chen, F. X. *J. Org. Chem.* **2018**, *83*, 3, 1576–1583.
[202] Xu, C.; Ma, B.; Shen, Q. *Angew. Chem. Int. Ed*. **2014**, *53*, 1–6.
[203] Nobile, E.; Hébert, J.; Castanheiro, T.; Ledoux, A.; Besset, T. *Org. Process Res. Dev.* **2022**, *26*, 8, 2415–2422.
[204] Umemoto, T.; Zhang, B.; Zhu, T.; Zhou, X.; Zhang, P.; Hu, S.; Li, Y. *J. Org. Chem.* **2017**, *15*, 7708–7719.

Additionally, another future perspective is to exploit the protocol developed in our laboratories to synthetize highly functionalized 2,6-*cis*-disubstituted piperidines through a sequence of three steps based on the use of acylzirconocene chlorides complexes. Indeed, via a sequential hydrozirconation/carbonylation followed by an intramolecular reductive amination, it is possible to prepare α-difluoromethyl **227a**, α-(phenylsulfonyl)difluoromethyl piperidines **227b** and α-trifluoromethyl **227c**, which are not easy to prepare with alternative methods and with biological properties still little explored. For this purpose the best electrophilic candidates, -CF_2H **214**,[205] -CF_2SO_2Ph **217**, [206] -CF_3 **218**,[207] moieties may be particularly appealing and might be smoothly incorporated using various electrophilic agents reported in the literature. Definitely, their inert nature makes them the perfect candidates to be used in these transformations. Clearly, this synthetic strategy can be employed also for the preparation of smaller heterocycles such as highly functionalized 2,5-disubstituted pyrollidines, indeed reducing the number of carbon atoms of the starting material a contraction of the ring can be envisioned **231** (Scheme 161).



Scheme 161. Copper-catalyzed carbonylative cross-coupling for the synthesis of functionalized 2,6-disubstituted piperidine.

[205] Noto, N.; Koike, T.; Akita, M. *Chem. Sci.* **2017**, *8*, 6375–6379.
[206] Nobile, E.; Hébert, J.; Castanheiro, T.; Ledoux, A.; Besset, T. *Org. Process Res. Dev.* **2022**, *26*, 8, 2415–2422.
[207] Umemoto, T.; Zhang, B.; Zhu, T.; Zhou, X.; Zhang, P.; Hu, S.; Li, Y. *J. Org. Chem.* **2017**, *15*, 7708–7719.

Second part: Trifluoromethylation of vinylsiloxanes

Chapter 4: Development of a new copper-catalyzed reaction of trifluoromethylation of vinylsiloxanes

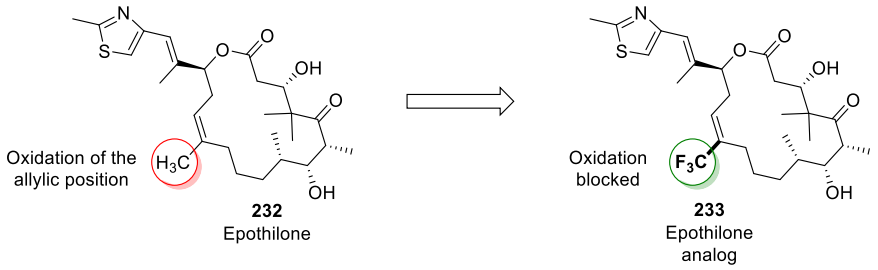
Chapter 4. Copper-catalyzed trifluoromethylation of vinylsiloxanes

4.1. Introduction

In this chapter, still remaining in the domain of copper-catalysis, a second independent subject dedicated to the development of a new synthetic strategy for the preparation of trifluoromethylated alkenes based on a copper-catalyzed trifluoromethylation of vinylsiloxanes was studied in our laboratory. This second research axis is closely related to the development of new copper-catalysed cross-coupling reactions, which is the main focus of this manuscript. We will introduce the chemistry of vinyl siloxanes, which are powerful synthetic equivalents of vinyl anions, and then our main focus will be on showcasing the most cutting-edge metal-catalyzed catalytic systems that enable the preparation of trifluoromethylated alkenes. This area of copper-catalysis is still largely unexplored, despite a strong synthetic potential. For these reasons, after presenting the general lines of the research area on which we conducted our investigation, we will outline the research done to develop a new methodology that enables the preparation of trifluoromethylated alkenes. In this chapter, our main focus will be on presenting the cross-coupling reaction that we have developed, the optimization phase and the investigation of the scope that has been accomplished. All the phases will be discussed in detail.

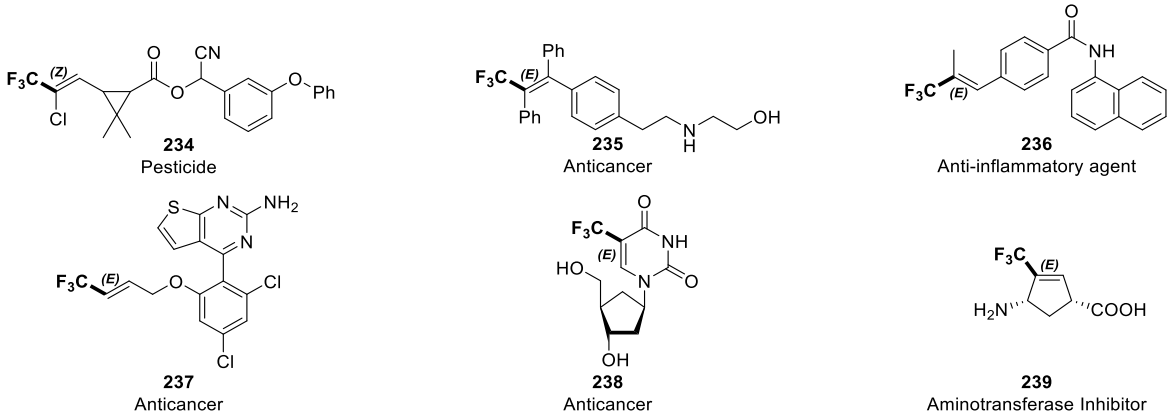
Organic molecules containing fluorine are very rare to the biosphere. Fluorine is a special atom of the periodic table because it is both particularly small and the most electronegative element. Therefore, the installation of one or more fluorine atoms can significantly alter the properties of the parent molecules.[208] This element is widely employed in diagnostic tools like positron emission tomography (PET)[209] or in the chemistry of materials.[210] Additionally, fluorine has undoubtedly had the greatest impact in agrochemistry[211] and medicinal chemistry.[212] Indeed, in medicinal chemistry one or more fluorine atoms are present in nearly 25% of marketed human medicines and 30% of agrochemical products, therefore fluorine nowadays holds a privileged position in these two fields of science.[213] The introduction of fluorine or fluorinated moiety can be useful to prepare molecules which exhibit new physico-chemical properties. For instance, the conversion of epothilone **232**, a potent anticancer compound, in the corresponding fluorinated analogue **233** has been exploited to increase the stability of this molecule. Indeed, the parent molecule showed moderate inhibitor activity due to metabolic reactions. Indeed, the substitution of a methyl group by a trifluoromethylated one avoided the oxidation of the allylic position. In this way, oxidative pathways were blocked by the incorporation of fluorine and inducing a higher inhibitory activity compared to the parent molecule (Scheme 162).[214]

[208] (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008**, *37*, 320–330.
[209] Francis, F.; Wuest, F. *Molecules* **2021**, *26*, 6478–6503.
[210] Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496–3508.
[211] Fujiwara, T.; O'Hagan, D. *J. Fluor. Chem.* **2014**, *167*, 16–29.
[212] (a) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *21*, 8315–8359. (b) Hagmann, W. K. *J. Med. Chem.* **2008**, *15*, 4359–4369.
[213] Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; Del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V.A.; Liu, H. *Chem. Rev.* **2014**, *4*, 2432–2506.
[214] Chou, T. C.; Dong, H.; Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Cho, Y. S.; Tong, W. P.; Danishefsky, S. J. *Angew. Chem*. **2003**, *115*, 4909–4915.



Scheme 162. Trifluoromethylated analogue of epothilone.

It follows that the discovery and development of biologically active compounds have greatly benefited from the incorporation of fluorinated functional groups in pharmaceutical and agrochemical molecules. Among all the family of fluorinated molecules, vinyltrifluoromethylated derivatives are broadly employed in chemistry as pesticides **234**, enzymatic inhibitors **239** and anticancer agents **235**, **237-238**. Trifluoromethylated alkenes, also named C_{vinyl}-CF_3, from a structural point of view contain a double bond with a $–CF_3$ moiety as substituent with an electron-withdrawing character. In molecules of biological interest, the control of the configuration of the double bond is crucial for the preparation of the active compound as depicted in Scheme 163.[215] Due to the fact that fluorinated molecules are widely employed in pharmaceutical, agrochemical and drug discovery industries, the demand for innovation is important and leads to a significant and fast-growing research area. Therefore, the design and the development of new technologies to access fluorinated scaffolds is of great interest for the scientific community. In the next paragraph, before starting the description of the research project we carried out, a brief introduction will be devoted to presenting the trifluoromethylating agents available in the literature.



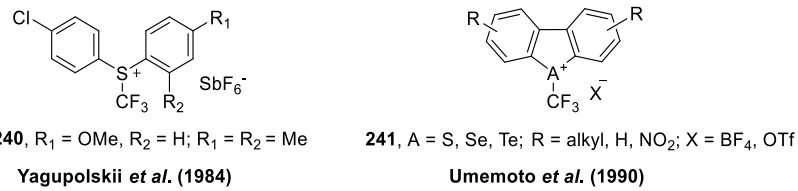
Scheme 163. Examples of biologically active compounds containing the vinyl trifluoromethylated moiety.

4.2. Electrophilic trifluoromethylating agents

Recent years have seen the discovery of a large number of novel trifluoromethylation reagents, including electrophilic, nucleophilic and radical trifluoromethyl sources, which provide numerous options for the development of novel trifluoromethylation reactions. In this section, we will briefly discuss a particular class of trifluoromethylating reagents characterized by having an electrophilic nature since are the best candidates able to combine with the nucleophilic nature of vinyl siloxanes which we will discuss later in this chapter. Since the seminal discovery of the Yagupolskii's reagent (S-trifluoromethyl diarylsulfonium salts) in 1984 **240** (Scheme 164),[216] one of the first trifluoromethylating reagent used in organic synthesis, the design of new chemicals have undergone extensive development due to the significant impact of

[215] Hong, H.; Li, Y.; Chen, L.; Li, B.; Zhu, Z.; Chen, X.; Chen, L.; Huang, Y. *J. Org. Chem.* **2019**, *9*, 5980–5986.
[216] Yagupolskii, L. M.; Kondratenko, N. V.; Timofeeva, G. N. *J. Org. Chem.* **1984**, *20*, 103–106.

trifluoromethylated compounds on chemistry. Due to their high stability, reactivity, and wide substrate range, a number of reagents have been developed and nowadays are commercially available. The initial product of each of these reagents is an electrophilic trifluoromethylating species, which smoothly reacts with nucleophiles. Due to the narrow range of applications was very limited with the Yagupolskii's reagent, the Umemoto group **241** (Scheme 164) led to subsequent major advancements in the early 1990s using chalcogenide salts.[217] A wide variety of nucleophilic substrates can be smoothly trifluoromethylated, depending on the heteroatom and substituents present on the chalcogenide salts. The relative trifluoromethylation power of these salts increases with the electronegativity S > Se > Te and is enhanced by the presence of electron-withdrawing group on the aromatic rings.[218]



240, R_1 = OMe, R_2 = H; R_1 = R_2 = Me — **Yagupolskii *et al.* (1984)**

241, A = S, Se, Te; R = alkyl, H, NO_2; X = BF_4, OTf — **Umemoto *et al.* (1990)**

Scheme 164. Electrophilic trifluoromethylating agents of Yagupolskii and Umemoto.

Recently, Shreeve and Shibata have come up with sulfur-derived trifluoromethylating reagents that have expanded the scope of organic substrates that can undergo trifluoromethylation reactions **242**-**243** (Scheme 165). Generally, these chemicals are employed to promote trifluoromethylation reactions typically forming *in-situ* an electrophilic trifluoromethyl (CF_3^+) species that undergoes reaction with soft and hard nucleophiles. The Shreeve and Shibata salts show a similar structure and reactivity to those of Umemoto **241** with preferences to certain substrate classes.[219] Based on neutral S-CF_3 systems of the sulfoximine type, another class of electrophilic agents was patented by the Adachi group at Daikin laboratories in 2003, **244** and **245** (Scheme 165). These trifluoromethylating agents can be used to perform the trifluoromethylation onto carbanions, enamines and thiolates anions, albeit in low to moderate yields.[220] Due to their chemical structure, they are milder reactants that are much more tolerant and compatible with many functional groups.

R = F,NO_2 — **242**, **Shreeve *et al.* (1998)**

R = Ph, cyclopropane — **243**, **Shibata *et al.* (2010)**

A = CO, SO_2 — **244**, **Adachi *et al.* (2003)**

245, **Adachi *et al.* (2003)**

Scheme 165. Electrophilic trifluoromethylating agents of Shreeve, Shibata and Adachi.

[217] (a) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757–1777. (b) Umemoto, T; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156–2164. (c) Umemoto, T.; Ishihara, S.; Adachi, K. *J. Fluor. Chem.* **1995**, *74*, 77–82. (d) Umemoto, T.; Ishihara, S. *Tetrahedron Lett.* **1990**, *31*, 3579–3582.

[218] (a) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010**, *6*, 1–19. (b) Ma, J. A.; Cahard, D. *J. Fluor. Chem.* **2007**, *128*, 975–996.

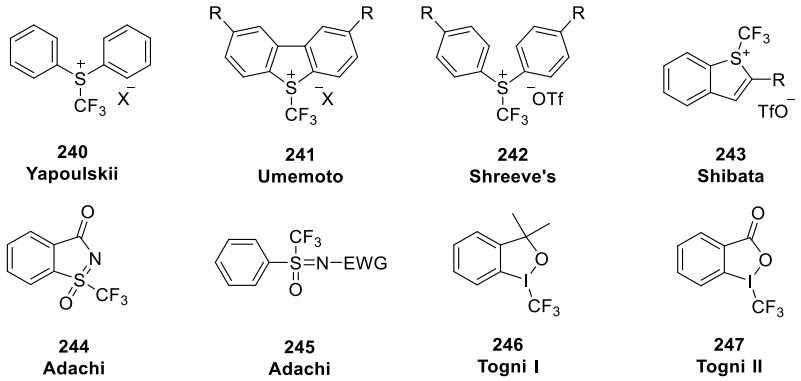
[219] (a) Matsnev, A.; Noritake, S.; Nomura, Y.; Tokunaga, E.; Nakamura, S.; Shibata, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 572–576. (b) Yang, J. J.; Kirchmeier, R. L.; Ne, J.; Shreeve, M. *J. Org. Chem.* **1998**, *63*, 2656–2660.

[220] Adachi, K.; Ishihara, S. Japanese Patent 20030388769, **2003**.

Hypervalent iodinated (III) derivatives are the last category of the most commonly used trifluoromethylating reagents that we have decided to summarize in this paragraph. Umemoto and Yagupolskii made the initial attempts through electrophilic perfluorinations using (perfluoroalkyl)phenyliodonium salts.[221] Unfortunately, due to their stability these salts were completely useless for inking a trifluoromethyl moiety. The Togni group was able to solve the issues by adding iodine to a 5-membered ring system where the trifluoromethyl group is directly connected.[222] In their seminal paper two hypervalent iodine compounds, 1-(trifluoromethyl)-1,2-benziodoxol-3(1H)-one **246** and trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole **247**, were described in 2006 for trifluoromethylation of a variety of substrates.[223] For these reagent, the Togni's Group has also been developed a *one-pot* syntheses (Scheme 166) .[224]

Scheme 166. Togni's electrophilic trifluoromethylating agents.

In summary, a variety of electrophilic trifluoromethylating agents are now commercially available **240**-**247** and few of them need to be previously prepared. A compendium of the most important trifluoromethylation reagents employed today in literature is reported in the following Scheme 167.[225]

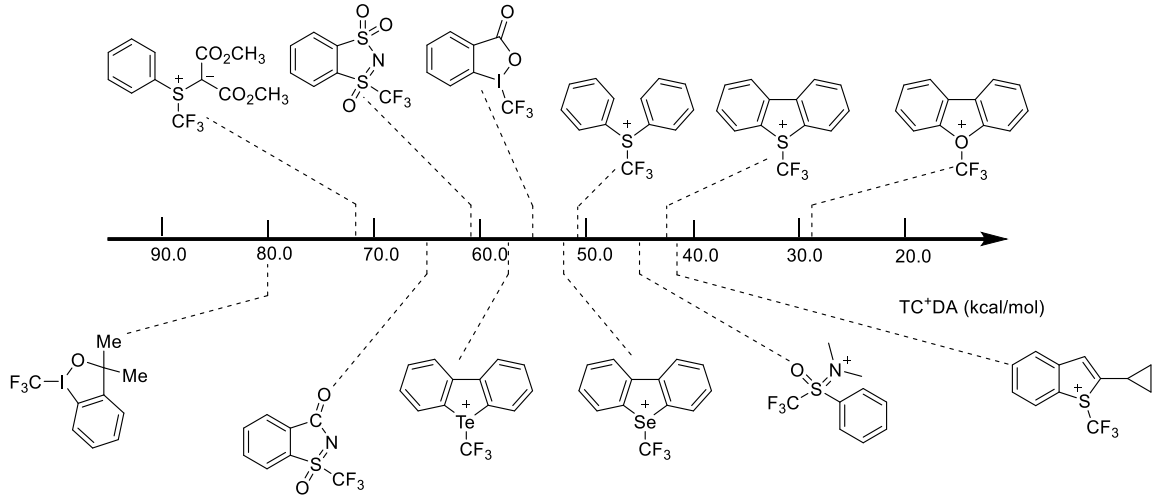


Scheme 167. Electrophilic trifluoromethylating reagents.

Among all the electrophilic trifluoromethylating reagents currently employed, the Umemoto and Togni's reagent are those most frequently used in the literature. Following the developments of this extensive panel of reagents, an energy guide that enables the estimation of the trifluoromethyl cation donation ability was designed and built (TC^+DA).[226] These computational studies are based on the evaluation of the heterolytic dissociation enthalpies of the X-CF_3 bond (Scheme 168). These quantitative informations are useful for the rational design of novel trifluoromethylating reagents and careful selection of suitable chemicals for investigating novel trifluoromethylation reactions.

[221] Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757–1777.
[222] Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650–682.
[223] Eisenberger, P.; Gischig, S.; Togni, A. *Chem. Eur. J.* **2006**, *12*, 2579–2586.
[224] Matoušek, V.; Pietrasiak, E.; Schwenk, R.; Togni, A. *J. Org. Chem.* **2013**, *13*, 6763–6768.
[225] Barata-Vallejo, S.; Lantaño, B.; Postigo, Al. *Chem. Eur. J.* **2014**, *20*, 1–25.
[226] Li, M.; Xue, X. S.; Guo, J.; Wang, Y.; Cheng, J. P. *J. Org. Chem.* **2016**, *81*, 3119–3126.

It should be noted that during the course of this chapter our attention has been focused on the use of the Umemoto's reagent because it is commercially available and it has a good trifluoromethyl cation donation ability (TC^+DA, around 40 Kcal/mol). This means that the Umemoto's reagent is one of the most reactive reagent available to perform trifluoromethylation reactions because it has a low heterolytic dissociation enthalpy of the X-CF_3 bond, making it easier the releasing of the "CF_3^+" cation. In this way the "CF_3^+" cation can easily reacts with its nucleophile partner and furnish the target product. For this purely theoretical reason the Umemoto's reagent was considered as the preferred and the most suitable candidate to carry out our investigation.



Scheme 168. Energy guide for the estimation of the trifluoromethyl cation donation ability (TC^+DA).

4.3. Synthesis of trifluoromethylated alkenes

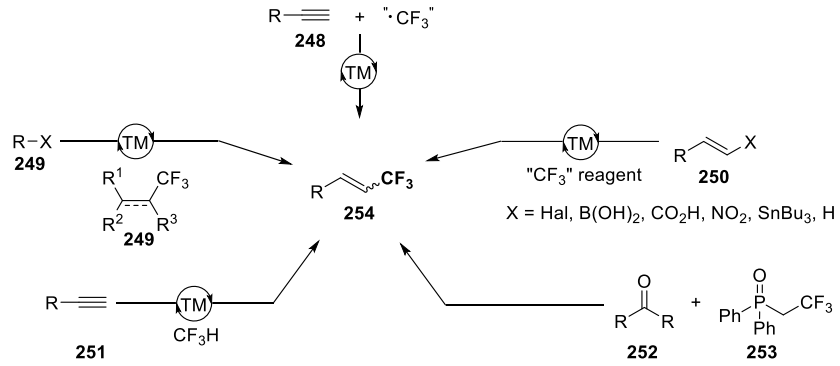
Trifluoromethylated alkenes are basically non-natural molecules and need to be constructed through the procedures available in the literature. The growth of actual and efficient methods for the introduction of the trifluoromethyl moiety (–CF_3) into organic framework is a highly strenuous research field. The synthesis of trifluoromethylated aliphatic olefins is still a relatively recent area of organic chemistry when compared to the synthesis of trifluoromethylated arenes. As a matter of fact, several efficient procedures for the construction of C_{alkyl}–CF_3 and C_{aryl}–CF_3 bonds have been developed in the past years. Fewer protocols have been reported for the preparation of $C_{alkenyl}$–CF_3 bonds, although alkenes are key intermediates in many reactions. Therefore, nowadays the development of catalytic trifluoromethylation reactions for the preparation of trifluoromethylated olefins is highly demanded in synthetic organic chemistry. Unfortunately, this field of study has long been limited by the challenge of developing new protocols capable of install the "CF_3" moiety controlling at the same time the configuration of the double bond.

Generally, trifluomethylated olefins **254** are typically prepared through the following synthetic processes: 1) olefination reactions of carbonyl compounds **252**,[227] 2) cross-coupling reactions with suitable trifluoromethylated coupling partners **249**,[228] 3) trifluoromethylation of pre-functionalized olefin derivatives

[227] a) Landge, S.; Borkin, D.; Török, B. *Lett. Org. Chem.* **2009**, *6*, 439–443; b) Kobayashi, T.; Eda, T.; Tamura, O.; Ishibashi, H. *J. Org. Chem*. **2002**, *67*, 3156–3159.

[228] a) Ramachandran, P.V.; Mitsuhashi, W. *Org. Lett*. **2015**, *17*, 1252–1255; b) Prakash, G. K. S.; Krishnan, H. S.; Jog, P. V.; Iyer, A. P.; Olah, G. A. *Org. Lett*. **2012**, *14*, 1146–1149; c) Kathiravan, S.; Nicholls, I. A. *Org. Lett*. **2015**, *17*, 1874–1877; d) Omote, M.; Tanaka, M.; Ikeda, A.; Nomura, S.; Tarui, A.; Sato, K.; Ando, A. *Org. Lett*. **2012**, *14*, 2286–2289.

250,[229] 4) hydrotrifluoromethylation of alkynes **251**,[230] and 5) radical trifluoromethylation of alkynes **248**,[231] (Scheme 169). However, it should be noted that most of the procedures in the literature rely on using pre-functionalized olefin derivatives in the presence of a trifluoromethylating agent and a metal catalyst. This preferential choice is mainly due to the abundance of the starting materials that are easily available. Unfortunately, the majority of these strategies suffer from limited substrate scope, multistep synthesis and/or produce toxic waste. Despite the fact that these synthetic methods are effective and useful for preparing trifluoromethylated olefins, their widespread application was severely hindered by the lack of selectivity seen in some instances where an E/Z mixture was obtained. Furthermore, many methodologies are limited to aromatic C_{vinyl}-CF_3 derivatives.



Scheme 169. Synthetic strategies for the preparation of trifluoromethylated alkenes.

Based on our long-standing interest in metal catalysis, we focused our attention on the preparation of trifluoromethylated olefins via cross-coupling reactions with suitable trifluoromethylated coupling partners. This method typically involves the trifluoromethylation of vinyl derivatives (such as vinyl halides, vinyl carboxylic acids, or vinyl boronates) in the presence of various transition metals using trifluoromethylating reagents. These methods allow the introduction of CF_3 groups in site-selective manner and required the use of pre-functionalized alkenes as substrates. In this section, we will describe the most innovative synthetic procedures based on the use of pre-functionalized alkenes as starting materials and metal catalysts for the preparation of trifluoromethylated olefins.

In 2011, the Buchwald group described a novel protocol for the palladium catalyzed trifluoromethylation of vinyl triflates and nonaflates **254** using around 6 mol% of $Pd(dba)_2$ and 12 mol% of *t*-BuXPhos **257**, a monodentate biaryl phosphine ligand (Scheme 170).[232] With this protocol a large library of trifluoromethylated cyclohexenes **256** were obtained with this catalytic system under mild reaction conditions. A combination of $TMSCF_3$ **255** and KF was suitable to the trifluoromethylation of vinyl triflates, in contrast the use of $TESCF_3$ and RbF gave better results for vinyl nonaflate. Interestingly, the vinyl triflates and nonaflates are easily prepared from commercially available ketones. The main disadvantage of this protocol is the use of a phosphine ligand, *t*-BuXPhos **257**, which is quite expensive.

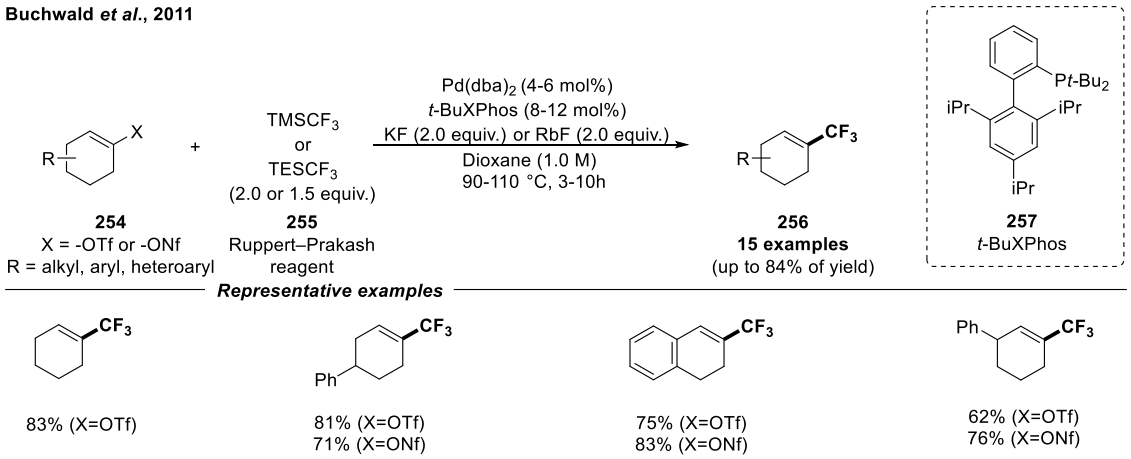
[229] a) Feng, Z.; Min, Q. Q.; Zhao, H. Y.; Gu, J. W.; Zhang, X. *Angew. Chem. Int. Ed*. **2015**, *54*, 1270–1274; b) Zejiang, L.; Cui, Z.; Liu, Z. Q. *Org. Lett*. **2013**, *15*, 406–409; c) Wang, X.; Zhao, S.; Liu, J.; Zhu, D.; Guo, M.; Tang, X.; Wang, G. *Org. Lett*. **2017**, *19*, 4187–4190; d) He, Z.; Luo, T.; Hu, M.; Cao, Y.; Hu, J. *Angew. Chem. Int. Ed*. **2012**, *51*, 3944–3947; *Angew. Chem. Int. Ed*. **2012**, *124*, 4010–4013; e) Liu, T.; Shen, Q. *Org. Lett*. **2011**, *13*, 2342–2345.

[230] a) Iqbal, N.; Jung, J.; Park, S.; Cho, E. J. *Angew. Chem. Int. Ed*. **2014**, *53*, 539–542; *Angew. Chem. Int. Ed*. **2014**, *126*, 549–552. b) He, L.; Yang, X.; Tsui, G. C. *J. Org. Chem*. **2017**, *82*, 6192–6201; c) Choi, S.; Kim, Y. J.; Kim, S. M.; Yang, J. W.; Kim, S. W.; Cho, E. J. *Nat. Commun*. **2014**, *5*, 4881–4887; d) Gao, P.; Song, X. R.; Liu, X. Y.; Liang, Y. M. *Chem. Eur. J*. **2015**, *21*, 7648–7661.

[231] Gao, P.; Song, X. R.; Liu, X.Y.; Liang, Y. M. *Chem. Eur. J.* **2015**, *21*, 1–15.

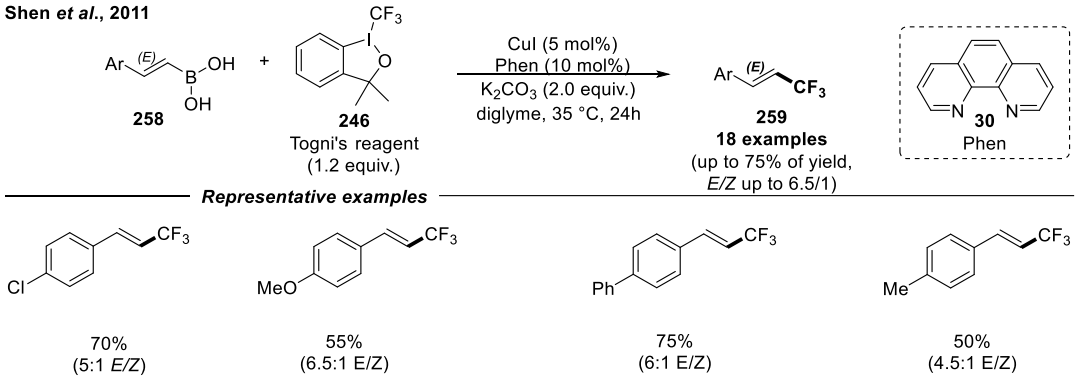
[232] Cho, E. J.; Buchwald, S. L. *Org. Lett.* **2011**, *13*, 6552–6555.

In the same year, the Shen group reported the first copper-catalyzed trifluoromethylation of alkenylboronic acids **258** in the presence of Togni's reagent **246** (Scheme 171).[233] Under the best conditions: 5 mol% CuI and 10 mol% of phenanthroline **30** in diglyme at 35 °C, this reaction with a broad range of boronic acids and the Togni's reagent formed the corresponding trifluoromethylated olefins **259** in moderate to good yields for a variety of different substrates with a good functional group tolerance.



Scheme 170. The palladium-catalyzed trifluoromethylation of vinyl sulfonates.

Notably, the relatively low catalytic loading for a cheap non-noble metal catalyst and the low temperature makes this protocol very appealing for industrial and academic purposes. The reaction is highly stereospecific for the formation of *(E)*-aryl-vinyltrifluoromethylated olefins **259**. Unfortunately, the resulting trifluoromethylated olefins were partially isomerized. Notably, this protocol is particularly appealing because it employs commercially available boronic acids.

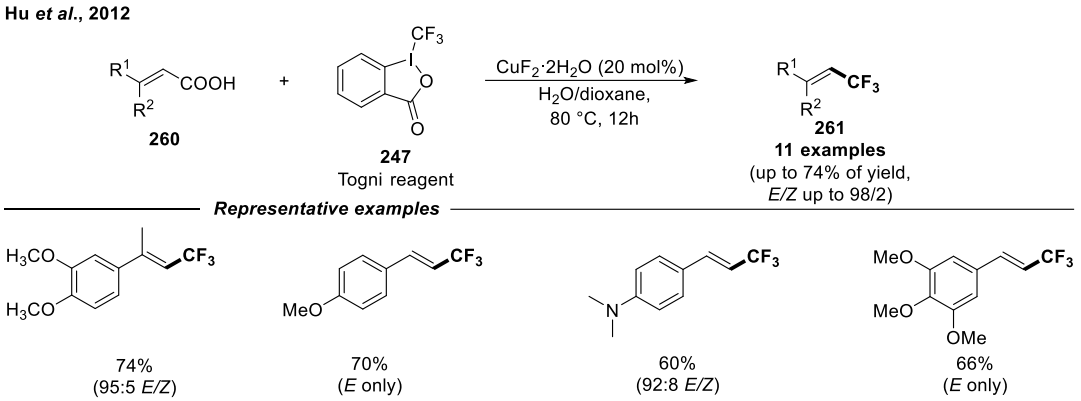


Scheme 171. Copper-catalyzed trifluoromethylation of aryl and vinyl boronic acids with Togni's reagent.

In parallel, the Hu group in 2012 described an effective protocol for the decarboxylative trifluoromethylation of α, β-unsaturated carboxylic acids **260** using the Togni's reagent **247** (Scheme 172).[234] The reaction is performed in the presence of 20 mol% of $CuF_2 \cdot 2H_2O$. This Lewis acid efficiently catalyzed the reaction between the Togni's reagent **246** and the unsaturated carboxylic acid **258** by dually activating both reactants. Indeed, the $CuF_2 \cdot 2H_2O$ revealed to be efficient to enhance the electrophilicity of the Togni reagent and promoting the decarboxylation of the unsaturated carboxylic acid. Additionally, the reaction showed to be highly efficient to furnish the target olefins **261** in high yields with good *E*/*Z* selectivity, up to 98/2 E/Z ratio. The reaction is very mild and performed at relatively low temperature (80 °C) in a mixture of water and

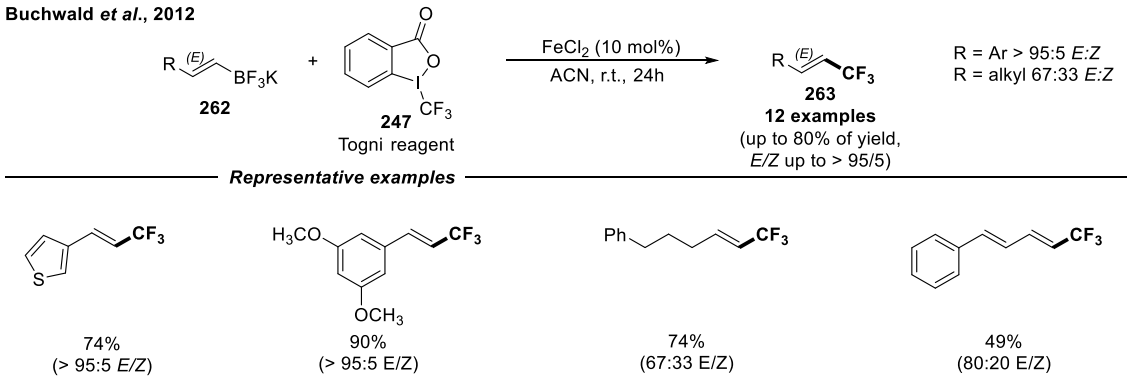
[233] Liu, T.; Shen, Q. *Org. Lett.* **2011**, *13*, 2342–2345.
[234] He, Z.; Luo, T.; Hu, M.; Cao, Y.; Hu, J. *Angew. Chem. Int. Ed*. **2012**, *51*, 3944–3947.

dioxane. Notably, this protocol is highly attractive due to is based on the use of carboxylic acids as starting materials, which are abundant in nature and commercially available on the market.



Scheme 172. Copper-catalyzed trifluoromethylation of α, β-unsaturated carboxylic acids with the Togni's reagent.

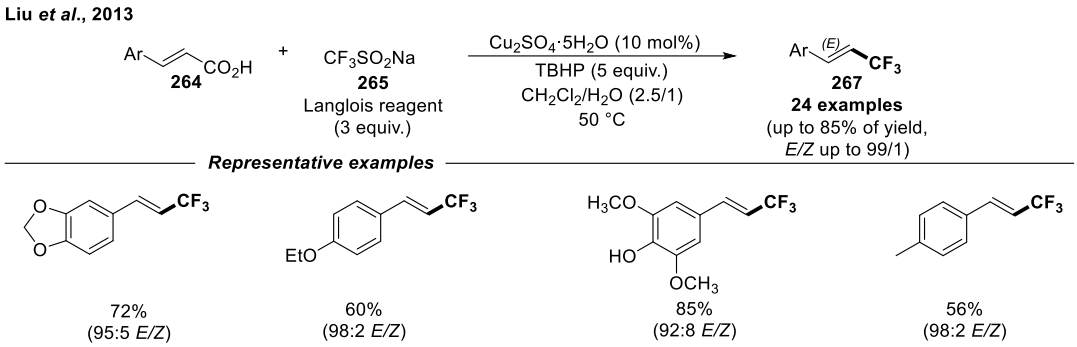
In 2012, the Buchwald group developed a novel iron(II)-catalyzed trifluoromethylation of potassium vinyltrifluoroborates **262** to synthesize trifluoromethylated olefins **263** (Scheme 173).[235] With a catalytic amount of $FeCl_2$ (10 mol%) in the presence of the Togni's reagent **247**, a range of trifluoromethylated olefins were prepared in good yields and excellent E/Z ratios under exceedingly mild reaction conditions (acetonitrile at room temperature). The reaction is highly stereospecific when *(E)*-arylvinyltrifluoroborates are used as starting material, however when *(E)*-alkylvinyltrifluoroborates are employed much lower *E*/*Z* ratios are obtained. Unfortunately, the control of the stereochemistry is completely lost when (*Z*)-vinyltrifluoroborate are used under the optimized reaction conditions. Unfortunately, the mechanism of the reaction is still under investigation and most probably involve the generation of a radical or a carbocationic intermediate.



Scheme 173. Iron(II)-catalyzed trifluoromethylation of potassium vinyltrifluoroborates.

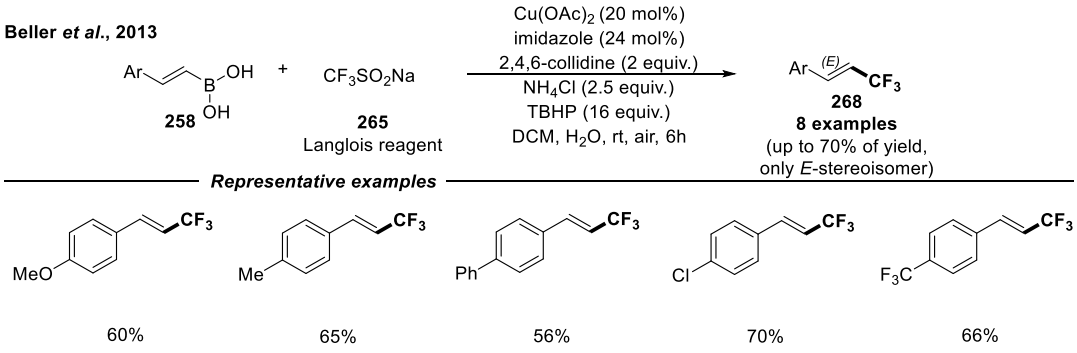
In 2013, the Liu group described a novel copper-catalyzed decarboxylative trifluoromethylation of a broad range of α, β-unsaturated carboxylic acids **264** by using the Langlois's reagent **265** as a cheap trifluoromethylating agent in combination with $CuSO_4 \cdot 5H_2O$ (10 mol%) in CH_2Cl_2/H_2O (Scheme 174).[236] The reaction is promoted with the addition of a large excess of TBHP (5 equiv.). This procedure offers an advantageous and practical method for the stereospecific synthesis of CF_3-substituted *E*-alkenes **267**. Unfortunately, the resulting trifluoromethylated olefins were partially isomerized. Unfortunately, only aryl-substituted acrylic acid substrates can be used with this protocol. Indeed, alkyl-substituted acrylic acids were totally unsuccessful to form the desired target olefins **267**, which may be related to the radical intermediate's stability.

[235] Parsons, A. T.; Senecal, T. D.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 2947–2950.
[236] Li, Z.; Cui, Z.; Liu, Z. Q. *Org. Lett.* **2013**, *15*, 406–409.



Scheme 174. Copper-catalyzed decarboxylative trifluoromethylation of cinnamic acids.

In the same year, the Beller group reported an innovative copper-catalyzed trifluoromethylation of vinyl boronic acids **258** in the presence of copper catalysts, *t*-BuOOH and the Langlois' reagent **265**, Scheme 175.[237] Advantageously, the protocol can be carried out at room temperature under air atmosphere in a mixture of DCM/H_2O. Although an excess of TBHP was required, the mild reaction conditions allow a wide range of functional groups to be well tolerated. It is noteworthy that this protocol uses both CF_3 radical formation and cooperative transition metal catalysis, which is a novel approach tremendously innovative. Notably, this transformation is also applicable on aryl boronic acids **258** to furnish the corresponding trifluoromethylated arenes **268**. In all the cases, the radical $\cdot CF_3$ involved in the reaction mechanism is generated from the reaction of the Langlois reagent **265** and the TBHP. Noteworthy, the trifluoromethylation occurred highly selective for the formation of the *E*-isomer, no formation of the *Z*-isomer was observed using this protocol.

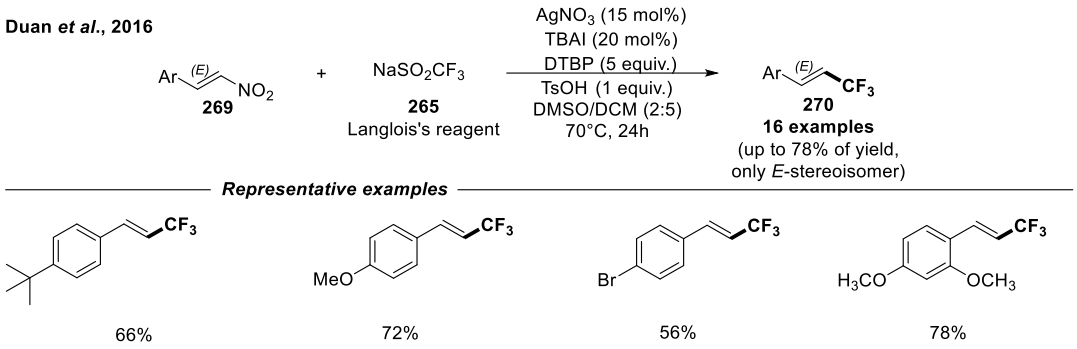


Scheme 175. Copper-catalyzed trifluoromethylation of vinylboronic acids with the Langlois reagent.

Recently, the Chunying group reported in 2016 an efficient protocol for the preparation of trifluoromethylated olefins **270** through a silver(I)-catalyzed denitrative trifluoromethylation of β-nitrostyrenes **269** using the Langlois' reagent **265**.[238] Noteworthy, no formation of *Z*-isomers of target products was found in the reaction mixture (Scheme 176). With 15 mol% of $AgNO_3$, TBAI (20 mol%) and 5 equiv. of DTBP, the reaction with a range of β-nitrostyrenes **269** gave the corresponding trifluoromethylated olefins in good yields and under mild reaction conditions. This method is highly tolerant towards a variety of functional groups and is a convenient strategy for the stereospecific preparation of (*E*)-trifluoromethylated olefins. For this transformation, the authors proposed that the Langlois' reagent in the presence of silver(II) ions is oxidized to SO_2 and a trifluromethyl radical. Thereafter, the $\cdot CF_3$ radical adds onto the double bond of

[237] Li, Y.; Wu, L.; Neumann, H.; Beller, M. *Chem. Commun*. **2013**, *49*, 2628–2630.
[238] Huang, P.; Li, Y.; Fu, X.; Zhang, R.; Jin, K.; Wang, W.; Duan, C. *Tetrahedron Lett.* **2016**, *57*, 4705–4708.

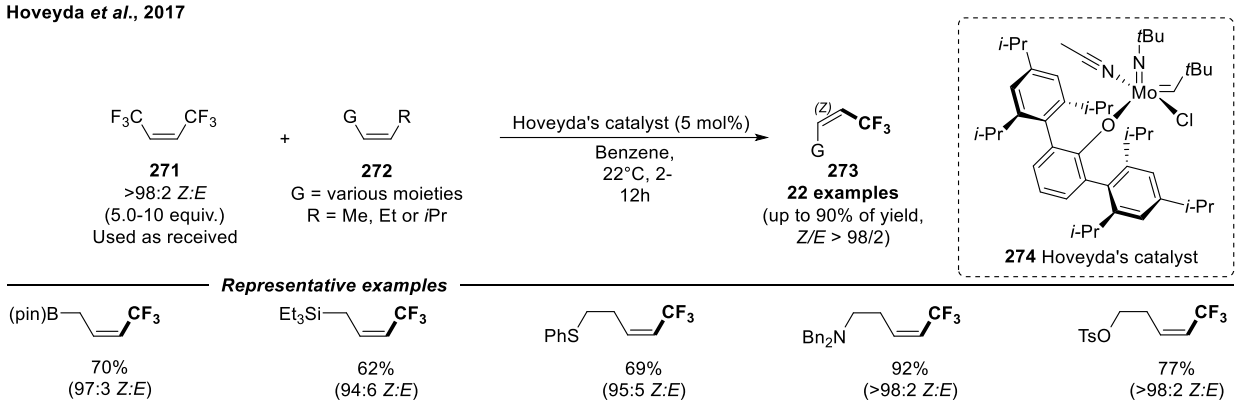
the β-nitrostyrenes **269** to furnish an alkyl radical intermediate which undergoes the elimination of NO_2 radical to give the target product.



Scheme 176. Silver(I)-catalyzed denitrative trifluoromethylation of nitrostyrenes with CF_3SO_2Na.

As can be seen from the examples reported in this section, most of the methods described are based on the use of pre-functionalized aromatic olefins. In addition, these methods frequently lead to the formation of reaction mixtures containing the *E/Z* stereoisomers, where the main product is the most thermodynamically stable stereoisomer with the *E* configuration of the double bond. For what concern the preparation of trifluoromethylated olefins with the *Z*-configuration of the double bond the number of procedures available in the literature is very restricted to few examples. Additionally, these protocols are not based on the use of pre-functionalized olefins but rely on the use of alternative synthetic strategies.

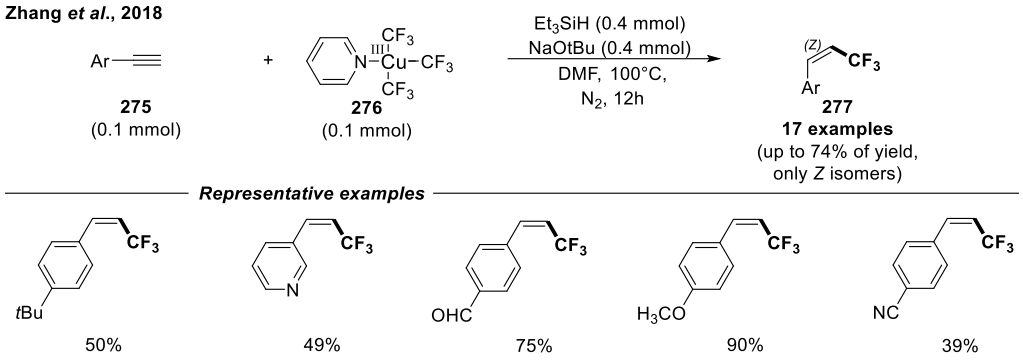
In 2017, the Hoveyda group reported the development of a molybdenum monoaryloxide chloride complexes **274** for the stereoselective olefin metathesis to prepare higher-energy (*Z*)-stereoisomers of trifluoromethyl-substituted olefins **273** (Scheme 177).[239] This protocol employs the use of a commercially available and inexpensive *Z*-1,1,1,4,4,4-hexafluoro-2-butene **271** to perform a cross-metathesis reaction. With this protocol is possible to access trifluoromethylated *(Z)*-olefins with highly controlled configuration of the double bond. This robust methodology has been applied for the preparation of a broad library of trifluoromethylated *(Z)*-olefins, including biologically active molecules, with good yields and excellent *Z:E* ratios. Despite the broad scope, the main disadvantage of this methodology is the exotic nature of the molybdenum catalyst **274** used that requires numerous synthetic steps for its preparation and the use of a highly toxic solvent such as benzene.



Scheme 177. Molybdenum chloride catalysts for *Z*-selective olefin metathesis reactions.

[239] Koh, M. J.; Nguyen, T. T.; Lam, J. K.; Torker, S.; Hyvl, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *542*, 80–85.

One year later, the Zhang group reported a powerful and selective hydro-trifluoromethylation procedure to promote the synthesis of trifluoromethylated *Z*-olefins **277** from terminal alkynes **275**, Et_3SiH and a copper(III)-CF_3 complex **276** (Scheme 178).[240] This methodology is applicable only on acetylene derivatives and not rely on the use of pre-functionalized olefins. This transformation with an unusual *Z*-selectivity make this reaction complementary to other protocols which produce dominantly *E*-products or a mixture of *E*, *Z*-isomers. In addition, the mild reaction conditions of this transformation makes this protocol highly appealing for its functional group compatibility and tolerance.



Scheme 178. *Z*-selective hydrotrifluoromethylation of terminal alkynes with a copper(III)-CF_3 complex.

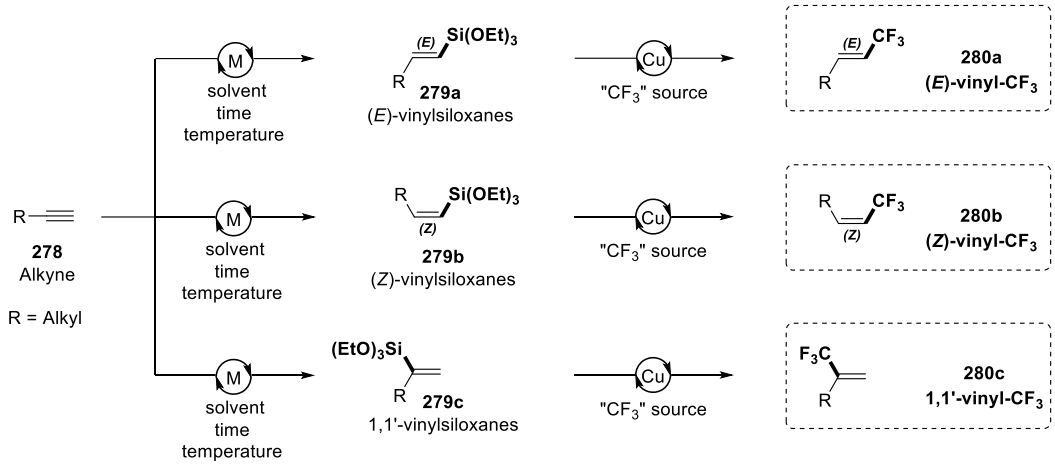
In summary, as it was possible to appreciate in the past years most of the efforts have been devoted to the use of pre-functionalized olefins in order to develop new catalytic trifluoromethylation reactions for the synthesis of CF_3-olefins, which produce dominantly *E*-products or a mixture of *E*, *Z*-isomers. In addition, most of these protocols are limited to aromatic trifluoromethylated olefins and only few examples are reported for the preparation of aliphatic trifluoromethylated olefins, which are more challenging to prepare. For what concern the preparation of *Z*-trifluoromethylated olefins is important to highlight that the number of articles is very limited and rely on the use of costly and exotic catalyst as in the case of Hoveyda.

Based on our ongoing research interests and considering all the advantages of non-noble metals, we became interested to investigate an unexplored area of copper catalysis to develop a novel copper-catalyzed cross-coupling reaction for the trifluoromethylation of trifluoromethylation of vinyl siloxanes, pre-functionalized starting materials which are readily prepared from alkynes. In the next paragraphs we will introduce the objectives of our experimental research which will be used as starting point to present our investigation and the results collected.

[240] Zhang, S. L.; Xiao, C. *J. Org. Chem.* **2018**, *18*, 10908–10915.

4.4. Objectives

Due to the prevalence of fluorinated molecules in material sciences, drug discovery or agrochemistry, there is still an increasing demand for the development of novel, efficient and straightforward processes for the synthesis of fluorinated molecules as well as novel fluorinated building blocks. Therefore, motivated by the interest to explore an understudied area of copper catalysis, the main goal of this research project has been focused on the development of a novel copper-catalyzed cross-coupling reaction for the trifluoromethylation of vinylsiloxanes, starting materials that are readily prepared from alkynes **278**. The vinylsiloxanes have been prepared in a stereodivergent manner from alkynes using Pt, Ru, and Rh catalyst. Herein, we report a novel stereodivergent copper-catalyzed cross coupling for the trifluoromethylation of *cis*-, *trans*-, as well as challenging 1,1'-disubstituted vinylsiloxanes **279a**-**279c** under mild reaction conditions (Scheme 179).



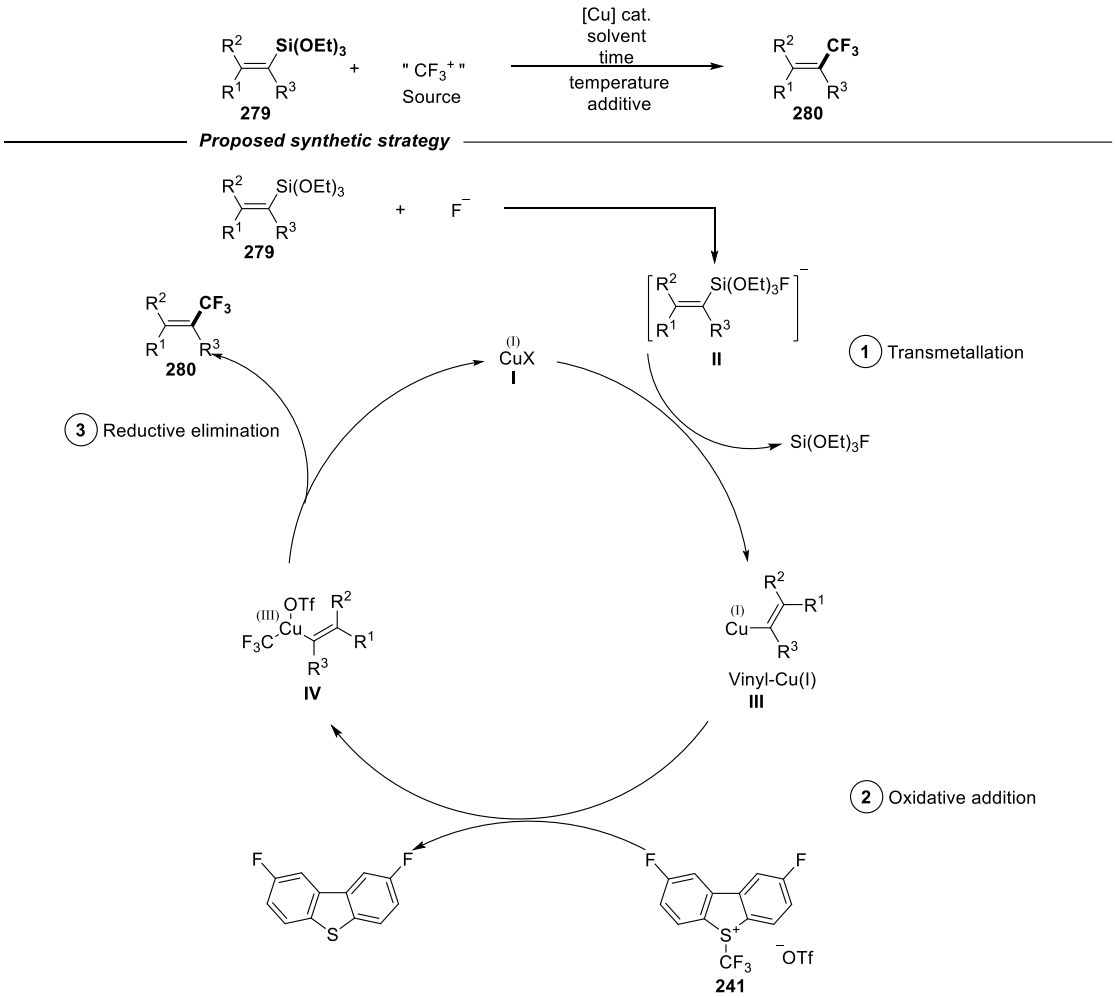
Scheme 179. Stereodivergent copper-catalyzed trifluoromethylation of vinylsiloxanes.

As can be seen graphically, the development of this project will be divided into three distinct sections.

Firstly, based on our literature investigation, we will describe the selection of the catalysts and the results collected for the stereodivergent hydrosilylation of alkynes **278**. Secondly, our attention will be devoted to describe the optimization that has been done to optimize all the reaction parameters. Finally, with the optimal reaction conditions the reaction will be applied to prepare a library of trifluoromethylated olefins **280a**-**280c** in order to demonstrate the scope of the reaction. In this way, employing aliphatic alkynes as starting materials, it will be possible to smoothly access to aliphatic trifluoromethylated alkenes which are far more valuable from a synthetic point of view.

Specifically, we envisaged a strategy based on the *in-situ* generation and reactivity of vinyl copper(I) complex, vinylcopper(I): such organometallic intermediates can be generated through a range of elementary mechanisms as depicted in the Scheme below. During the design of the catalytic cycle, we proposed that the mechanism for this transformation is based on the well-established vinyl copper chemistry. First of all, the vinylsiloxanes **279** would be activated by a fluoride ion (intermediate **II**), which is essential to start the reaction and induce the transmetallation, the first step of our catalytic cycle. Thereafter, in an analogous way to the Hiyama coupling, is generated *in-situ* a vinyl-copper species **III**. At this point, the transient vinyl-copper intermediate **III** follows an oxidative addition with the Umemoto's reagent **241**, which is a "CF_3^+" donor.

In this way, it is formed a Cu(III) complex **IV** which following a reductive elimination step releases the desired trifluoromethylated olefin **280**. The proposed catalytic cycle is reported in the Scheme 180 below.



Scheme 180. Proposed synthetic strategy for the development of a novel copper-catalyzed trifluoromethylation cross-coupling of vinylsiloxanes.

Therefore, in this chapter we will summarize the efforts that have been made to develop a novel copper-catalyzed trifluoromethylation reaction. Noteworthy, the model system used for our investigation will be discussed first, after which the optimization for the development of novel cross-coupling will be presented describing the systematic variation of all crucial parameters (nature of the copper salt, additives, solvent, temperature, etc). Thus, having developed a protocol for the copper-catalyzed trifluoromethylation of vinylsiloxanes we will describe, along with a methodical variation of the nature of both reaction partners, the scope of this chemical transformation and highlight its uses and limitations. In order to demonstrate the effectiveness of our new straightforward method for accessing trifluoromethylated olefins by using affordable commercially available starting materials and copper as catalyst. The achievement of these objectives will allow to investigate an unexplored area of copper catalysis providing attractive perspectives for the future.

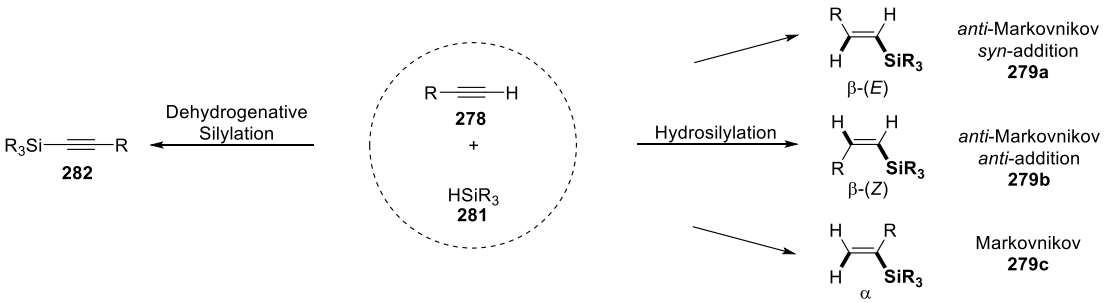
This project was conducted in collaboration with Logan Salamone (Master student) and Michela Marchese (PhD student). Specifically, Mr. Logan Salamone conducted the optimization and Ms. Michela Marchese has collaborated to prepare the library of trifluoromethylated olefins.

4.5. Optimization of the reaction conditions

To test the feasibility of our strategy and then to optimize it, we had to identify, select and test the catalysts required to perform the stereodivergent hydrosilylation of alkynes **278**. Thereafter, we have optimized the reaction conditions to perform the copper-catalyzed cross-coupling for the trifluoromethylation of vinylsiloxanes in order to obtain the trifluoromethylated olefins, the desired target product. Finally, in order to investigate the scope of the reaction, we have prepared a library of trifluoromethylated olefins using the optimized reaction conditions. Each part of this work will be described in a dedicated section below.

4.5.1. Hydrosilylation of alkenes and alkynes: general overview

The hydrosilylaton of alkenes and alkynes is one of the most important methods for the construction of silicon-carbon bonds. Specifically, the hydrosilylation of alkynes **278** is a straightforward method to prepare vinylsilanes, which are useful intermediates broadly employed in organic synthesis,[241] such as coupling partners in Hiyama cross coupling reactions.[242] Nowadays, the development of a transition-metal catalyzed hydrosilylation in which there is a full control of the region- and stereoselectivity is still a challenging and too little explored field of organometallic chemistry. Generally, the hydrosilylation of terminal alkynes **278** can furnish three vinylsilanes isomers: the β-(*Z*), β-(*E*) and the α-isomers **279a**-**279c**, Scheme 181. The β-(*Z*) is formed with an *anti*-Markovnikov /*anti*-addition and the β-(*E*) is formed with an *anti*-Markovnikov/*syn*-addition. For what concerns the α-vinylsilane, this isomer is formed with a Markovnikov addition. Typically, β-(*E*)-vinylsilanes are prepared with excellent selectivity, whereas the β-(*Z*) and the α-isomers are more difficult to prepare with high stereoselectivity.



Scheme 181. Potential products of terminal alkynes hydrosilylation.

Therefore, in this field of chemistry a number of β-(*Z*)-selective noble-metal-based catalysts containing Rh,[243] Ir,[244] and Ru[245] have been developed in the past years. Unfortunately, many of these catalysts show two main disadvantages as low reactivity or substrate-dependent selectivity.

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[241] Somfai, P.; Seashore-Ludlow, B. *Organosilicon reagent: vinyl-, alkynyl-, and arylsilanes. In Comprehensive Organic Synthesis*, 2th ed.; Vol. 1; *Springer*, **2014**.

[242] Komiyama, T.; Minami, Y.; Hiyama, T. *ACS Catal.* **2017**, *1*, 631–651.

[243] Zhao, X.; Yang, D.; Zhang, Y.; Wang, B.; Qu, J. *Org. Lett.* **2018**, *17*, 5357–5361.

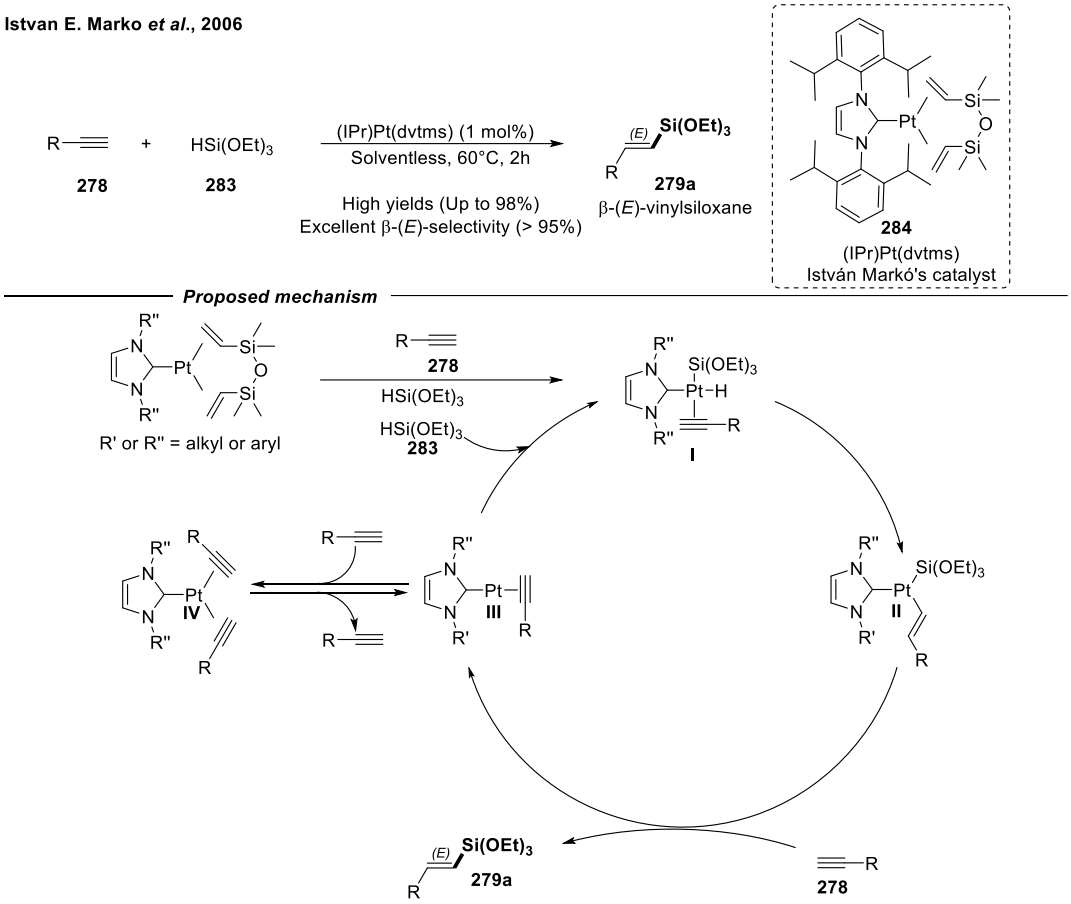
[244] (a) Corre, Y.; Werle, C.; Brelot-Karmazin, L.; Djukic, J. P.; Agbossou-Niedercorn, F.; Michon, C. *J. Mol. Catal. A: Chem*. **2016**, *423*, 256–263. (b) Iglesias, M.; Perez-Nicola´ s, M.; Sanz Miguel, P. J.; Polo, V.; Fernandez-Alvarez, F. J.; Perez-Torrente, J. J.; Oro, L. A. *Chem. Commun*. **2012**, *48*, 9480–9482. (c) Sridevi, V. S.; Fan, W. Y.; Leong, W. K. *Organometallics* **2007**, *26*, 1157–1160.

[245] (a) Conifer, C.; Gunanathan, C.; Rinesch, T.; Hölscher, M.; Leitner, W. *Eur. J. Inorg. Chem*. **2015**, *2*, 333–339. (b) Na, Y.; Chang, S. *Org. Lett*. **2000**, *2*, 1887–1889.

Thus, a mixture of vinylsilanes is formed. The same results have been established employing catalysts of earth-abundant transition-metal such as cobalt,[246] iron,[247] and manganese,[248]. For these reasons, the development of much more effective catalysts to prepare the less thermodynamically stable β-(*Z*)-vinylsilane and α-isomers with wider applicability remains still a challenging task to reach in this field.

4.5.2. Identification of the catalyst for the highly selective β-(*E*)-hydrosilylation

Following a thorough review of the literature, we used a bulky platinum catalyst named (IPr)Pt(dvtms) **284** to carry out the highly stereoselective hydrosilylation for the β-(*E*)-vinylsiloxane **279a** (Scheme 182). This catalyst has been developed in the laboratory of Prof. István Markó and it is characteristic to have a bulky *N*-heterocyclic carbene (NHC) as ligand.[249] Additionally, the (IPr)Pt(dvtms) **284** is known to furnish high yields with an excellent *β-(E)*-selectivity.



Scheme 182. Hydrosilylation of alkynes with the Markó catalyst for the preparation of β-(*E*)-vinylsiloxane.

[246] (a) Chen, J.; Guo, J.; Lu, Z. *Chin. J. Chem*. **2018**, *36*, 1075–1109. (b) Du, X.; Hou, W.; Zhang, Y.; Huang, Z. *Org. Chem. Front*. **2017**, *4*, 1517–1521. (c) Teo, W. J.; Wang, C.; Tan, Y. W.; Ge, S. *Angew. Chem. Int. Ed*. **2017**, *56*, 4328–4332. (d) Sun, J.; Deng, L. *ACS Catal*. **2016**, *6*, 290–300.

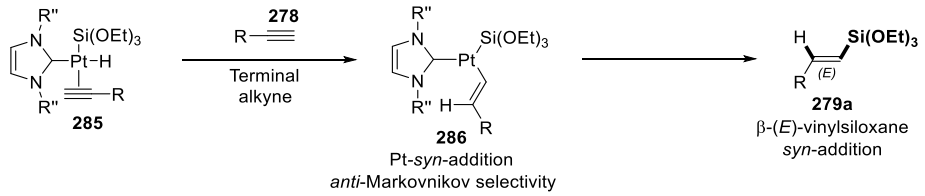
[247] (a) Challinor, A. J.; Calin, M.; Nichol, G. S.; Carter, N. B.; Thomas, S. P. *Adv. Synth. Catal.* **2016**, *358*, 2404–2409. (b) Greenhalgh, M. D.; Frank, D. J.; Thomas, S. P. *Adv. Synth. Catal*. **2014**, *356*, 584–590.

[248] Liang, H.; Ji, Y. X.; Wang, R. H.; Zhang, Z. H.; Zhang, B. *Org. Lett*. **2019**, *21*, 2750–2754.

[249] (a) Dierick, S.; Vercruysse, E.; Berthon-Gelloz, G.; Markõ, I. *Chem. Eur. J.* **2015**, *21*, 17073–17078. (b) Berthon-Gelloz, G.; Schumers, J. M.; de Bo, G.; Markó, I. E. *J. Org. Chem.* **2008**, *73*, 4190–4197. (c) de Bo, G.; Berthon-Gelloz, G.; Tinant, B.; Markó, I. *Organometallics* **2006**, *25*, 1881–1890.

The mechanistic cycle for this catalyst is based on the classical Chalk and Harrod mechanism.[250] Firstly, the dvtms ligand is displaced by the alkyne **278** to furnish an NHC-Pt(η^2–alkyne) fragment **III**. Thereafter, the Pt-complex reacts with $(EtO)_3SiH$ **283** through an oxidative addition to yield the intermediate **I**. At this point, a migratory insertion of the alkyne into the Pt–H bond takes place to form a platinum(silyl)alkene **II**. Finally, after reductive elimination, the Pt catalyst coordinates again an alkyne **278**, affording the starting complex **III**, in this way a new catalytic cycle can start again.

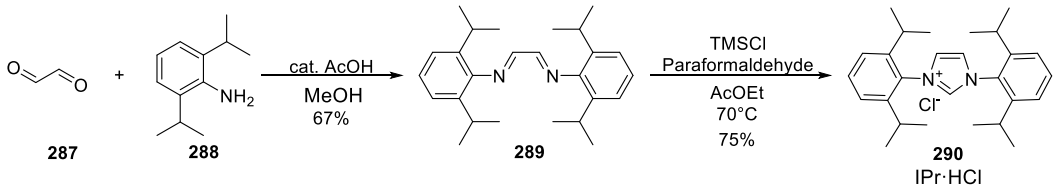
For what concerns the regioselectivity, the hydrosilylation of alkynes typically involves *anti*-Markovnikov addition, where the silicon atom is attached to the less substituted carbon of the alkyne with terminal selectivity. Furthermore, the addition onto the alkyne is *syn*, this means that after hydrosilylation, the hydrogen and platinum are on the same side of the double bond **286** (Scheme 183).



Scheme 183. Regioselectivity of Pt-catalyzed hydrosilylation of terminal alkyne with Markó's catalyst.

The key step in the catalytic cycle is the migratory insertion, indeed when the aliphatic alkyne coordinates to the platinum metal center the coordination is nonsymmetrical and can be qualitatively described by the strength of the orbital interactions between the platinum d orbitals and the alkyne π^*. Considering the work of Tsipis,[251] when the alkyne is aliphatic the strongest interaction of the molecular orbital occurs between Pt and the terminal carbon atom of the alkyne, favouring the formation of the β-(*E*)-vinylsiloxane.

The synthesis of the Markó's catalyst was performed in four-step. Firstly, the IPr ligand was prepared with the acid-catalyzed condensation of glyoxal **287** in a solution of methanol using 2 equiv. of diisopropyl aniline **288**, in order to furnish the diimine of interest **289**. Thereafter, the diimine was cyclised in 75% yield to the corresponding IPr·HCl **290** using TMSCl and paraformaldehyde in ethyl acetate as solvent (Scheme 184).[252]



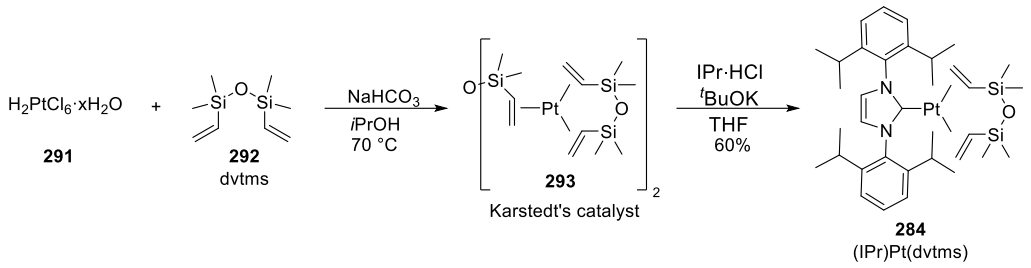
Scheme 184. Synthesis of the IPr·HCl ligand.

[250] a) Harrod, J. F.; Chalk, A. J. *In Organic Synthesis via Metal Carbonyls*, 1th ed.; Vol. 2; Wender, I. Eds. John Wiley & Sons Ltd., **1977**. (b) Tilley, T. D.; Patai, S.; Rappoport, Z. *The Chemistry of Organic Silicon Compounds*; 1th ed.; Vol. 2; Eds. John Wiley & Sons Ltd., **1989**. (c) Ojima, I.; Patai, S.; Rappoport, Z. *The Chemistry of Organic Silicon Compounds*, Eds. John Wiley & Sons Ltd., **1989**. d) Chalk, A. J.; Harrod, J. F. *J. Am. Chem. Soc*. **1965**, *87*, 16–21.

[251] Tsipis, C. A. *J. Organomet. Chem*. **1980**, *188*, 53–61.

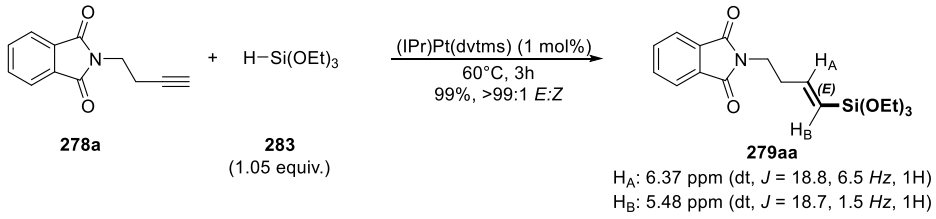
[252] Hintermann, L. *Beilstein J. Org. Chem*. **2007**, *3*, 1–5.

With the ligand in our hand, the attention was dedicated to the preparation of the (IPr)Pt(dvtms) catalyst **284**. Firstly, it was prepared a solution of the Karstedt's catalyst **293** by mixing together hexachloroplatinic acid **291** in isopropanol as solvent with an excess of divinyltetramethylsiloxane ligand **292** (dvtms). Thereafter, the imidazolium salt **290** was added to a solution of the Karstedt's catalyst **293** in presence of ^{t}BuOK as organic base, and isolated the (IPr)Pt(dvtms) catalyst in 60% yield **284** (Scheme 185).



Scheme 185. Synthesis of the (IPr)Pt(dvtms) catalyst.

An alkyne derivative of phthalimide **278a** was chosen as the model substrate due to its polarity, inertness, and structural simplicity. Subsequently, with the Markó's catalyst **284**, under the reported reaction conditions and in presence of $HSi(OEt)_3$ **283**, we prepared the corresponding *β-(E)*-vinylsiloxanes **279aa** confirming its high selectivity. The hydrosilylation reaction with the (IPr)Pt(dvtms) catalyst led to the formation of the target product with very high yields and stereoselectivity. The formation of the target product was evaluated considering the ^{1}H-NMR spectrum, in which is possible to identify the characteristic signal of the proton onto the double bond at 6.37 ppm (dt, *J* = 18.8, 6.5 Hz, 1H) and 5.48 ppm (dt, *J* = 18.7, 1.5 Hz, 1H) with the typical coupling constant for the *E*-stereoisomer (J_{trans} = 18 Hz), (Scheme 186). Consequently, this catalyst was used for the synthesis of a library of *β-(E)*-vinylsiloxanes.



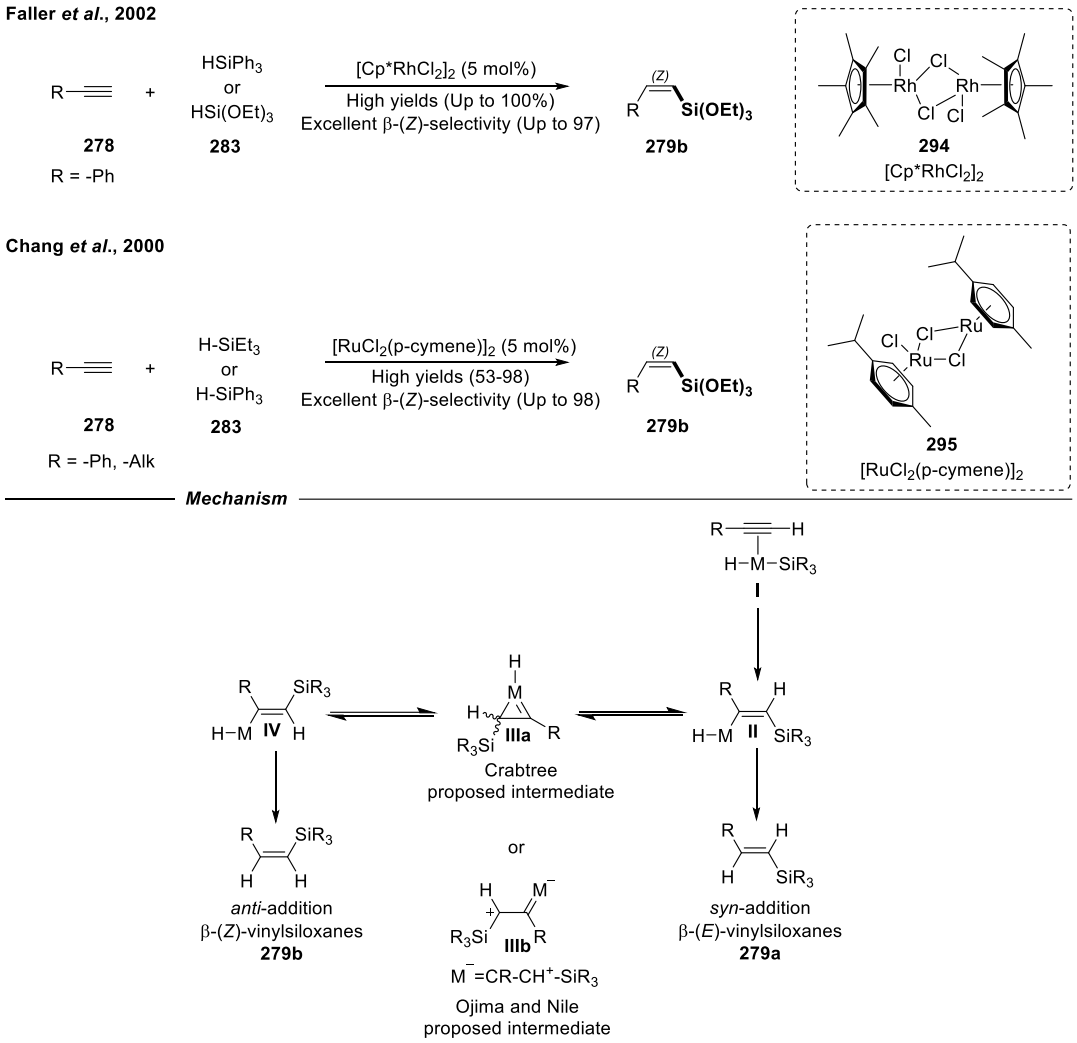
Scheme 186. Test of the platinum catalyst (IPr)Pt(dvtms) on a phthalimide derivative as model substrate.

4.5.3. Identification of the catalyst for the highly selective β-(*Z*)-hydrosilylation

Based on a thorough review of the literature, the synthesis of β-(*Z*)-vinylsiloxanes is much more difficult, and many catalysts are restricted to arylacetylene derivatives. Considering the literature and the catalysts available in our laboratory, we tested the $[Cp^*RhCl_2]_2$ **294**,[253] and $[RuCl_2(p\text{-cymene})]_2$ **295**,[254] which are known to promote the synthesis of β-*(Z)*-vinylsiloxanes **279b** (Scheme 187). For these reasons, we evaluated the hydrosilylation of alkynes **278** using these two catalysts. Noteworthy, as stated in 1993 by Crabtree and co-workers,[255] the stereoselectivity of these catalysts can be explained considering that the *anti*-addition product **II** is formed by initial insertion of the alkyne into the M–Si bond. Thereafter, the isomerization of the vinyl species takes place **III**, to the isomer **IV**. Crabtree proposed an η^2–vinyl species **IIIa**,

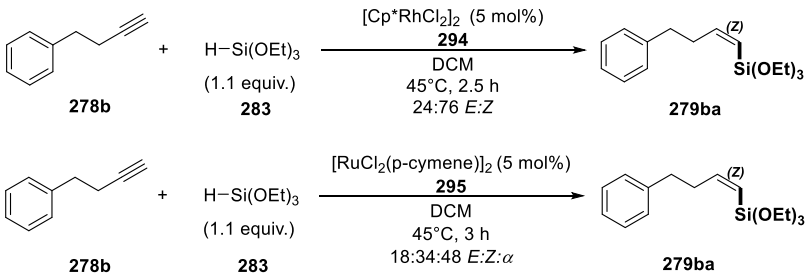
[253] Faller, J. W.; D'Alliessi, Darlene G. *Organometallics* **2002**, *21*, 1743–1746.
[254] Na, Y.; Chang, S. *Org. Lett.* **2000**, *13*, 1887–1889.
[255] Crabtree, R. H.; Jun, C. H. *J. Organomet. Chem*. **1993**, *447*, 177–187.

as the most probably intermediate for this isomerization, but Ojima and Nile prefer an exotic zwiterrionic carbene formulation **IIIb**, M^{-}=CR–CH^{+}–SiR_3.[256]



Scheme 187. $[Cp^*RhCl_2]_2$ and $[RuCl_2(p\text{-cymene})]_2$ catalysts for the synthesis of β-*(Z)*-vinylsiloxanes.

After identifying two possible candidates, we tested the catalysts with a commercial terminal alkyne **278b**, and the ratio of the various stereoisomers was then assessed with a quantitative isolated yield (Scheme 188).



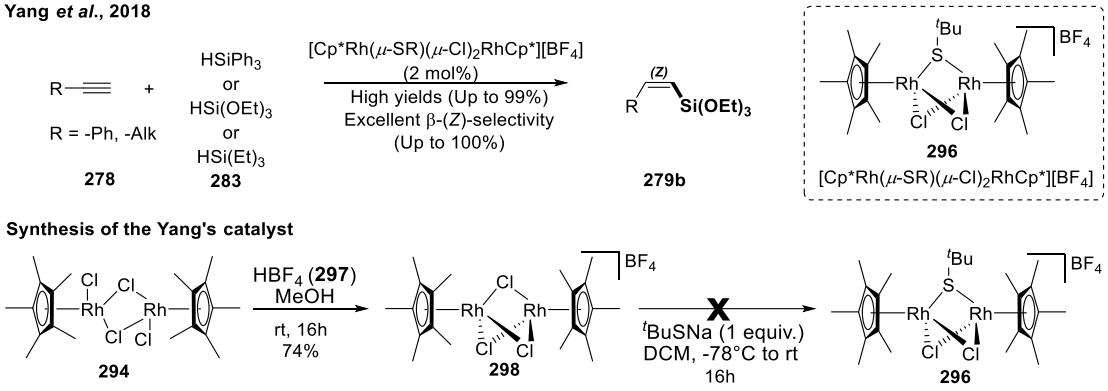
Scheme 188. Tests of the selective β-(*Z*) catalysts available in the laboratory on a commercial terminal alkyne.

[256] (a) Ojima, I.; Clos, N.; Donovan, R. J.; Ingallina, P. *Organometallics* **1990**, *12*, 3127–3133. (b) Hill, E.; Nile, T. A. *J. Organomet. Chem.* ***1977****, 137,* 293–300.

Unfortunately, both the results collected for the catalysts tested are contrary to the ones reported in the literature. With the Rh catalyst which was applied to phenylacetylene derivatives provided an *E:Z* ratio of 24:76 with an aliphatic alkyne. Instead the $[RuCl_2(p\text{-cymene})]_2$ **295**, which is reported to be applicable on aliphatic alkynes, revealed to be unselective on the selected model substrate and provided a mixture of isomers with a ratio 18:34:48 E:Z:α ratio.

Therefore, due to the lack of β-(*Z*)-selectivity of the tested catalysts $[Cp^*RhCl_2]_2$ **294** and $[RuCl_2(p\text{-cymene})]_2$ **295**, we then turned our attention to other known catalysts in the literature to promote the preparation of β-(*Z*)-vinylsiloxanes **279b**. The first candidate selected is a monothiolate-bridged dirhodium complex, named $[Cp^*Rh(\mu\text{-SR})(\mu\text{-Cl})_2RhCp^*][BF_4]$ **296**, and developed in 2018 by Yang and co-workers.[257] The second candidate selected is a cyclometalated Rh(III)−NHC complex, named [Cp*RhI(C, C')-Triaz] **301**, and developed in 2020 by Álvarez and co-workers.[258] As these catalysts were not commercially available, our attention was first dedicated to their preparation. Both the catalysts were prepared from the corresponding commercially available rhodium dimer, $[Cp^*RhCl_2]_2$ **294**.

First of all, we tried to prepare the Yang's catalyst **296** following the procedure reported in literature, such protocol relies on a two-step sequence. In the first step, the commercial Rh dimer **294** was treated with a solution of tetrafluoroboric acid **297** in methanol. Thereafter, the corresponding cationic complex containing the tetrafluoroborate anion it was treated with ^{t}BuSNa, at low temperature and under high dilution conditions (4 mM) in order to obtain the mono-substituted complex **296**. Although this step is reported in the literature with a 67% yield, we have not been able to reproduce this result and could not isolate the target rhodium complex **296**. Indeed, in the ^{13}C-NMR were missing the peaks of the *tert*-butyl thiol bridge (Scheme 189).



Scheme 189. $[Cp^*Rh(\mu\text{-SR})(\mu\text{-Cl})_2RhCp^*][BF_4]$ catalysts for the synthesis of β-*(Z)*-vinylsiloxanes.

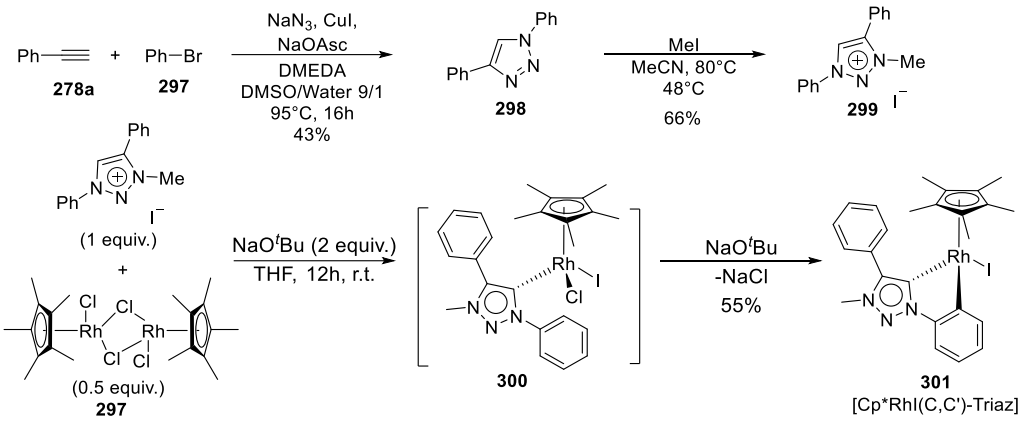
Having failed the preparation of the first catalyst **296**, we devoted our attention to the preparation of the Alvarez's catalyst **301**, [Cp*RhI(C, C')-Triaz]. The first step of the synthesis of the ligand was a copper-catalyzed 1,3-dipolar cycloaddition between bromobenzene **297**, phenylacetylene **278a** and sodium azide.[259] Phenyl azide was formed *in-situ* by the copper-catalyzed reaction between bromobenzene **297** and sodium azide. Then, the aromatic azide formed smoothly reacted with phenylacetylene **278a** through a regioselective cycloaddition which led to the formation of a 1,4-triazole **298** in a moderate yield of 43%. The second step

[257] Zhao, X.; Yang, D.; Zhang, Y.; Wang, B.; Qu, J. *Org. Lett.* **2018**, *17*, 5357–5361.

[258] Sánchez-Page, B.; Munarriz, J.; Jiménez, M. V.; Pérez-Torrente, J. J.; Blasco, J.; Subias, G.; Passarelli, V.; Álvarez, P. *ACS Cat.* **2020**, *10*, 13334–13351.

[259] (a) Potratz, S.; Mishra, A.; Bäuerle, P. *Beilstein J. Org. Chem.* **2012**, *8*, 683–692. (b) Saravanakumar, R.; Ramkumar, V.; Sankararaman, S. *Organometallics* **2011**, *30*, 1689–1694.

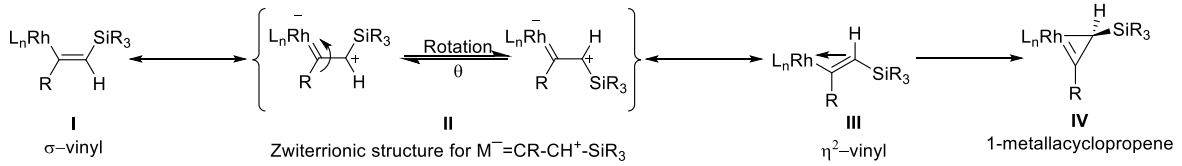
required for the preparation of the Alvarez's catalyst **301** was the methylation of the 1,4-triazole with iodomethane in order to furnish with a yield of 66% the desired product **299**. With the ligand in our hands, the Alvarez's catalyst **301** was prepared in one single step in 55% yield. The reaction proceeds via the formation of an intermediate that was not isolated **300**, but observed by the authors when the reaction was carried out in presence of 1 equivalent of NaO^{t}Bu (Scheme 190).



Scheme 190. Synthesis of the Alvarez's catalyst, [Cp*RhI(C, C')-Triaz].

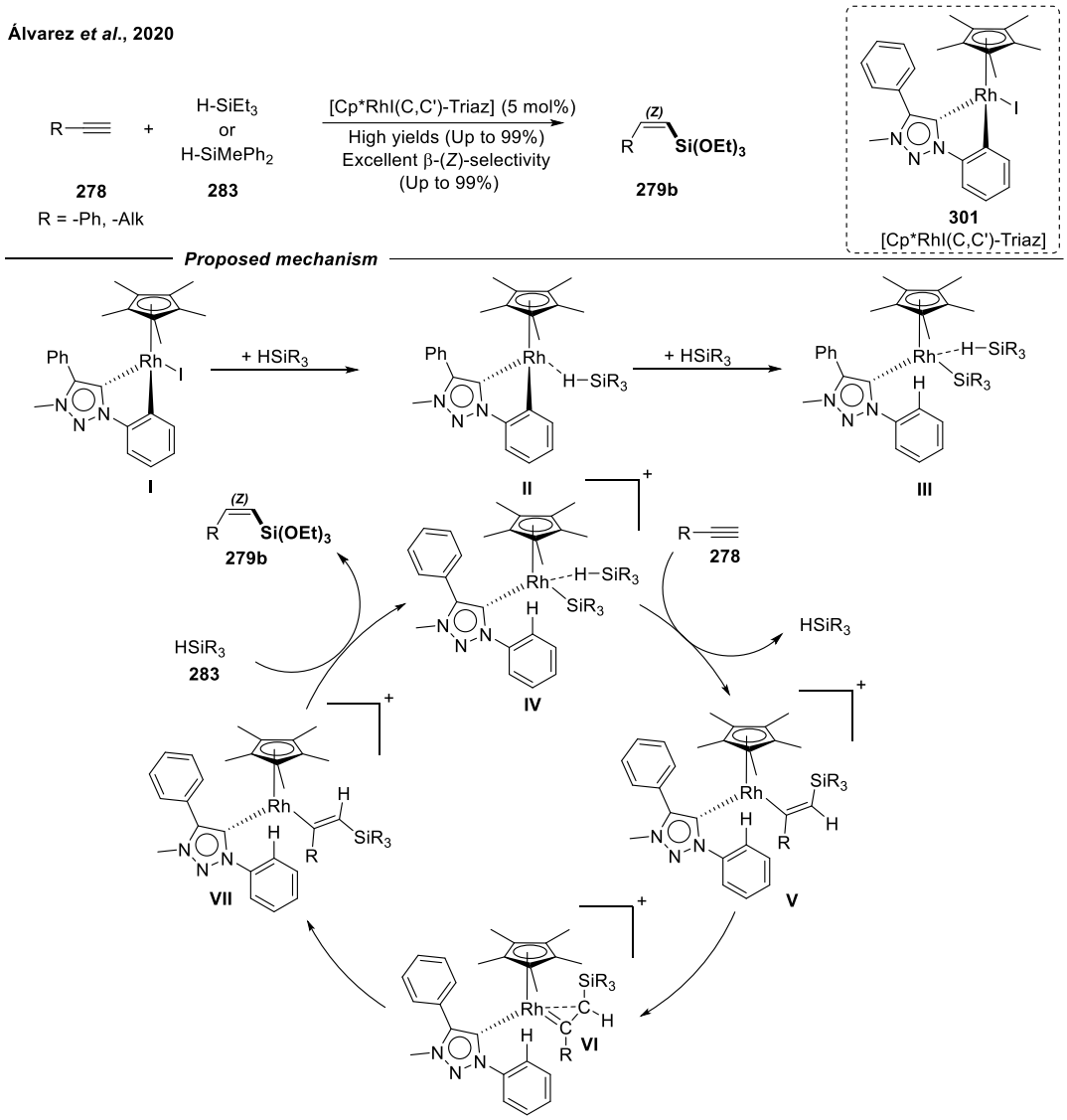
This catalyst was described in the literature to promote efficiently the hydrosilylation of terminal alkynes with complete region- and stereoselectivity toward the thermodynamically less stable β-(*Z*)-vinylsilane isomer at room temperature in chloroform or acetone. This catalyst has been applied to the hydrosilylation of a plethora of linear alkynes with several hydrosilanes, including $HSiMePh_2$, $HSiMe_2Ph$, and $HSiEt_3$ to furnish the corresponding β-(*Z*)-vinylsilanes in good to excellent yields.

Noteworthy, from a mechanistic point of view, the authors explained that this transformation is stereoselective for the formation of a β-(*Z*)-vinylsilanes because, after the *anti*-Markovnikov addition of silicon onto the triple bond of the alkyne, a metallacyclopropene intermediate **IV** is generated, also named η^2–vinylsilane metal species (**III**, Scheme 191),[260] which led to the isomerization of the double bond as depicted in the Scheme 192 below. This mechanism was proposed on the basis of DFT-calculations.



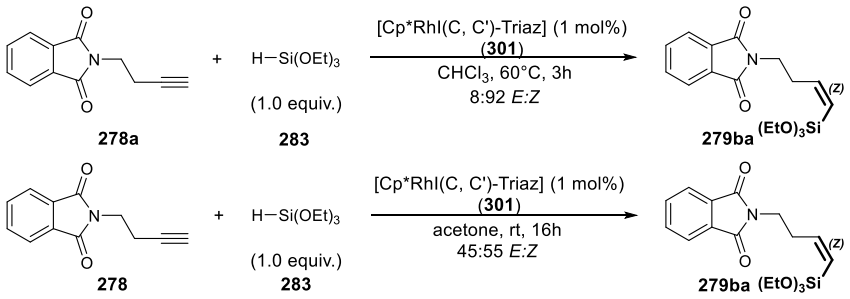
Scheme 191. Metal η^2-vinyl complexes.

[260] Frohnapfel, D. S.; Templeton, J. L. *Coord. Chem. Rev*. **2000**, *206*, 199−235.



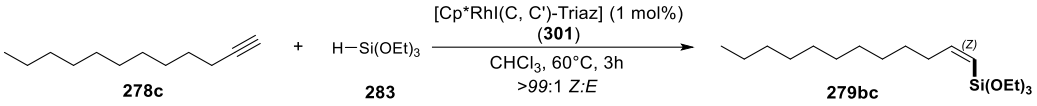
Scheme 192. Synthesis of the Alvarez's catalyst, [Cp*RhI(C, C')-Triaz].

Then, the Alvarez's catalyst, [Cp*RhI(C, C')-Triaz] **301** was tested under the reaction conditions reported in the article onto a phtalimide derived alkyne **278a** chosen as model substrate. The hydrosilylation was carried out in $CHCl_3$ at 60 °C allowing us to isolate the target compound with an acceptable *E:Z* ratio of 8:92. The ratio of the two isomers decreased to almost 50:50 by changing to acetone as solvent. Thus, following these first two tests, it appeared that $CHCl_3$ was the most suitable solvent to perform the hydrosilylation (Scheme 193).



Scheme 193. Tests of the Alvarez's with the model substrate.

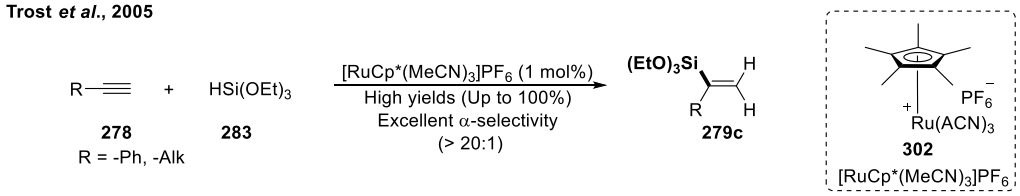
Furthermore, we also tested 1-dodecyne **278c** to confirm the high *β-(Z)*-stereoselectivity of the Alvarez's catalyst **301** under the optimal reaction conditions. To our delight, also with this substrate a good yield and an excellent stereoselectivity was demonstrated, as we observed only the *(Z)*-stereoisomer **278cb**.



Scheme 194. Tests of the Alvarez's onto a model substrate.

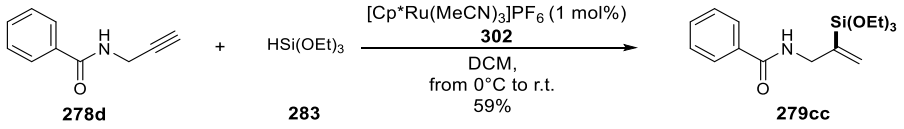
4.5.4. Identification of the catalyst for the highly selective α-hydrosilylation

After selecting the Alvarez's catalyst, [Cp*RhI(C, C')-Triaz] **301** for the synthesis of *β-(Z)*-vinylsiloxanes **279b** and the Markó's catalyst **284** for the synthesis of *β-(E)*-vinylsiloxanes **279a**, we focused our attention to the identification of the catalyst for the preparation of *α*-vinylsiloxanes **279c** which are more challenging to prepare and very little reported in the literature. In 2005, Trost and Ball reported a catalytic system to catalyzed the hydrosilylation of alkynes catalyzed by cyclopentadienylruthenium complexes such as [Cp*Ru(MeCN)$_3$]PF$_6$ **302** (Scheme 195).[261]



Scheme 195. Alkyne hydrosilylation catalyzed by a cationic ruthenium complex: synthesis of *α*-vinylsiloxanes.

The formation of the *α*-vinylsiloxane **279c** depends on the unique nature of the ruthenium catalyst which occupies an intermediate place on the periodic table and which acts through polar mechanisms due to the inaccessibility of oxidation-reduction cycles. From a mechanist point of view, the authors explained that with this catalyst, the oxidative addition into the Si–H bond is not energetically favoured. Therefore, the siloxane is activated through the formation of a σ-complex. This transformation is stereoselective for the formation of a α-vinylsiloxanes **279c** because the addition of silicon onto the triple bond of the alkyne is Markovnikov. Having identified the suitable catalyst for the preparation of α-vinylsiloxanes **279c**, we have tested the Trost-Ball's catalyst **302** under the reaction conditions reported in the paper onto a benzamide derivative chosen as model substrate and available in our laboratory. The hydrosilylation was carried out in dichloromethane at room temperature allowing us to isolate the target α-vinylsiloxanes **279cc** (Scheme 196).



Scheme 196. Tests of the Trost-Ball's catalyst onto the model substrate.

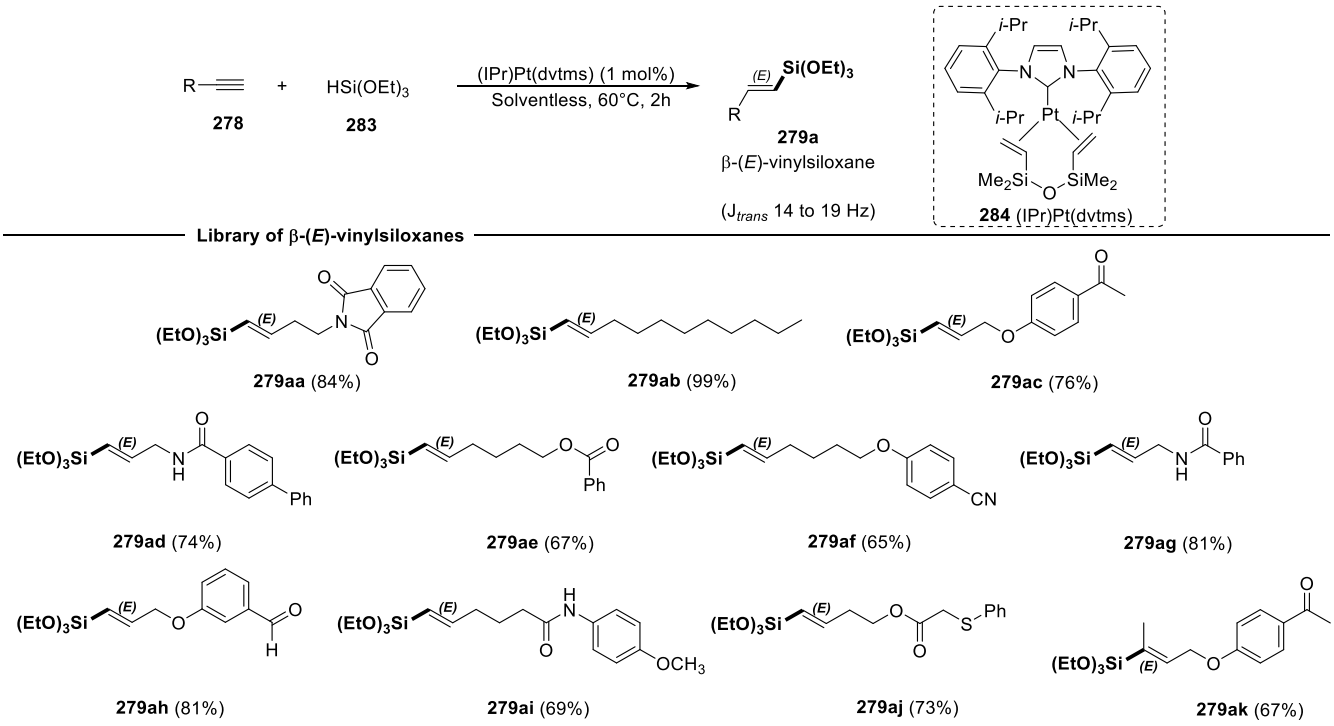
Having demonstrated the efficiency of the Trost-Ball's catalyst **302** for the preparation of *α*-vinylsiloxanes **279c** we decided to employ the Trost-Ball's catalyst for the purposes of our project. Indeed, starting from alkynes available in the laboratory with the [Cp*Ru(MeCN)$_3$]PF$_6$ we prepared a small library of *α*-vinylsiloxanes. In this way, we have identified the catalysts to prepare in a stereodivergent manner a library

[261] Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc*. **2005**, *127*, 17644–17655.

of *β-(E)*-vinylsiloxanes **279a**, *β-(Z)*-vinylsiloxanes **279b** and *α*-vinylsiloxanes **279c** using Pt, Rh and Ru catalysts. The results obtained will be described in the next paragraph.

4.6. Preparation of a library of β-(*E*)-vinylsiloxanes

After having identified the catalysts for the stereodivergent hydrosilylation, our attention has been devoted toward the preparation of a library of vinylsiloxanes (Scheme 197). Therefore, using the Markó's catalyst **284**, a library of β-(*E*)-vinylsiloxanes **279a** was smoothly prepared employing commercially available and homemade alkynes **278**. As described in the previously paragraphs, the Markó's catalyst **284** is highly stereoselective for the preparation of β-(*E*)-vinylsiloxanes in good to excellent yields in range between 65 and 99% yields. In all the cases, the formation of the β-(*E*)-vinylsiloxanes was confirmed by ^{1}H-NMR analysis evaluating the typical coupling constant which was J_{trans} 14 to 19 Hz. No formation of the β-(*Z*)-vinylsiloxanes stereoisomer was detected in all the cases tested. Generally, the hydrosilylation offers good yields, however in some case we have encountered difficulties in purifying the desired products due to their high polarity. The Pt-catalyzed hydrosilylation is highly compatible with a wide range of electron-deficient (-CO_2R, -CN, -$COCH_3$) functional groups, indeed the desired vinylsiloxanes **279ac**, **279ae** and **279af** were prepared in 76%, 67% and 65% yields, respectively. Good results were also obtained with electron-donating (-OCH_3, -SPh) functional groups as in the case of compound **279ai** and **279aj**, where the desired products were prepared in 69% and 73% yields. Surprisingly, also compound **279ah**, which contains a highly reactive aldehydic moiety, has shown to be stable under the reaction conditions furnishing the desired vinyl siloxanes in 81% yield. Interestingly the reaction proved to be fully stereospecific even when an internal alkyne was used, as in the case of compound **279ak** which was obtained in 67% yield. Notably, the yield obtained using the internal alkyne **279ak** is slightly lower than that obtained using the terminal alkyne **279ac**.



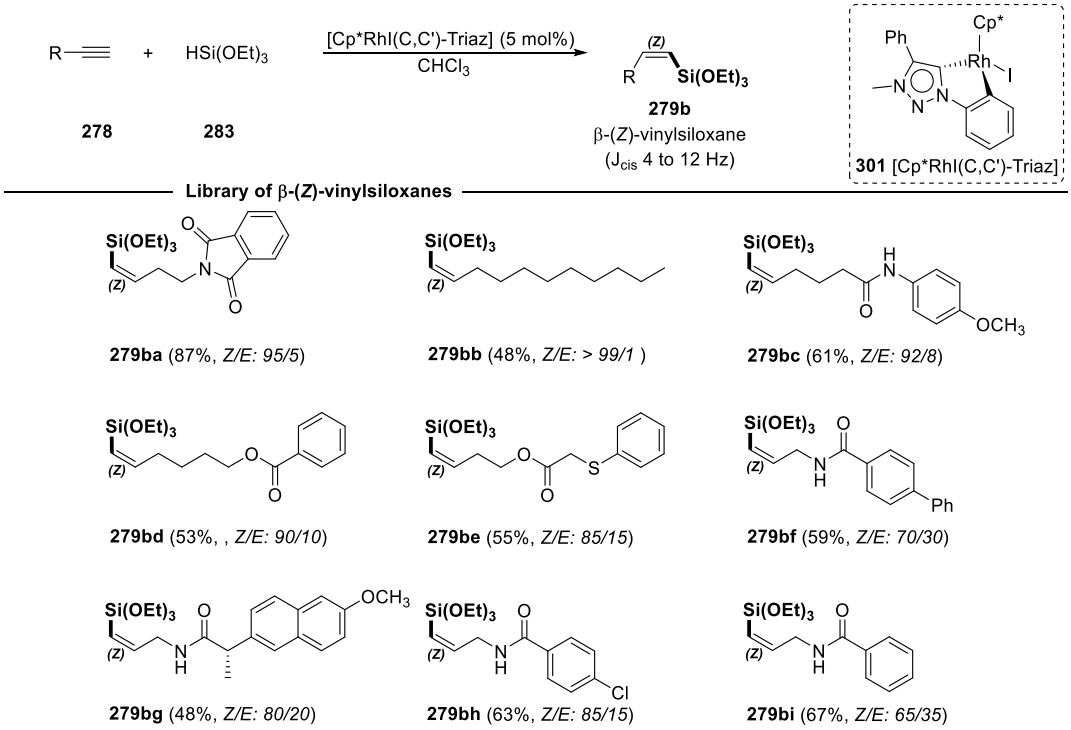
Scheme 197. Library of β-(*E*)-vinylsiloxane prepared with the Markó's catalyst.

As far as we can see, the main problem with this reaction is the purification of the compounds because they are highly polar and tend to remain well supported on silica dust during the chromatographic purification,

even when very polar solvent as methanol is used. Remarkably, this catalyst has the advantage of being chemoselective towards alkynes and highly compatible with sensitive functional groups like aldehydes and ketone.

4.7. Preparation of a library of β-(*Z*)-vinylsiloxanes and α-vinylsiloxanes

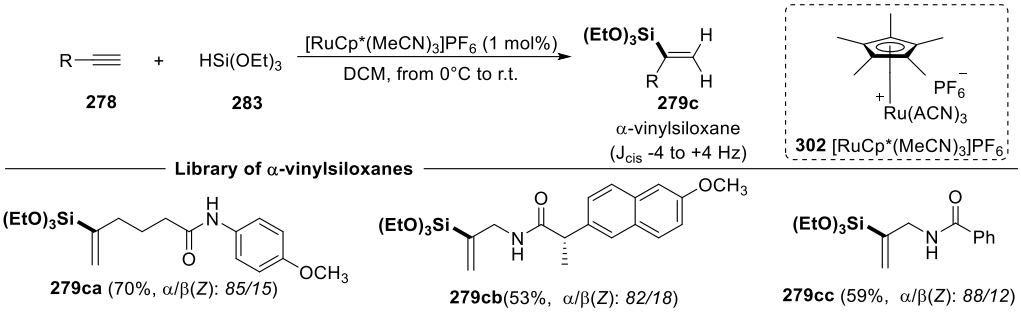
After having identified the catalysts for the stereodivergent hydrosilylation, our attention has been also devoted toward the preparation of a library of β-(*Z*)-vinylsiloxanes **279b** and α-vinylsiloxanes **279c** (Scheme 198). Therefore, using the Alvarez **301** and the Trost-Ball's catalyst **302**, a library of β-(*Z*)-vinylsiloxanes and α-vinylsiloxanes was prepared employing commercially available and homemade alkynes **278**. In order to simplify the complexity of the systems under our investigation, we performed the hydrosilylation reactions on alkynes with similar structures to those selected for the preparation of β-(*E*)-vinylsiloxanes. In this way, the attribution of the double bond configuration was easier to evaluate, since the coupling constants were totally different in the ^{1}H-NMR spectra. The target products were prepared in good yields in range between 48 and 87% yields. In all the cases, the formation of the β-(*Z*)-vinylsiloxanes **279b** was confirmed by ^{1}H-NMR analysis evaluating the typical coupling constant which was J_{cis} 4 to 12Hz. The Alvarez catalyst is stereoselective for the formation of β-(*Z*)-vinylsiloxanes as a major product. Traces of the β-(*E*)-stereoisomer can be identified in the NMR spectra as minor by-product with a ratio *Z*/*E* in a range between 99/1 and 65/35. Fortunately, the two stereoisomers are separable through chromatographic purification. Thus, it was possible to isolate only the β-(*Z*)-vinylsiloxanes. Notably, for the preparation of a library of β-(*Z*)-trifluoromethylated olefin we used only the β-(*Z*)-vinylsiloxanes stereochemically pure.



Scheme 198. Library of β-(*Z*)-vinylsiloxane prepared with the Alvarez's catalyst.

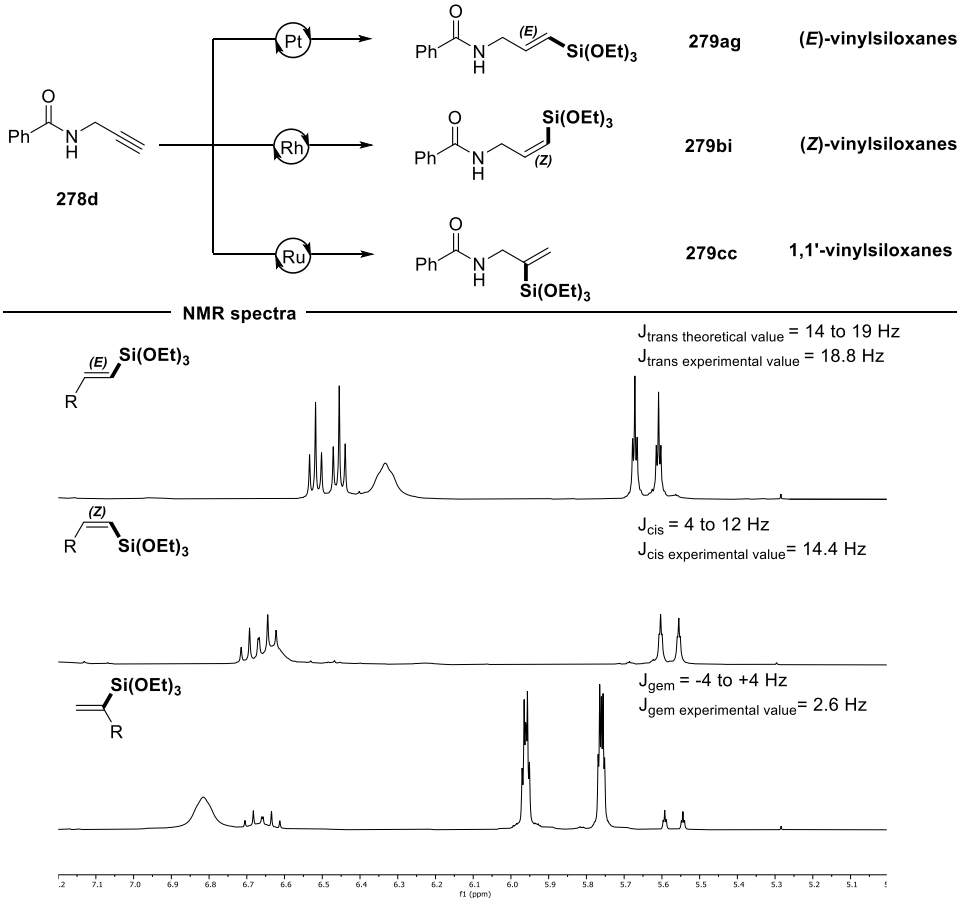
Finally, we prepared using the Trost-Ball catalyst **302** a small library of α-vinylsiloxanes, which are more challenging to synthetize (Scheme 199). Unfortunately, for reasons of lack of time the library of α-vinylsiloxanes **279c** was not further extended to other substrates. We simply tested and confirmed the efficiency of the Trost-Ball catalyst with alkynes available in the laboratory. Unfortunately, the Trost-Ball

catalyst is stereoselective for the formation of α-vinylsiloxanes **279c** as a major product, however traces of the *Z*-stereoisomer **279b** can be identified in the NMR spectra as minor by-product. The desired product **279ca-279cc** were prepared in good yields. Notably, the hydrosilylation was also applied onto a Naproxen derivative, which is a nonsteroidal anti-inflammatory drug (NSAID) used to treat pain, menstrual cramps and inflammatory diseases. The target product **279cb** was obtained with an acceptable yield of 53%.



Scheme 199. Small library of α-vinylsiloxane prepared with the Trost-Ball's catalyst.

The Trost-Ball catalyst **302** is stereoselective for the formation of α-vinylsiloxanes **279c** as a major product. Traces of the β-(*Z*)-stereoisomer **279b** can be identified in the NMR spectra as minor by-product with a ratio α/β-(*Z*) in a range between 82/15 and 88/12. Unfortunately, the two stereoisomers are not separable through chromatographic purification. Thus, it was not possible to isolate the α-vinylsiloxanes stereochemically pure. Notably, for the preparation of α-trifluoromethylated olefin we used the mixture α/β-(*Z*)-vinylsiloxanes. In the following Scheme 200, we have collected the NMR-spectra of the model substrate, named *N*-(prop-2-yn-1-yl)benzamide, onto we have performed the stereodivergent hydrosilylation using the three different catalysts, Pt, Rh and Ru.

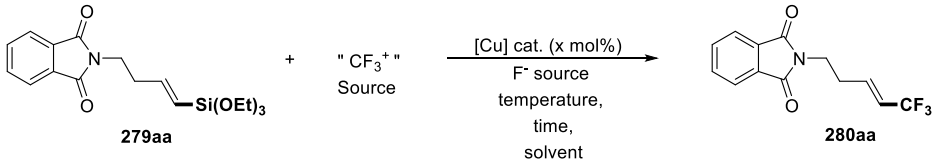


Scheme 200. β-(*E*), β-(*Z*) and α-vinylsiloxanes: NMR-spectra and coupling constants.

4.8. Optimization of the reaction conditions for the copper-catalyzed trifluoromethylation of vinyl siloxanes

Next, after identifying the best catalysts for the stereodivergent hydrosilylation and preparing a library of vinyl siloxanes, we worked to optimize the reaction conditions to promote a copper-catalyzed trifluoromethylation reaction of vinylsiloxanes (Scheme 201).

To test the feasibility of our strategy and optimize it, we had to choose a simple and easy model substrate. We selected a phthalimide derivative **279aa** for its simplicity and for its advantageous spectroscopic characteristics, which facilitate the analysis of the reaction crude by ^{1}H- and ^{19}F-NMR. In order to start we selected a model substrate with the *E*-configuration of the double bond.



Scheme 201. Model reaction under investigation.

Specifically, the proton and the fluorine spectrum (in $CDCl_3$ at 25 °C - room temperature) of the target product **280aa** has characteristic sharp signals of the protons onto the double bond which allow to evaluate easily the percentage yields and the coupling constants. The ^{19}F-NMR spectrum has a sharp singlet signal at -64.47 ppm correspond to the signal of the trifluoromethylated olefin (*E*-isomer). Furthermore, the formation of the target product can also be evaluate considering the ^{1}H-NMR spectrum, in which is possible to identify the characteristic signal of the proton onto the double bond at 6.37 ppm with its typical coupling constant (J_{trans} = 16 Hz) for the (*E*-isomer).

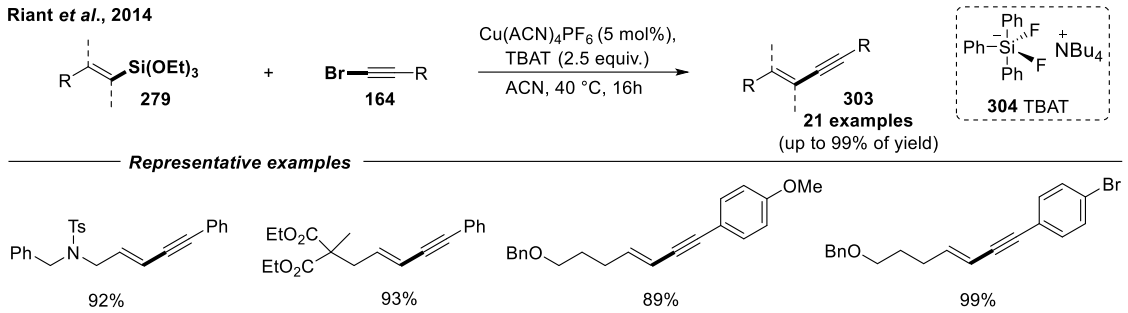
In order to analyse the various preliminary tests, it was agreed to avoid systematic isolation of the trifluoromethylated product formed in the several trials evaluated. With this in mind, it was decided to determine the ^{1}H-NMR yield NMR using 3,3'-*bis*(trifluoromethyl)benzophenone as internal standard and integrating the fluorine signals of the trifluoromethyl moiety installed onto the double bond. This internal standard has the advantage to have the signals which are easy to integrate and distant from the signals of the target product.

At the beginning of the investigation phase we considered all possible parameters that could be important for the course of the reaction. Considering the complexity of the reaction system, we kept some reaction parameters unchanged and we concentrated mainly on the most important ones. The nature of the copper(I) sources and of the trifluoromethylating electrophiles, which are recognized to be the most important parameters, have received special attention.

In 2014, Riant and co-workers described the first protocol for the copper-catalyzed cross-coupling of vinylsiloxanes **279** with bromoalkynes **164**.[262] This mild and effective protocol furnished a variety of sensitive enynes **303**, which are important building blocks in organic synthesis. Based on this original cross-coupling described in the literature, we fixed several parameters, including the solvent (ACN), the time (15 hours), the temperature (40 °C) and TBAT **304** as fluorine source (Scheme 202). Notably, TBAT is the preferred fluorine source because is highly soluble in organic solvents and a non-hygroscopic fluoride donor. This parameter was not changed since it was identified optimal in the previously studies. Indeed, other activating agents

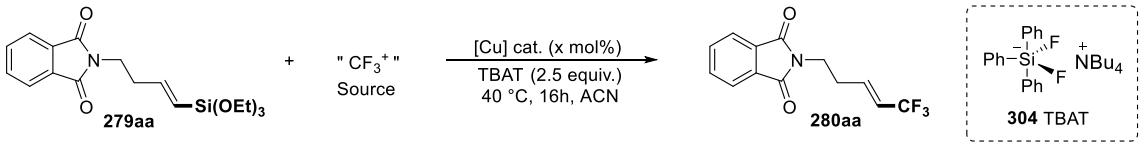
[262] Cornelissen, L.; Lefrancq, M.; Riant, O. *Org. Lett.* **2014**, *16*, 3024–3027.

were screened, but only TBAT was able to promote the copper cross-coupling with good yields. Although not particularly atom economic, TBAT is easily transformed into Ph_3SiOEt at the end of the reaction. This reaction by-product can be smoothly recovered and transformed into TBAT again, meaning an overall loss of nBu$_4$NF(TBAF).[263] Adopting the conditions established for bromoalkynes **164**, the β-(*E*)-vinyltriethoxysiloxane phthalimide derivative **279aa** was screened with different electrophilic trifluoromethylating agents and under different reaction conditions. Noteworthy, we selected a model compound with high molecular weight due to trifluoromethylated products are known to be relatively volatile.



Scheme 202. Copper-catalyzed cross-coupling of vinylsiloxanes with bromoalkynes: synthesis of enynes.

The simplified model reaction that we have tried to optimize and used as starting point considering the work of Riant and co-workers is described below in the following Scheme 203.

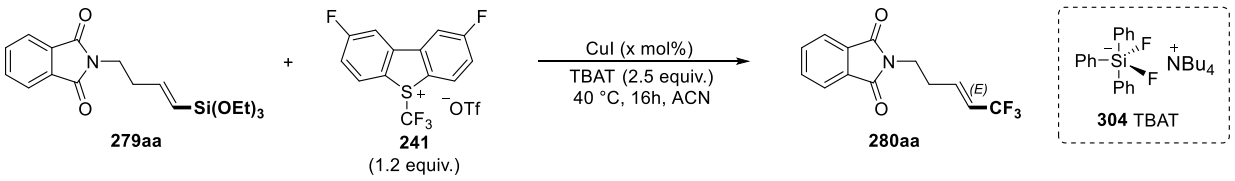


Scheme 203. Simplified model under investigation.

4.8.1. Influence of the catalytic loading of the copper source

We have begun the investigation for the development of a novel copper-catalyzed trifluoromethylation reaction evaluating the influence of the copper catalyst onto the model reaction system chosen (Scheme 204). Therefore, we turned our attention to the nature of the copper source which is an extremely important parameter to control the chemical reactivity and solubility of the catalyst, indeed it depends on the nature of the counter ions associated to the copper cation. At the beginning of our investigation, copper iodide was used as copper catalyst due to is a standard copper source commonly used in copper catalysis. For what concern the trifluoromethylating agent, the Umemoto reagent **241** was used as trifluoromethyl source("CF_3"), due to is commercially available, cheap and widely used to introduce the trifluoromethyl moiety in organic molecules.[264] The first parameter of interest we tried to modify was the catalytic loading introduced in the reaction mixture (Scheme 204). The best result obtained was with CuI with a catalytic loading of 20 mol%, indeed under these reaction conditions the formation of the target product was observed in 61% NMR yield (Table 13, entry 2). We selected 20 mol% copper as the standard amount, but it's important to note that catalytic loading screening reactions were only carried out once and that yields are fairly similar.

[263] (a) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166–5167. (b) Handy, C. J.; Lam, Y. F.; DeShong, P. *J. Org. Chem*. **2000**, *65*, 3542–3543.
[264] Umemoto, T.; Zhang, B.; Zhu, T.; Zhou, X.; Zhang, P. *J. Org. Chem.* **2017**, *82,* 7708–7719.



Scheme 204. Screening of the catalytic loading.

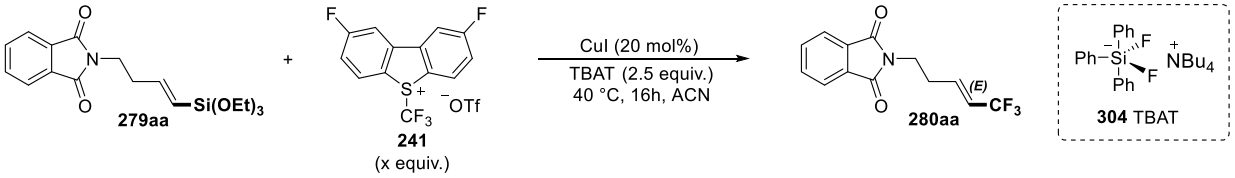
Entry	Catalytic loading	Yield (%)[a]
1	10 mol%	57
2	20 mol%	61
3	30 mol%	53

[a] Yields determined by NMR spectroscopy using 3,3'-*bis*(trifluoromethyl)benzophenone as an internal standard.

Table 13. Screening of the catalytic loading.

4.8.2. Influence of the amount of Umemoto's reagent

Thereafter, we have evaluated the amount of Umemoto's reagent **241** needed for the trifluoromethylation reaction (Scheme 205). A raise to 1.5 equivalents of Umemoto's reagent allow to slightly increase the yield. Given the high molecular weight of the Umemoto's reagent and its by-product, to comply with the principles of the atom economy we have not increased the amount of this chemical. The reaction conditions tested are here summarized in the table below. The best result collected were obtained with 1.5 equiv. of Umemoto's reagent, and we kept this amount of trifluoromethylating agent constant in the next steps of optimization (Table 14, entry 2).



Scheme 205. Screening of the equivalent of Umemoto's reagent.

Entry	Equivalent of Umemoto's reagent	Yield (%)[a]
1	1.2 equiv.	57
2	1.5 equiv.	65
3	2.0 equiv.	55

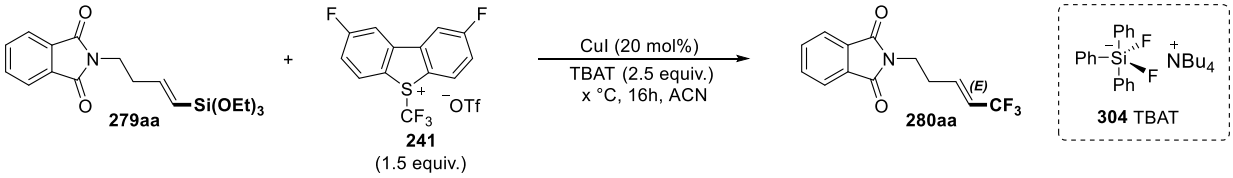
[a] Yields determined by NMR spectroscopy using 3,3'-*bis*(trifluoromethyl)benzophenone as internal standard.

Table 14. Screening of the equivalent of Umemoto's reagent.

4.8.3. Influence of the temperature

Thereafter, we were careful to assess the reaction yield through changing the reaction temperature (Scheme 206). Indeed, the reaction temperature is a crucial parameter which can very often increase the efficiency of the reaction performance. Thus, our model reaction has been tested at 25 °C, 40 °C and 60 °C. The optimal reaction temperature is 40 °C (Table 15, entry 2), indeed an increase or decrease does not lead to a better

yield. It is important to note that high temperatures were not tested because we thought it might be a strong point of our methodology to operate under mild reaction conditions.



Scheme 206. Evaluation of the influence of the reaction temperature.

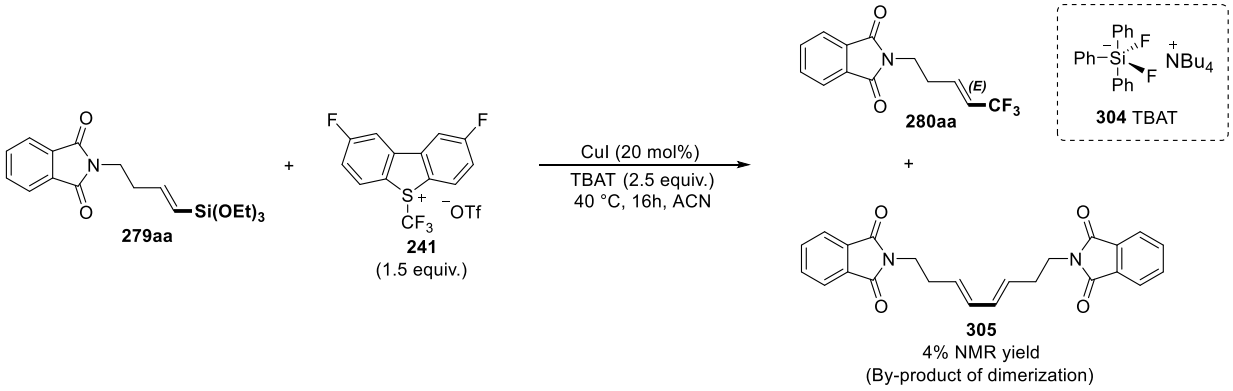
Entry	Temperature	Yield (%)[a]
1	25 °C	59
2	40 °C	65
3	60 °C	58

[a] Yields determined by NMR spectroscopy using 3,3'-*bis*(trifluoromethyl)benzophenone as an internal standard.

Table 15. Evaluation of the influence of the reaction temperature.

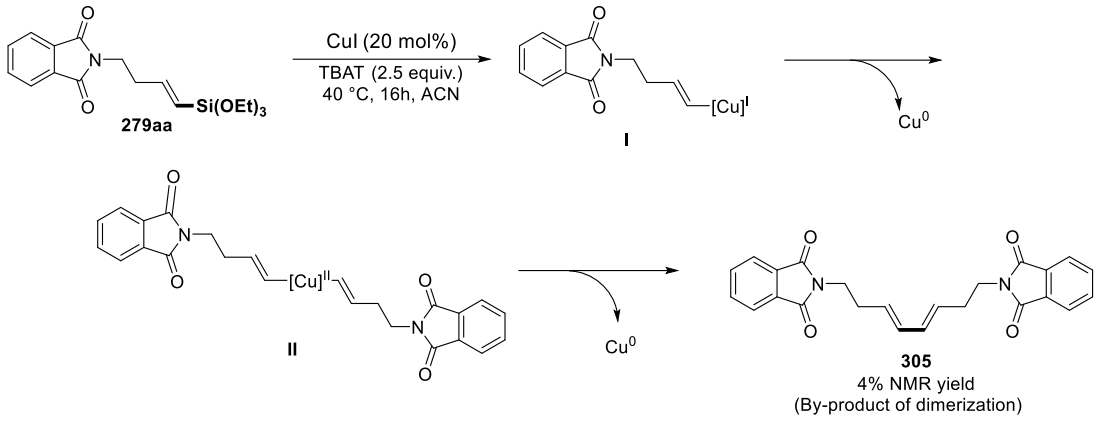
4.8.4. Nature of the copper source

Next, we focused our attention on the identity of the copper source which is also a crucial parameter as the chemical reactivity, solubility in the organic solvents and stability of the copper source used is dependent of the counter ions associated to the copper cation (Scheme 207). To our surprise, our first trial using 20 mol% of CuI as a catalyst led to the formation of the target product in 65% yield **280aa**. Unfortunately, using CuI as catalyst the purifications were severely hampered by the formation of a by-product which was very difficult to separate from the target product. Fortunately, the impurity was separated from the reaction crude and isolated due to the substrate's sufficient polarity. The NMR-analysis revealed the formation of an unwanted phthalimide-dimer **305**. Despite being present in small amounts, the by-product's structural similarity to the target molecule makes purifications tedious, indeed in many cases our final products **280aa** were contaminated by the presence of these by-products **305**.



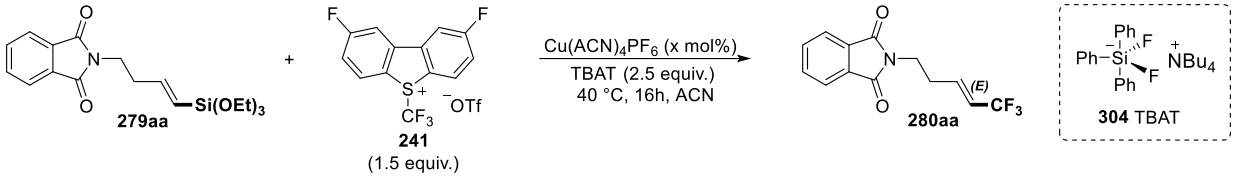
Scheme 207. Identification of the by-product of dimerization in the reaction of trifluoromethylation.

Due to the observed dimer formation, the reaction most likely involves a vinyl copper intermediate. Most probably, two vinyl copper(I) intermediate **I** react together and disproportionate into one vinyl copper(II) **II** and a Cu(0). Thereafter, the reductive elimination of Cu(II) intermediate **II** generates the unwanted dimer **305** by releasing an additional Cu(0) species. The proposed reaction mechanism for the formation of the dimer **305** is described in the following Scheme 208.



Scheme 208. Mechanism of dimerization of the vinylsiloxanes via disproportion of the vinyl copper intermediate.

Faced with this challenge, we further studied how to limit the formation of the dimer **305** and we could appreciate that using a different copper source, the formation of the dimerization product was minimized. Indeed, using $Cu(MeCN)_4PF_6$ as catalyst the formation of the dimerization product was reduced and an easier purification in chromatographic column was permitted. Therefore, our model reaction was further tested under the same reaction conditions using $Cu(MeCN)_4PF_6$ as catalyst with different catalytic loading (Scheme 209). The results collected are reported in following Table 16.



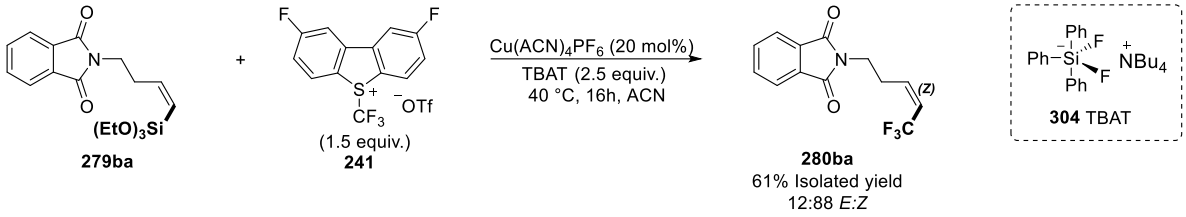
Scheme 209. Evaluation of the catalytic loading of $Cu(MeCN)_4PF_6$.

Entry	Copper source	Yield (%)[a]	*E:Z* ratio
1	10	59	>99:1
2	20	65 (61)[b]	>99:1

[a] Yields determined by NMR spectroscopy using 3,3'-*bis*(trifluoromethyl)benzophenone as an internal standard. [b] Isolated yield.

Table 16. Evaluation of the catalytic loading of $Cu(MeCN)_4PF_6$.

When the new copper source was tested, the reaction maintained its high stereospecificity in which the dominant product was the *E*-trifluoromethylated olefin **280aa** with a yield of the same order of magnitude as that obtained with copper iodide. The main difference consists in the most accessible and easy purification of the reaction product. As can be seen, the maximum yield was obtained by using 20 mol% of $Cu(MeCN)_4PF_6$ and the yield continued to be of the same order of magnitude as before, when it was employed 20 mol% of CuI. Thereafter, also the *Z*-isomer **280ba** was employed to test the trifluoromethylation reaction under these modified conditions based on the use of $Cu(MeCN)_4PF_6$. The results were very interesting with the *(Z)*-isomer **280ba**. Indeed, the target product was obtained in 61% with a 12:88 *E:Z* ratio (Scheme 210). Nevertheless, we note a very slight loss of stereochemistry, however these conditions seemed robust enough to start the investigation of the scope.



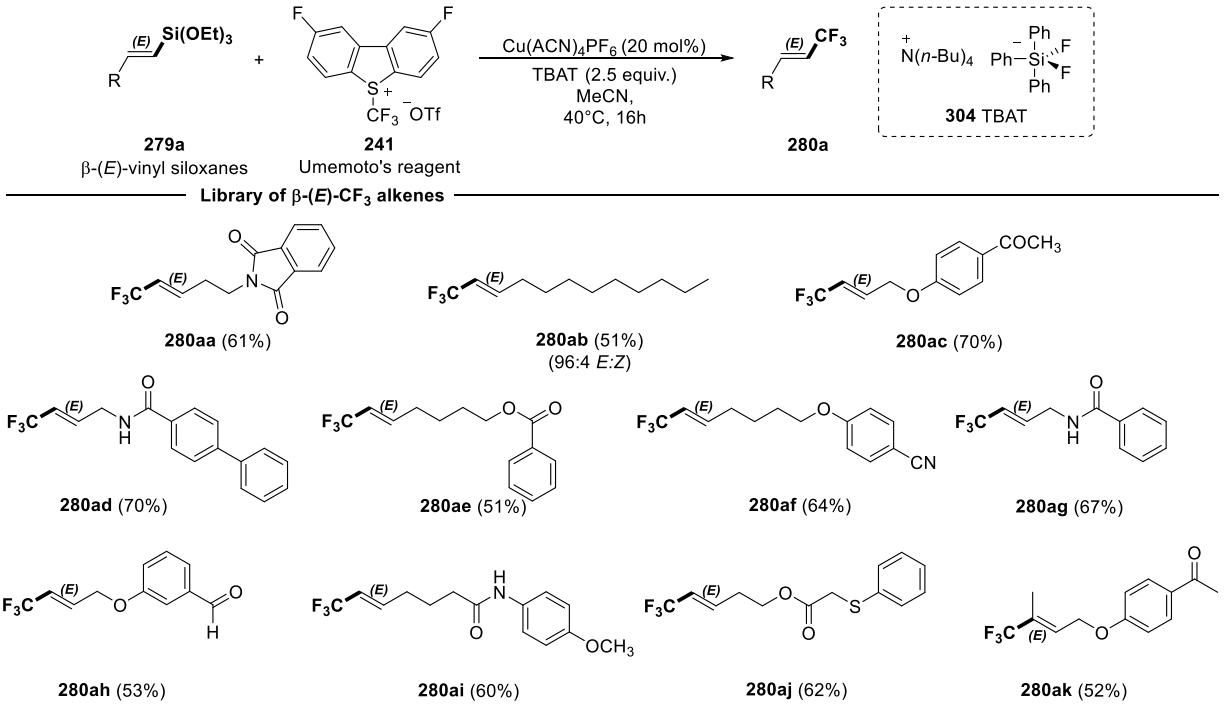
Scheme 210. Trifluoromethylation reaction of the *Z*-isomer with $Cu(MeCN)_4PF_6$.

4.9. Investigation of the scope and applications

Having in hand the optimized reaction conditions, the substrate scope was then investigated with the vinylsiloxanes previously prepared with the aim of delineating both the potential and limitations of our protocol. The scope was studied with respect to the nature of the vinyl siloxanes using the Umemoto's reagent **241** as fluorine source. Thus, we tried to evaluate the robustness of the optimised reaction conditions and evaluate the functional group compatibility using starting material containing different functional groups. Our protocol was then applied onto a library of β-(*E*)-vinylsiloxanes **279a**, β-(*Z*)-vinylsiloxanes **279b** and α-vinylsiloxanes **279c**. The results collected will be described in the following paragraphs.

4.9.1. Preparation of β-(*E*)-trifluoromethylated alkenes

With the optimized reaction conditions in hand, we then explored the substrate scope of the reaction with various β-(*E*)-vinylsiloxanes **279a** coupled with the Umemoto's reagent **241** (Scheme 211). In all cases, β-(*E*)-trifluoromethylated olefins **280aa-280ak** were prepared in moderate to good yields as reported in the following Scheme 211. In most cases, the reaction resulted to be fully stereospecific for the formation of the β-(*E*)-trifluoromethylated olefins, with full retention of the configuration of the double bond of the β-(*E*)-vinylsiloxanes.



Scheme 211. Library of β-(*E*)-trifluoromethylated alkenes.

The reaction is compatible towards a broad range of functional group such as amide **280ad**, **280ag** and **280ai**, phthalimide **280aa**, ester **280ae** and nitrile **280af** in good yields (67%, 61%, 51% and 64%, respectively). To our delight, the protocol resulted to be compatible with sensitive functional groups like aromatic ketone **280ac** and aldehyde **280ah** which have been prepared in acceptable yields in 70% and 53% yield. A lower yield of 51% for the trifluoromethylated olefin derived from 1-dodecyne **280ab** was highlighted. Probably, it is caused by its volatility and low molecular weight, indeed under reduced pressure these compounds can easily evaporate. Additionally, for this substrate we noticed that the trifluoromethylation reaction is not fully stereospecific, but stereoselective for the formation of the β-(*E*)-trifluoromethylated olefin in an acceptable ratio 96:4 *E:Z*. A number of functional groups such as phenyl **280ad**, methoxy **280ai**, and phenyl sulfide **280aj** were all well tolerated resulting in the formation of the target products in moderate isolated yields (70%, 60%, 62%, respectively). In all the cases, the formation of the β-(*E*)-trifluoromethylated olefin has been confirmed by ^{1}H-NMR analysis evaluating the coupling constant (J_{trans} = 14 to 19 Hz) and by ^{19}F-NMR analysis evaluating the chemical shift of the fluorine peak (δ = -64 ppm).

Noteworthy, the purification of trifluoromethylated olefins is the main issue of this reaction, indeed during the course of the reaction are formed traces of unknown by-products with the same polarity of the target product. The chromatographic purifications were not easy at all and many times traces of these impurities contaminated the final products.

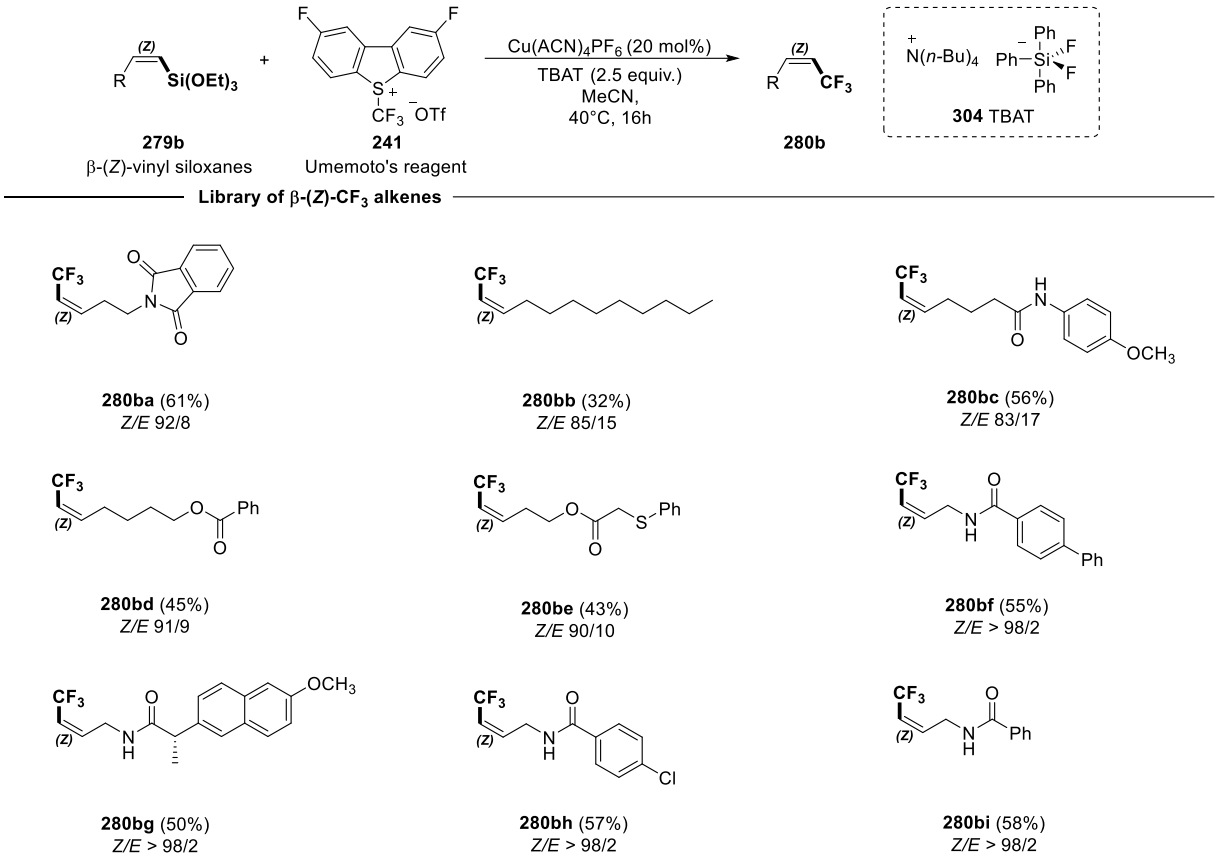
4.9.2. Preparation of β-(*Z*)-trifluoromethylated alkenes

With the optimized reaction conditions in hand, we then explored the substrate scope of the reaction with various β-(*Z*)-vinylsiloxanes **279b** which have been smoothly coupled with the Umemoto's reagent **241** (Scheme 212). For the preparation of a library of β-(*Z*)-trifluoromethylated olefin **280b** we used the β-(*Z*)-vinylsiloxanes **279b** stereochemically pure previously prepared. In all cases, the corresponding trifluoromethylated olefins have been obtained in acceptable to good yields under our catalytic conditions with good Z/E stereoselectivity, ranging from 98:2 to 83:17 as depicted in the following Scheme 212.

Functional groups such as amide **280bf**, **280bh** and **280bi**, ester **280 bd**-**280 be** and phthalimide **280ba** were generally well tolerated. To our delight, the protocol resulted to be also compatible with functional groups like methyl ether **280bc**, thioether **280be** and halogen **280bh** which have been prepared in acceptable yields in 56%, 43% and 57% yield, respectively. The trifluoromethylated olefin derived from 1-dodecyne **280bb** had a lower yield of 32% with a Z/E selectivities of 85/15, which is most likely due to the high volatility of this compound. Furthermore, the reaction was tested onto a Naproxen derivative **280bg**. Naproxen is a nonsteroidal anti-inflammatory drug used to trait pain and inflammatory diseases. To our delight, even using this vinyl siloxane derived from Naproxen was possible to isolate the corresponding trifluoromethylated olefin in 50% yield with a ratio Z/E > 98:2. The reaction resulted to be stereoselective for the formation of the β-(*Z*)-trifluoromethylated olefins **280b**, with retention of the configuration of the double bond. Unfortunately, traces of the corresponding β-(*E*)-trifluoromethylated olefins **280a** have been detected as minor by-products in the NMR spectra. Most likely, a reaction of isomerization occurs under the reaction conditions tested in the presence of copper through a radical mechanism. Thus, traces of β-(*E*)-trifluoromethylated olefin **280a** have been detected in the ^{19}F-NMR, probably is due to β-(*E*)-olefins are thermodynamically more stable than the corresponding β-(*Z*)-isomers. In addition, considering the results collected we have been able to highlight a general trend that is important to underline: the reaction of trifluoromethylation onto β-(*Z*)-vinylsiloxanes **279b** offers lower yields of the target products compared to the reaction performed onto the β-(*E*)-vinylsiloxanes **279a**. This result is probably due to the geometry of the

double bond. Probably, the vinyl copper is much more difficult to form (or to react) due to the geometrical constraints imposed.

In all the cases, the formation of the β-(*Z*)-trifluoromethylated olefin **280b** has been confirmed by ^{1}H-NMR analysis evaluating the coupling constant (J_{cis} = ~ 11 Hz) and by ^{19}F-NMR analysis evaluating the chemical shift of the fluorine peak (δ = -58 ppm). Notably, the primary challenge of this reaction is the purification of trifluoromethylated olefins; indeed, traces of unidentified by-products with the same polarity as the target product are formed during the reaction. Thus, the chromatographic purifications were very difficult to perform.

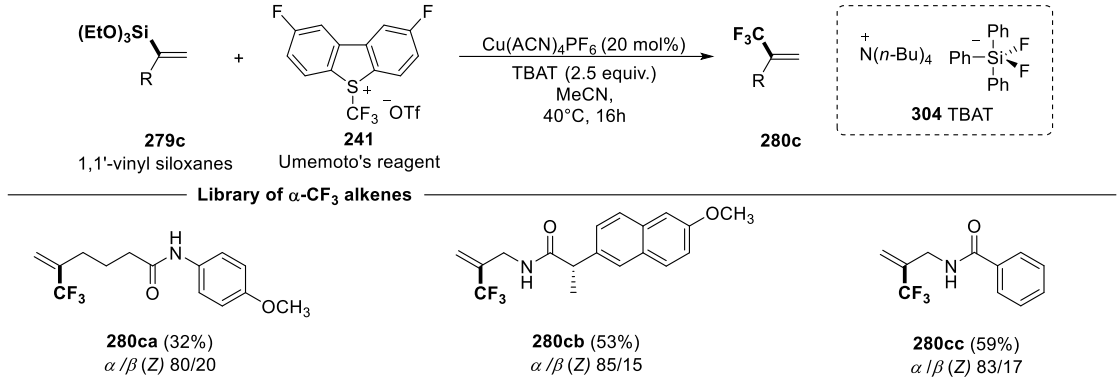


Scheme 212. Library of β-(*Z*)-trifluoromethylated alkenes.

4.9.3. Preparation of α-trifluoromethylated alkenes

Later, we devoted our attention to the preparation of a small library of 1,1'-disubstituted trifluoromethylated olefins **280c** which are known to be more challenging to prepare. α-Vinylsiloxanes **279c** were prepared according to the Trost and Ball protocol. The mixtures of isomers were coupled with the Umemoto's reagent **241** to furnish the corresponding trifluoromethylated olefins **280c** (Scheme 213). The α-trifluoromethylated olefins were prepared in good yield. Specifically, the compound **280cb** and **280cc** were obtained in 59% and 53% of yield, respectively with good α:β(*Z*) selectivities, ranging from 80:20 to 85:15. To our delight, even using a more complex vinyl siloxane derived from Naproxen was possible to isolate the corresponding α-trifluoromethylated olefin in 53% yield and with an acceptable α/β(Z) ratio 85/15. Indeed, compound **280ca** was obtained in a lower yield 32% due to the difficult encountered during the purification in a ratio α:β(*Z*) of 80:20. Unfortunately, for reasons of lack of time the library of α-trifluoromethylated olefins has not been further extended to other substrates.

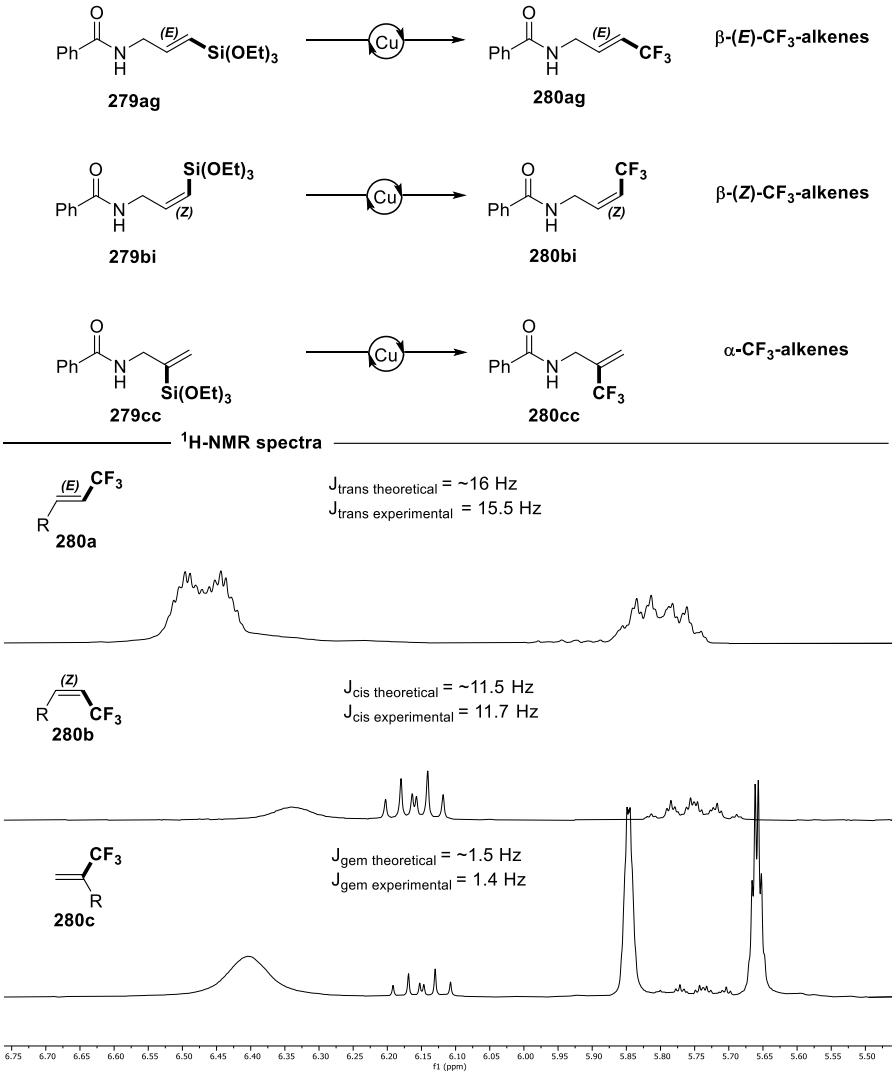
In all the cases, the formation of the α-trifluoromethylated olefin **280c** has been confirmed by ^{1}H-NMR analysis evaluating the coupling constant (J_{cis} = ~ 1.4 Hz) and by ^{19}F-NMR analysis evaluating the chemical shift of the trifluoromethyl peak (δ = -67.5 ppm). Remarkably, the primary challenge of this reaction is the purification of trifluoromethylated olefins; indeed, traces of unidentified by-products with the same polarity as the target product are formed during the reaction. Thus, the chromatographic purifications were very difficult to perform.



Scheme 213. Library of α-trifluoromethylated alkenes.

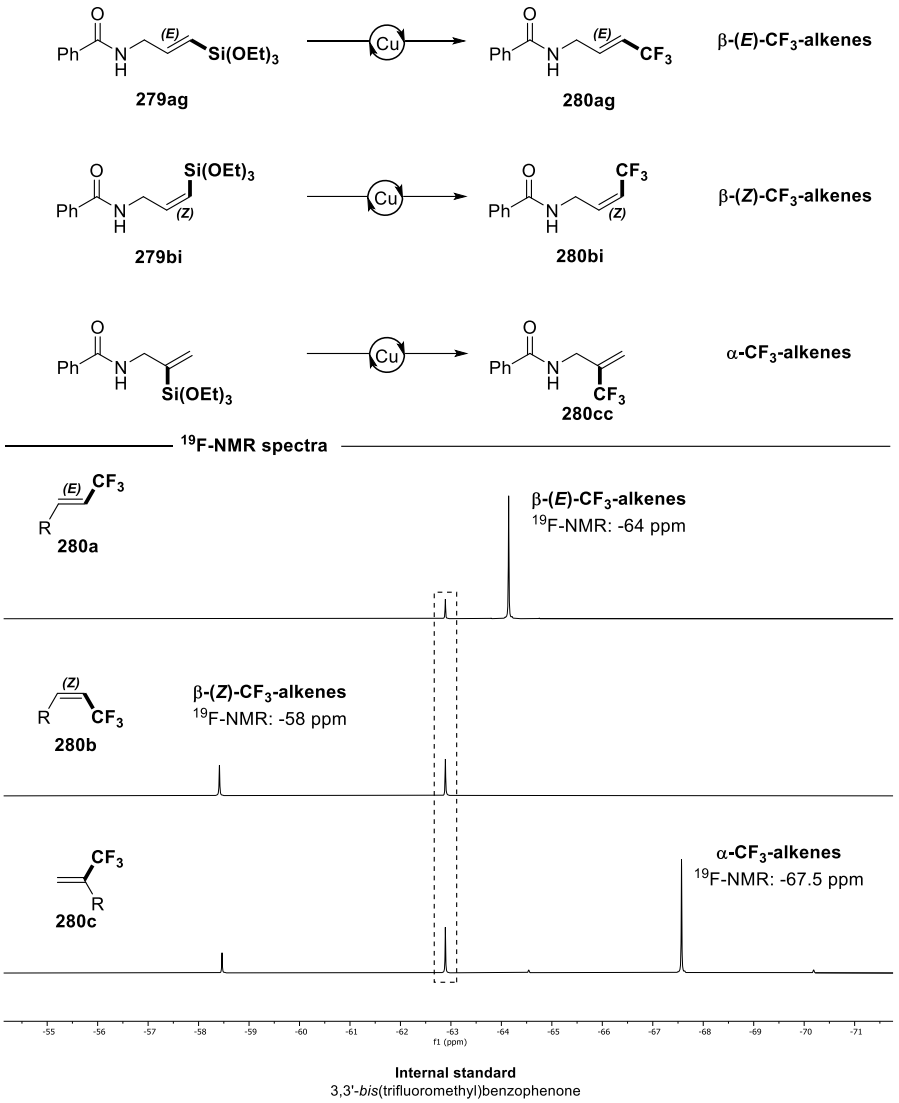
4.9.4. Considerations on trifluoromethylated olefins

In the following Scheme 214, we have collected the ^{1}H-NMR-spectra of a model substrate, named *N*-(4,4,4-trifluorobut-2-en-1-yl) benzamide. Of this compound we have prepared all its possible stereoisomers **280ag**, **280bi** and **280cc** using our copper-catalyzed protocol for the trifluoromethylation of β-(*E*), β-(*Z*) and α-vinylsiloxanes. As can be seen in Scheme 214, through the analysis of the coupling constants, the shape of the peaks, the multiplicity and their chemical shift, it is possible to distinguish the three different stereoisomers simply by analysing the ^{1}H-NMR spectra. Specifically, the β-(*E*)-CF_3-olefin has a coupling constant of 16Hz, the β-(*Z*)-CF_3-olefin has a coupling constant of 11 Hz and the α-CF_3-olefin has a coupling constant of 1.4 Hz. These values are totally in accordance with the values reported in the literature in which $J_{trans} > J_{cis} > J_{gem}$.



Scheme 214. NMR-spectra and coupling constants of the three stereoisomers.

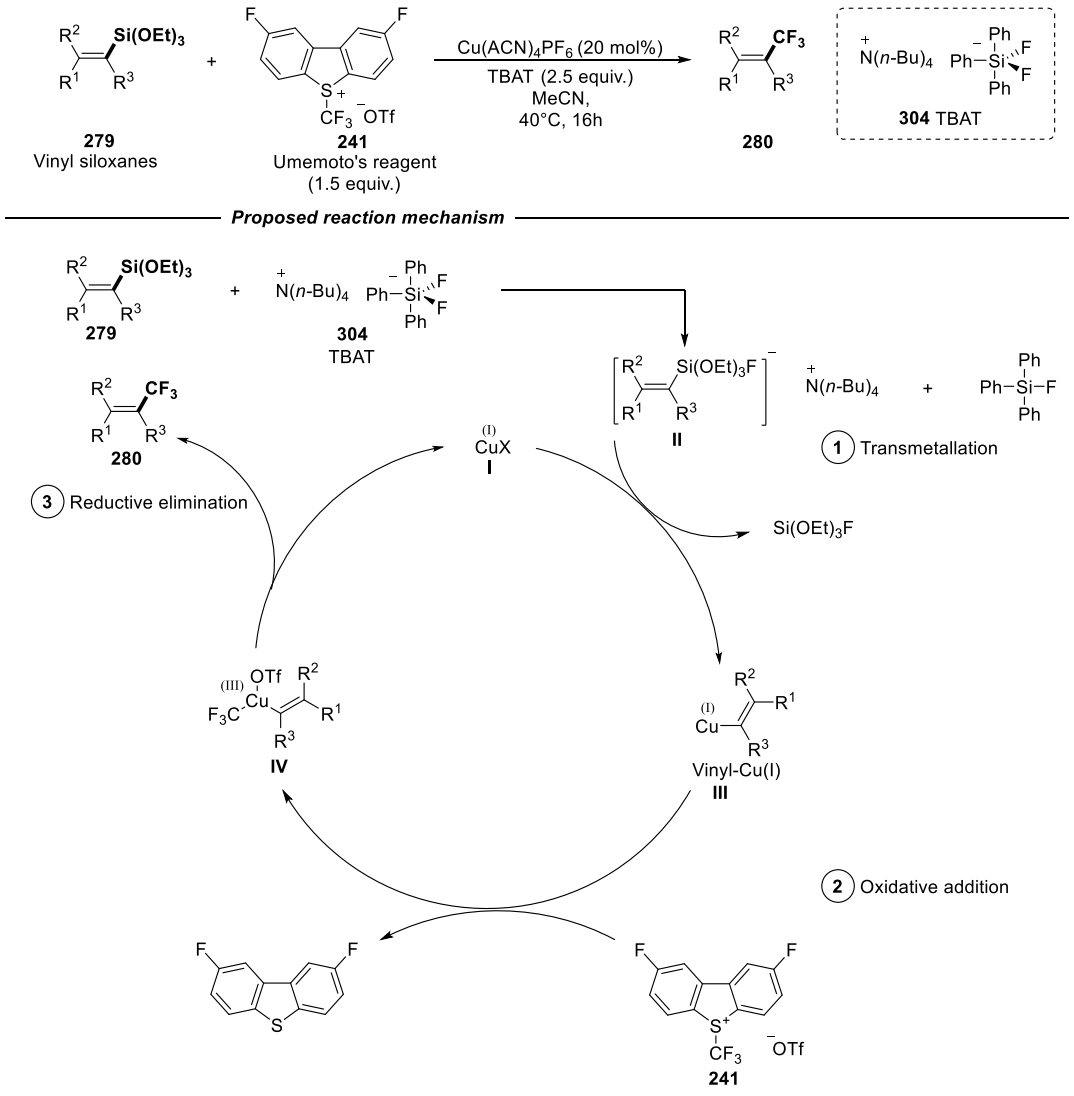
Additionally, the structure of these three different stereoisomers have been confirmed considering the ^{19}F-NMR-spectra. Notably, the β-(*E*)-CF_3-olefin **280ag** has a ^{19}F-NMR signal at -64 ppm, the β-(*Z*)-CF_3-olefin **280bi** has a ^{19}F-NMR signal at -58 ppm and the α-CF_3-olefin **280cc** at -68 ppm. These values allowed us to determine the identity of the stereoisomers formed and to evaluate the configuration of the double bond. Thus, it is possible to establish the following order for the fluorine signals in ^{19}F-NMR: $^{19}F_{\beta\text{-}(Z)} > {}^{19}F_{\beta\text{-}(E)} > {}^{19}F_{\alpha}$ as depicted in the following Scheme 215.



Scheme 215. ^{19}F-NMR-spectra of the three stereoisomers.

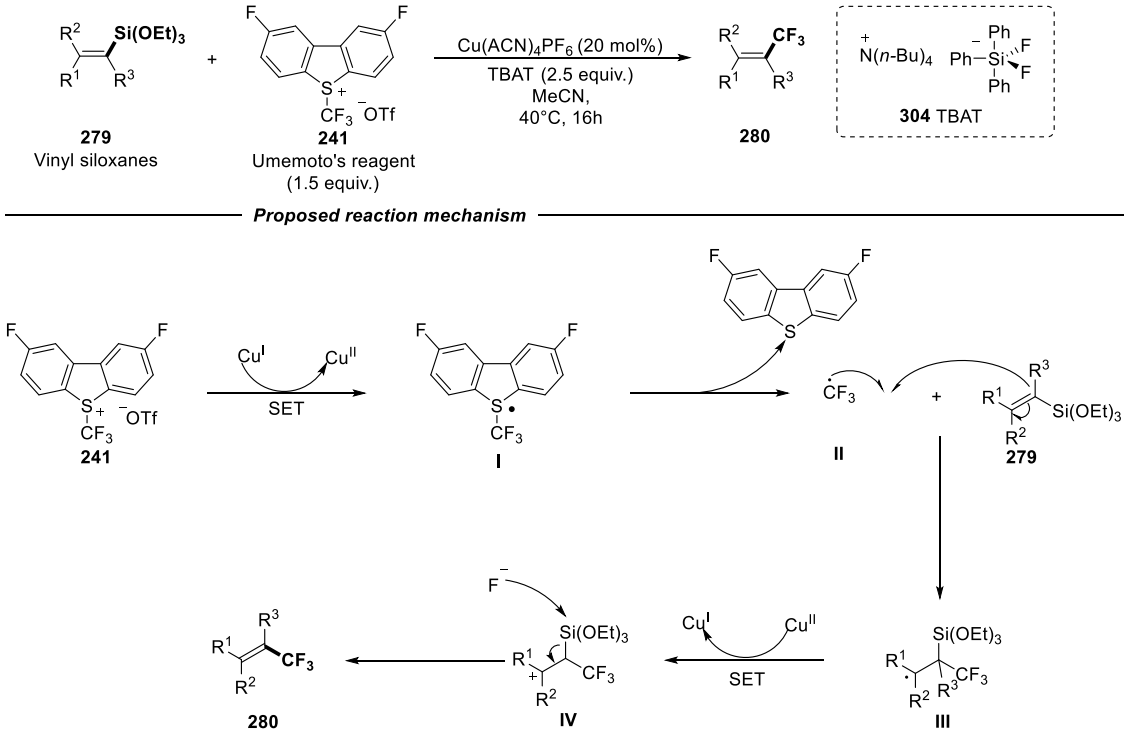
4.10. Proposed reaction mechanism

Considering the experimental results obtained and the literature available in the field of copper-catalyzed cross-coupling reaction, the most invoked mechanism for the cross-coupling investigated might be a Cu(I)/Cu(III) catalytic cycle based on two electrons redox process (Scheme 216). The proposed catalytic cycle is based on the *in-situ* generation and reactivity of vinyl copper(I) complex **III**. These carbon nucleophiles are generated through a range of elementary steps. Firstly, the vinylsiloxanes **279** is activated by the fluoride ion of TBAT **304**. In this way, the first step of the catalytic cycle can start with the transmetallation of the vinyl fragment from Si to the Cu(I) metal center **I**. Thereafter, in an analogous way to the Hiyama coupling, is generated *in-situ* a vinyl-copper species **III**. At this point, the transient vinyl-copper intermediate **III** follows an oxidative addition with the Umemoto reagent **241**, which is a "$^{+}CF_3$" donor. In this way, it is formed a transient Cu(III) complex **III** which following a reductive elimination step release the desired trifluoromethylated olefin **280**. Although the reaction mechanism has not yet been deeply elucidated, the one shown is the most plausible because it enables to rationalize how the reaction product could be formed. Unfortunately, despite the efforts we have made, it has not been possible to demonstrate experimentally the formation of all the reaction intermediates postulated in the catalytic cycle.



Scheme 216. Proposed catalytic cycle for the copper-catalyzed trifluoromethylation of vinyl siloxanes.

It is important to highlight that although a mechanism for the cross-coupling under consideration might be a Cu(I)/Cu(III) catalytic cycle based on two electrons redox process, it is also possible to envision a radical mechanism (Scheme 217). Indeed, the Umemoto reagent **241** can be employed to introduce the trifluoromethyl moiety in the form of "CF_3^+" but also in the form of "CF_3•" when is exposed in the presence of metals or photoredox catalysts as depicted in following Scheme 217.[265] Thus, Cu(I) can furnish an electron to the Umemoto's reagent **241** through a single electron transfer step (SET) and acts as a reducing agent. In this way, it is formed a poorly stable radical species **I** which evolve, after homolytic cleavage, to the corresponding "CF_3•" **II** radical and dibenzotiophene. Thereafter, the "CF_3•" radical adds onto the double bond of the vinylsiloxanes **279** to generate a radical in the β-position **II**. By reduction of the Cu(II) previously formed, it is generated a highly stabilized carbocation **IV**. Finally, the fluoride can activate the organosilicon intermediate **IV** and promote an elimination step generating the target trifluoromethyl olefin **280**.



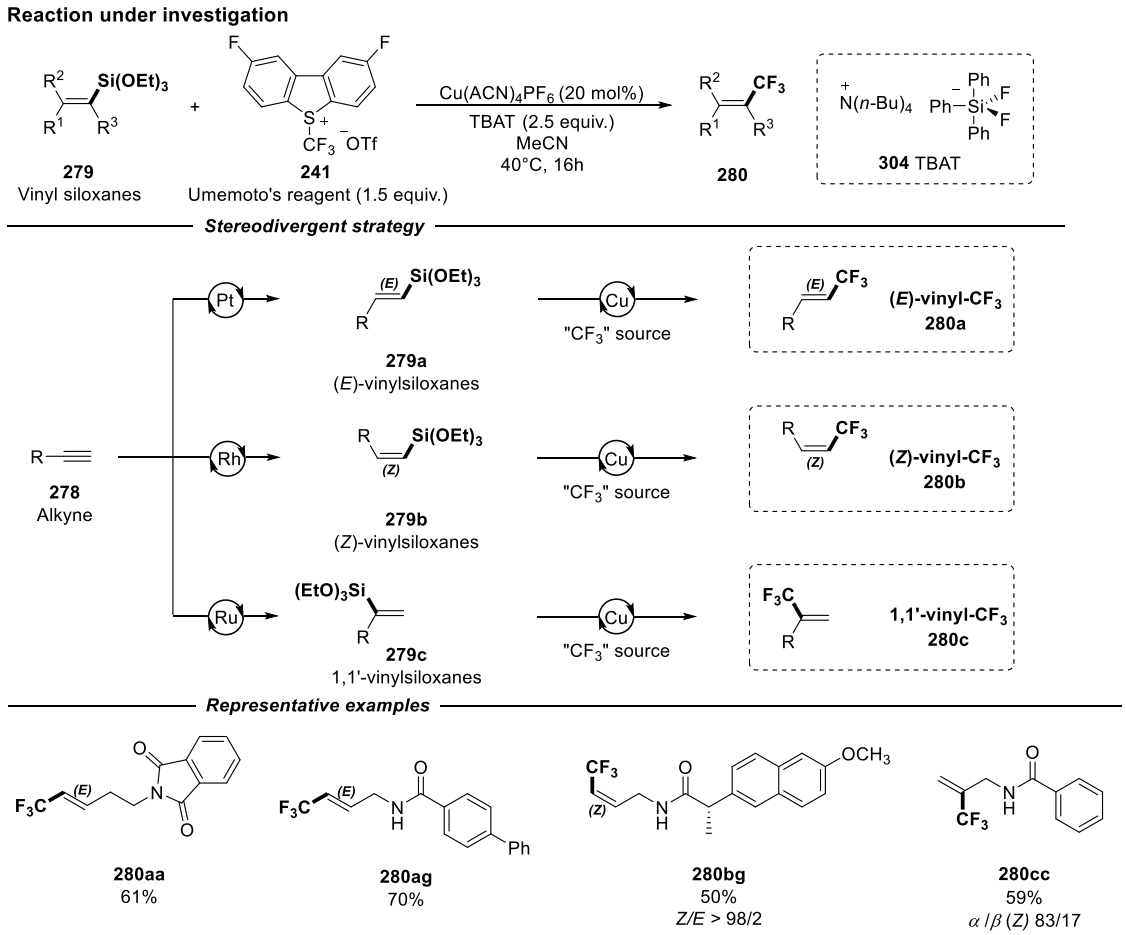
Scheme 217. Proposed radical pathway for the copper-catalyzed trifluoromethylation of vinyl siloxanes.

Clearly, both mechanisms proposed are valid and allow to rationalize the formation of the product, however for time restrictions was not possible to clarify experimental support for the suggested mechanisms. In our laboratories further studies are still ongoing to rationalize the mechanism and identifying the intermediates.

[265] (a) Dubinina, G. G.; Furutachi, H.; Vicic, D. A. *J. Am. Chem. Soc.* **2008**, *27*, 8600–8601. (b) Mizuta, S.; Verhoog, S.; Engle, K. M.; Khotavivattana, T.; O'Duill, M.; Wheelhouse, K.; Rassias, G.; Medebielle, M.; Gouverneur, V. *J. Am. Chem. Soc.* **2013**, *135*, 2505–2508. (c) Zhang, C. *Org. Biomol. Chem*. **2014**, *12*, 6580–6589.

4.11. Conclusion

In conclusion, during the investigation that was carried out we have tried to develop a novel, efficient and straightforward method for the synthesis of trifluoromethylated olefins **280** using vinylsiloxanes **279** as starting material. The vinylsiloxanes were prepared in a stereodivergent manner from alkynes using Pt, Ru, and Rh catalyst. Thus, in this chapter we reported a novel stereodivergent copper-catalyzed cross coupling for the trifluoromethylation of *trans*- **279a**, *cis*- **279b**, as well as challenging 1,1'-disubstituted vinylsiloxanes **279c** under mild reaction conditions (Scheme 218). First of all, an extensive optimization was required when we initiated our studies, this optimization being based on iterative screenings of the reaction parameters such as copper(I), catalytic loading, temperature, equivalent of trifluoromethylating reagent etc. After numerous attempts, it was found out that vinylsiloxanes **279** could be trifluoromethylation with the Umemoto's reagent **241** (1.5 equiv.) when reacting with 20 mol% of $Cu(ACN)_4PF_6$ in presence of TBAT **304** as non-hygroscopic fluoride donor at 40°C in acetonitrile.



Scheme 218. Copper-catalyzed trifluoromethylation of vinylsiloxanes with the Umemoto's reagent.

Once we optimized the reaction conditions, we then assessed the scope and limitations of our catalytic system. A systematic variation of the identity of the vinyl siloxanes **279** was carried out, which gratifyingly revealed a reasonably wide substrate range. Notably, the trifluoromethylation was carried out on β-(*E*)-vinyl siloxanes **279a**, β-(*Z*)-vinyl siloxanes **279b** and α-vinyl siloxanes **279c**. Through the identified reaction conditions, it was possible to prepare a library of 22 examples of trifluoromethylated olefins with the β-(*E*), β-(*Z*) and α-configuration of the double bond. Our protocol resulted to be fully compatible towards a broad range of functional groups such as amides, esters and nitriles. The target products have been

prepared in good yields. To our delight also sensitive functional groups like ketones and aldehydes have been fully compatible with our methods, although lower yields were recorded.

Trifluoromethylated olefins were prepared in moderate to good yields. In most cases, the reaction resulted to be fully stereospecific for the formation of the β-(*E*)-trifluoromethylated olefins **280a**, with full retention of the configuration of the double bond of the β-(*E*)-vinylsiloxanes **279a**. For what concern, the preparation of β-(*Z*)-trifluoromethylated olefins **280b** the yields are lower compared to the ones of the β-(*E*)-olefins, most likely is due to the configuration of the double bond. Additionally, the reaction is not fully stereospecific, but stereoselective for the *Z*-stereoisomer. Finally, we have also prepared few examples of α-trifluoromethylated olefins **280c**, which are more challenging to prepare with the traditional methods available in the literature. Here, the reaction promotes the formation of the α-stereoisomer, although traces of the *Z*-stereoisomer have been detected in the final products. These compounds have been fully characterized through ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, IR and HRMS. In the future, we are interested to apply this methodology to other electrophiles. Indeed, it is possible to imagine the preparation of new functionalized olefins through the reaction of vinylsiloxanes with other electrophiles using copper sources as reaction catalysts. In this way, simply adapting the identified reaction conditions and changing the nature of the electrophiles it will be possible to obtain functionalized olefins of significant synthetic interest.

General conclusions

In conclusion, the research work carried out during the course of this PhD thesis is devoted to the development of new copper-catalyzed cross-coupling reactions, an emerging area of homogeneous catalysis based on the use of copper catalysts capable of promoting new chemical transformations.

The main objective of this research project has been the development of new catalytic systems able to shorten conventional synthetic pathways used for the preparation of organic compounds, allowing a reduction of time and costs required for the preparation of target molecules. Therefore, this research work reflects the need of the scientific community to continue to develop new, more general, more selective and environmentally friendly processes to meet the growing demand of new catalytic systems and technologies. Among all metals that can efficiently catalyze a range of organic reactions, copper has been extensively studied and investigated during the course of this thesis, for various reasons. These include the low cost of this metal, which is actually one of the cheapest that can be used in catalysis, the limited toxicity of most copper complexes, and, more importantly, the broad range of transformations that can be efficiently catalyzed with copper-based catalysts.

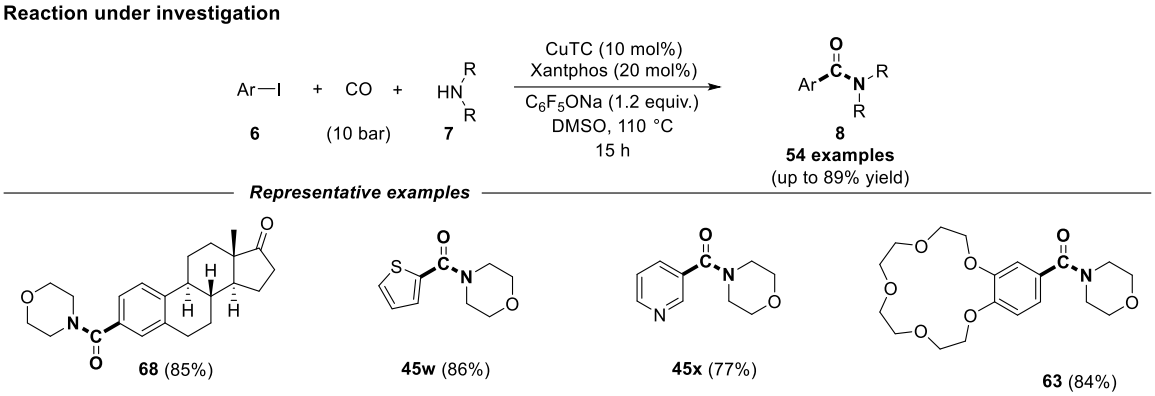
Specifically, the research work carried out during the course of this thesis is divided into two distinct parts which have been focused on the development of new copper-catalyzed carbonylative cross-coupling reactions and the development of a new copper-catalyzed cross-coupling for the trifluoromethylation of vinylsiloxanes.

- **Development of a novel copper-catalyzed carbonylative cross-coupling of aryl iodides and amines**

The first project under investigation was dedicated to the development of a novel copper-catalyzed carbonylative cross-coupling of aryl iodides and amines, a chemical transformation unexplored in literature. Indeed, most of the aminocarbonylative cross-coupling reported are based on the use of palladium, an expensive noble metal. For the development of this ambitious project, an extensive optimization was required based on iterative screenings of all reaction parameters. After numerous unsuccessful attempts, it was found out that 4-iodotoluene could be smoothly carbonylated with morpholine when reacting with 10 mol% of Liebeskind's catalyst (CuTC), 20 mol% of Xantphos and a slightly excess of sodium pentafluorophenoxide in DMSO at 110 °C under a pressure of 10 bar of carbon monoxide (Scheme 222). Once we optimized the reaction conditions, we then assessed the scope and limitations of our system for the copper-catalyzed aminocarbonylation of a series of aryl iodides and amines. Therefore, a systematic variation of the aryl halide and amine natures was carried out which allowed us to prepare a library of 54 examples of benzamides.

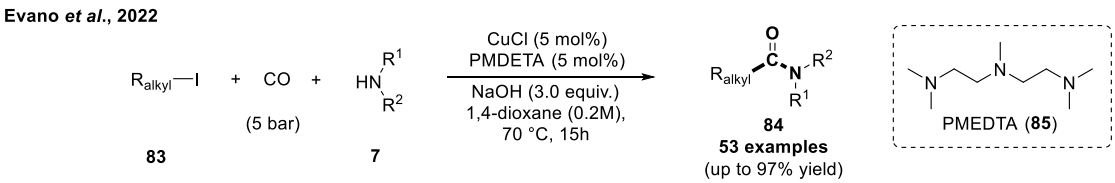
Regretfully, at the end of this project traces of palladium were found inside the CuTC (copper(I) thiophene-2-carboxylate) batch used through ICP-MS analysis for a value between 35 and 37 ppm. This finding, together with the addition of reproducibility issues brought on by the use of a high purity CuTC (99.99%), caused the project to be discontinued. Under the reaction conditions of the described protocol, the palladium traces discovered in the CuTC batch most likely sufficed to catalyze the aminocarbonylation reaction with high yields.

Therefore, despite the efforts made to develop a new cross-coupling reaction, it is evident that the original goal of this research project has not been accomplished. Indeed, being unable to reproduce the results collected it was decided it would be more reasonable to stop this project. However, it is extremely important to remember that these kinds of situations are very common in the field of homogenous catalysis, and that whenever they do arise, it is important to view them as opportunities, significant and constructive turning points. In fact, in this way it was possible to prevent the publication and diffusion of experimental results contaminated with palladium within the scientific community, thus raising problems of irreproducibility.



Scheme 222. Copper-catalyzed carbonylative arylation of alkenes with aryl iodonium salts.

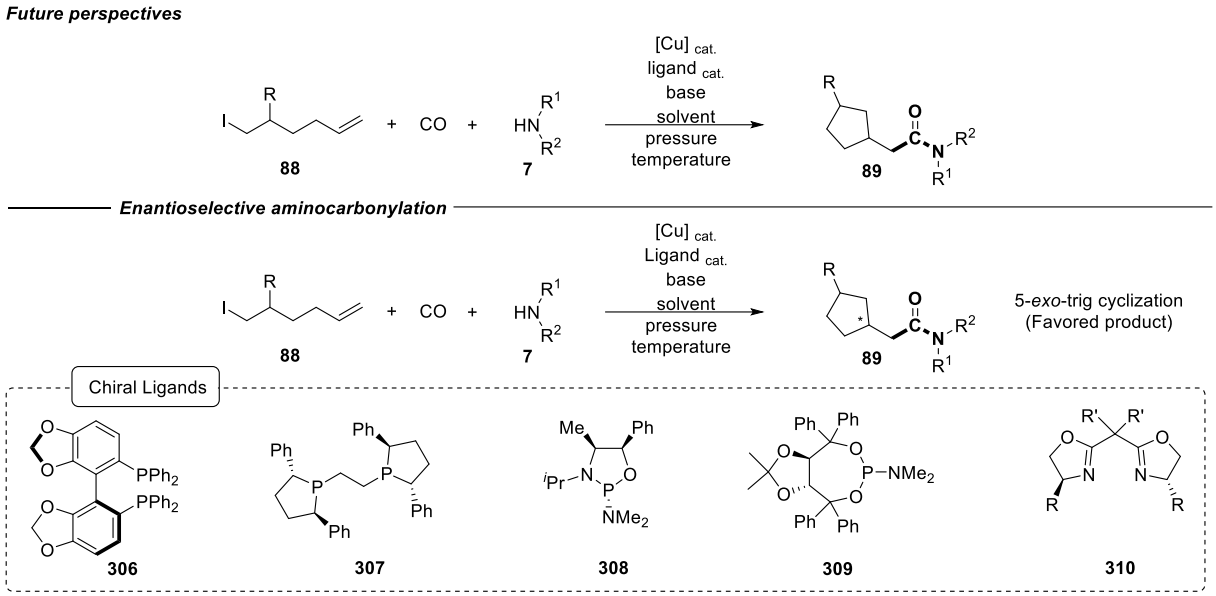
Later, our research group, continued to investigate this research field with the development of a new copper-catalyzed carbonylative cross-coupling reaction between amines **7** and alkyl iodides **83** (Scheme 223).[266] By using a catalytic system composed of copper(I) chloride and PMDETA **85** in presence of sodium hydroxide under a pressure of 5 bar of carbon monoxide. With this protocol, a broad range of alkyl iodides and amines can be successfully coupled to form the corresponding amides **84**.



Scheme 223. Copper-catalyzed carbonylative cross-coupling of alkyl iodides and amines.

In the future, under the same reaction conditions, it can be envisioned to perform an intramolecular carbonylation of alkyl iodides **88** to prepare cyclic amides **89** (Scheme 224). Indeed, starting from a properly functionalized alkyl iodide and operating under high dilution conditions it is possible to envision an intramolecular and promote the formation of the target cyclic amide **89**. Furthermore, it is also possible to envision an enantioselective intramolecular version of the aminocarbonylation cross-coupling developed in our laboratories, in which an attempt will be made to promote asymmetric induction of the new stereocenter formed during the intramolecular radical cyclization with a 5-*exo*-trig pathway.

[266] Ling, J.; Voisine, A. B.; Journot, G.; Evano, G. *Chem. Eur. J.* **2022**, *28*.



Scheme 224. Copper-catalyzed carbonylation for the preparation of cyclic amides.

Undoubtedly, for the successful development of an enantioselective aminocarbonylative cross-coupling will be required to identify the optimal copper source and a chiral ligand capable of promoting the reaction with good yields and a high level of enantioselection. In the literature, many examples of asymmetric reactions are already available suggesting the use of chiral ligands such as phosphines (**306**-**307**),[267] phosphoramidites (**308**-**309**),[268] and bisoxazolines (**310**).[269] Among all the examples of asymmetric reactions documented in the literature, enantioselective carbonylative cross-coupling reactions are still uncommon and this field still remains unexplored. Therefore, all the ligands previously mentioned will be screened in order to develop an enantioselective version capable of inducing high levels of enantioselection. In this way it will be possible to develop an enantioselective intramolecular version of the aminocarbonylation reaction developed in our laboratories to prepare enantiomerically pure amides.

A further future perspective that can be envisioned is to combine the Finkelstein reaction with the copper-catalyzed aminocarbonylativative cross-coupling developed in our laboratories (Scheme 225). The classic Finkelstein reaction entails the conversion of alkyl chlorides or alkyl bromides (**325**) to alkyl iodides by treatment with sodium iodide.[270] The key point for the success of this reaction is the addition of sodium iodide (NaI) to the reaction system, which leads to the formation of activated alkyl iodides as intermediates. This future perspective may be very interesting for promoting the extension of the aminocarbonylative cross-coupling developed on alkyl bromides and chlorides as well.

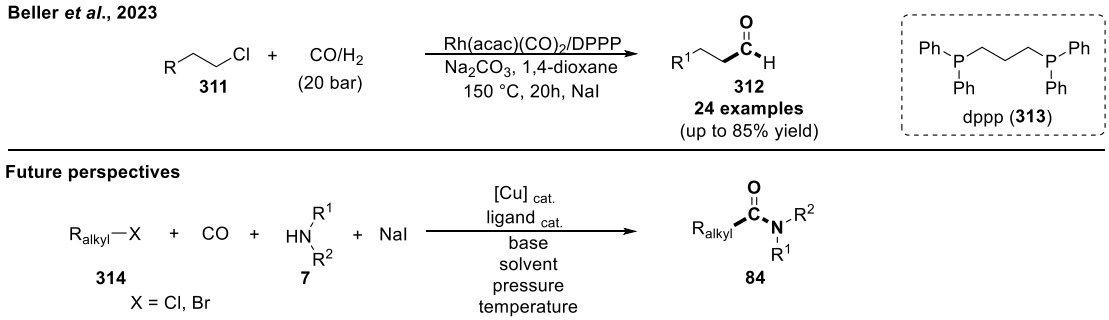
[267] a) Yuan, Y.; Zhao, F.; Wu, X. F. *Chem. Sci*. **2021**, *12*, 12676–12681. b) Yuan, Y.; Wu, F. P.; Schuenemann, C.; Holz, J.; Kamer, P. C.; Wu, X. F. *Angew. Chem. Int. Ed.* **2020**, *59*, 22441–22445.

[268] a) Bertozzi, F.; Pineschi, M.; Macchia, F.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Org. Lett*. **2002**, *16*, 2703–2705. b) Piarulli, U.; Claverie, C.; Daubos, P.; Gennari, C.; Minnaard, A. J.; Feringa, B. L. *Org. Lett*. **2003**, *23*, 4493–4496. c) Šebesta, R; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Adv. Synth. Catal*. **2007**, *349*, 1931 – 1937.

[269] a) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693. b) Bigot, A.; Williamson, A. E.; Gaunt, M. *J. Am. Chem. Soc*. **2011**, *133*, 13778–13781. c) Harvey, J. S.; Simonovich, S. P.; Jamison, C. R.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2011**, *35*, 13782–13785.

[270] Evano, G.; Nitelet, A.; Thilmany, P.; Dewez, D. F. *Front. Chem*. **2018**, *6*, 114–118.

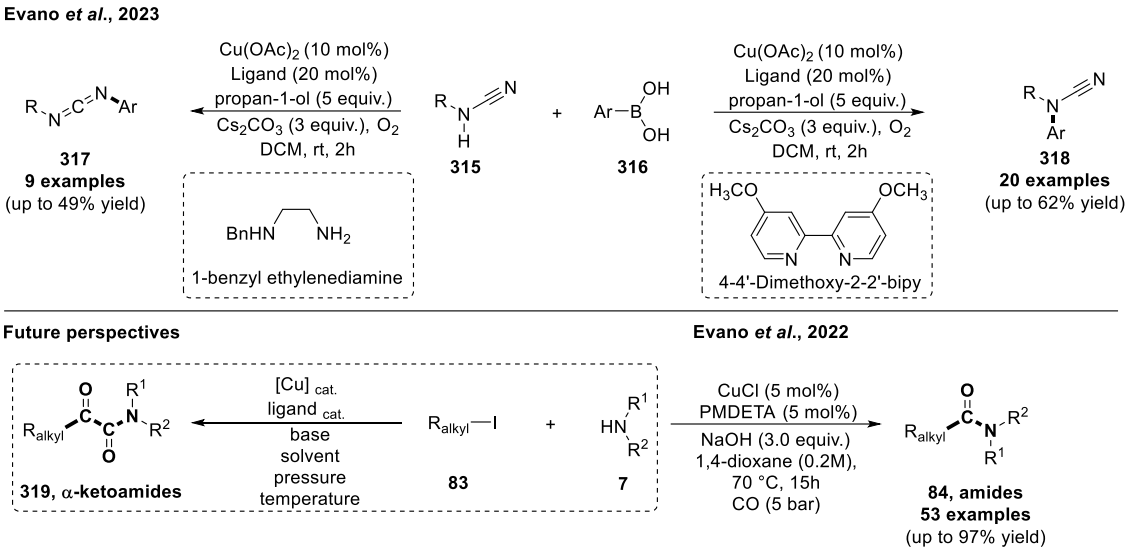
Because of their greater commercial abundance and lower prices, these substrates are frequently utilized as alternatives to the corresponding alkyl iodides. Unfortunately, these compounds have higher C–X bond dissociation energy and are less susceptible to activation, which is often translated into a reduced reactivity in carbonylative cross-coupling reactions. Therefore, it may be very attractive to optimize a novel catalytic system based on the addition of sodium iodide to promote the Finkelstein reaction on alkyl bromides and chlorides before the copper-catalyzed aminocarbonylative cross-coupling. Recently, an example of this synthetic strategy has been described by Beller and co-workers with the development of the first rhodium-catalyzed formylation of non-activated alkyl chlorides **311** with syn gas (H_2/CO) which allowed to produce aliphatic aldehydes **312** in high yields. Rh(acac)$(CO)_2$ in the presence of 1,3-bisdiphenylphosphinopropane (**313**, DPPP) was found to be the most active catalyst system for this transformation.[271] As we have assumed, for this transformation the addition of sodium iodide (NaI) to the reaction system lead to the *in situ* formation of alkyl iodides as reactive intermediates demonstrating the applicability also on our model catalytic system.



Scheme 225. Combination of the Finkelstein reaction and the copper-catalyzed aminocarbonylative cross-coupling.

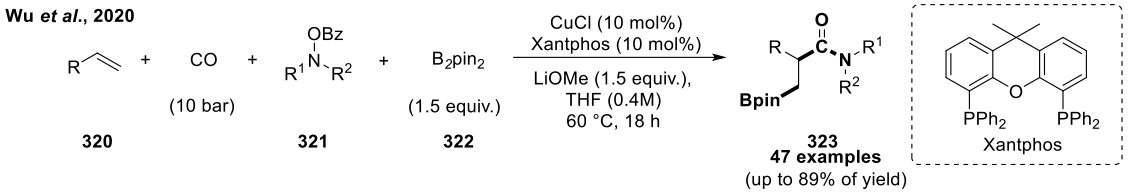
In addition, another interesting future perspective that can be developed is to adapt the reaction conditions developed in our laboratories for the aminocarbonylative cross-coupling of alkyl iodides and amine for the preparation of α-ketoamides **319** (Scheme 226). The formation of the product of double carbonylation can be obtained by the double insertion of two molecules of carbon monoxide on the alkyl iodide. To promote the formation of α-ketoamides **319**, it may be necessary to increase the pressure of carbon monoxide and/or change the identity of the copper salt and ligand employed. This divergent strategy has already been widely used in our laboratory in the research project developed by Jiaqi Fang, who has described for the first time a novel copper-catalyzed, ligand-controlled N(sp^3)- or N(sp)- selective arylation of cyanamides **315**.[272] The authors described an efficient copper-catalyzed ligand-controlled Chan-Lam-Evans arylation of cyanimides for the divergent preparation of *N*-aryl cyanamides **318** or dissymmetric carbodiimides **317**. As can be shown by this fascinating paper, the nature of the ligand, either a bipyridine or a diamine, controls the product distribution and thus offers a divergent entry to useful building blocks from readily available starting material.

[271] Wang, P.; Wang, Y.; Neumann, H.; Beller, M. *Chem. Eur. J.* **2023**, *29*, e202203342.
[272] Fang, J.; Bekkouch, O.; Zeiser, G.; Zubchuk, Y.; Bizet, V.; Blanchard, N.; Evano, G. *Org. Lett.* **2023**, *25*, 6446–6451.



Scheme 226. Copper-catalyzed aminocarbonylative cross-coupling for the preparation of α-ketoamides.

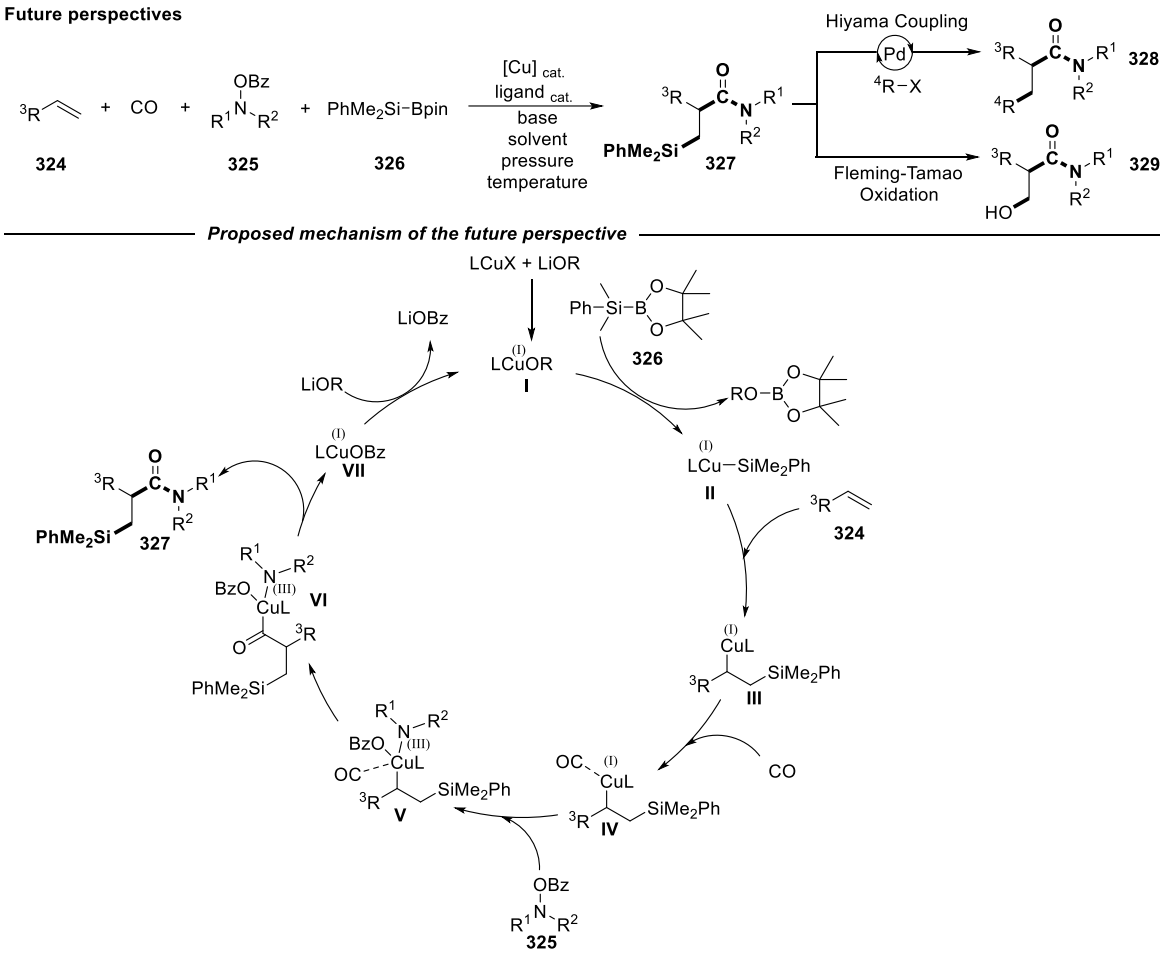
In addition, an interesting research perspective that can be investigated in the future concerns the carbonylation of alkenes using $PhMe_2SiBpin$ as reagent. Indeed, as evidenced by a careful bibliographical analysis in the literature is still not described the copper-catalyzed carbonylative silylamidation of olefins with hydroxylamines as electrophiles (Scheme 227). Indeed, the bibliographical analysis conducted in the first chapter of this PhD thesis revealed that there are no protocols available in the literature for the preparation of β-silyl amides, suggesting that their synthesis is still a relatively unexplored area of copper catalysis. The only similar reported example is the one described in 2020 by the Wu group which has reported the first copper-catalyzed carbonylative borylamidation of olefins **320** with hydroxylamines as electrophiles **321** to furnish the corresponding amides **323** using a combination of 10 mol% of CuCl/Xantphos under 10 bar of carbon monoxide and 1.5 equiv. of B_2pin_2 (Scheme 227).[273]



Scheme 227. Copper-catalyzed carbonylative borylamidation of olefins with hydroxylamines.

Therefore, it is possible to envision a similar reaction mechanism that leads to the preparation of β-silyl amides by using (dimethylphenylsilyl)boronic acid pinacol ester (**326**, $PhMe_2SiBpin$, Scheme 228) at the place of bis(pinacolato)diboron (**322**, B_2pin_2). The proposed reaction pathway starts with the formation of a $LCuSiMe_2Ph$ complex **II** which reacts with the alkene to generate a β-silylalkylcopper **III** intermediate which coordinate carbon monoxide **IV**. At this point, an oxidative addition with protected hydroxylamine (R_2NOBz) forms an alkyl-copper(III) intermediate **V** which evolve to acyl-copper(III) **VI** through the CO-insertion into the C-Cu bond. Finally, the target β-silyl amide is obtained with a reductive elimination which regenerates the copper complex **VII** required for the next catalytic cycle. The preparation of β-silyl amides **323** is of high interest due to these substrates can be further functionalized with the Hiyama cross-coupling and the Tamao-Fleming oxidation, thus allowing the preparation of highly functionalized amides **328** and β-hydroxy amides **329**, respectively.

[273] Wu, F. P.; Holz, J.; Yuan, Y.; Xiao, F. W. *CCS Chem*. **2020**, *2*, 2643–2654.

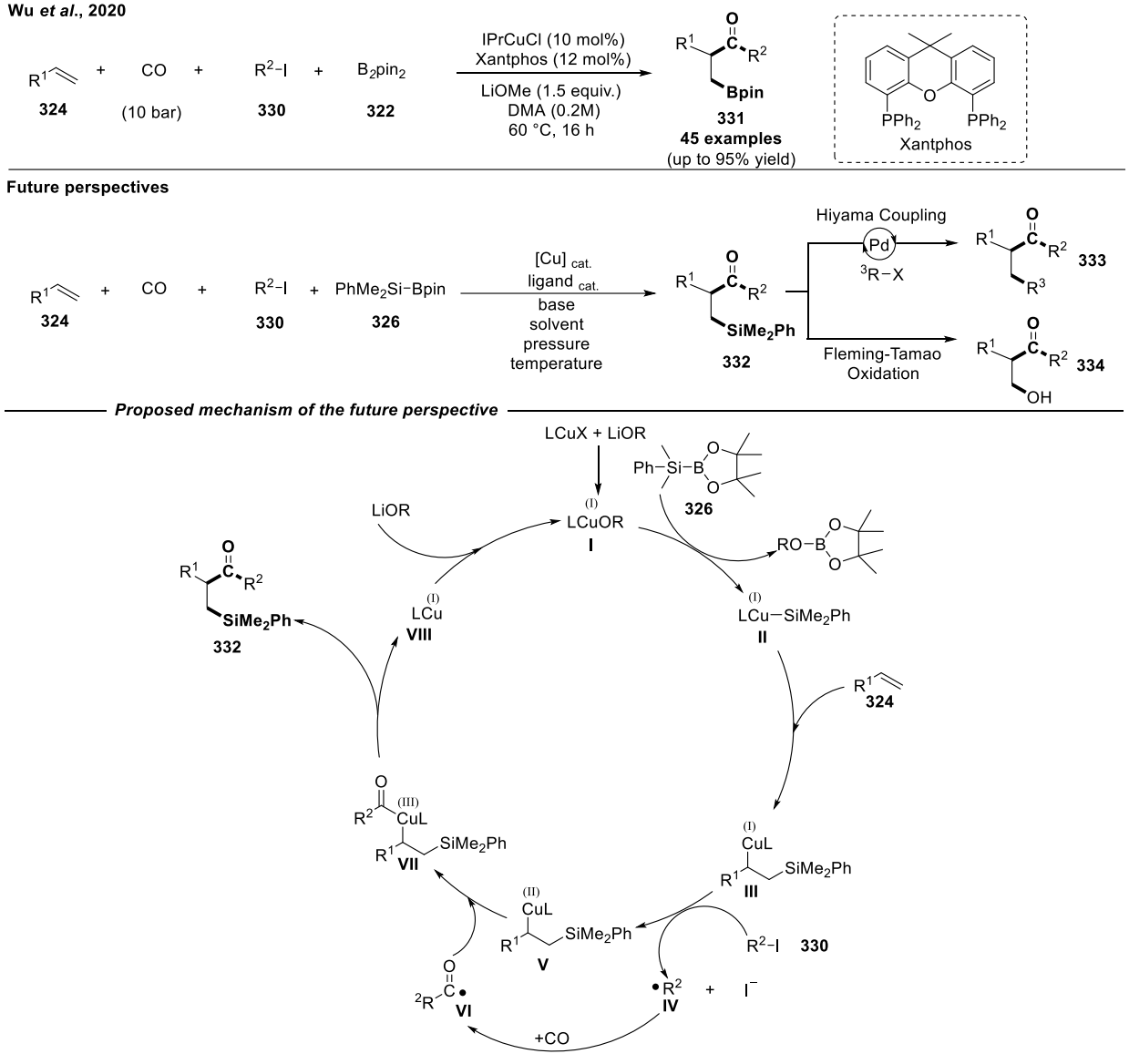


Scheme 228. Copper-catalyzed aminocarbonylative cross-coupling for the preparation of β-silyl amides.

In the future, this synthetic strategy in which (dimethylphenylsilyl)boronic acid pinacol ester (**326**, $PhMe_2SiBpin$) replaces bis(pinacolato)diboron (**322**, B_2pin_2) can be also exploited for the preparation of β-silyl ketones **332** (Scheme 229). Indeed, the preparation of β-silyl ketones have not yet been documented through the development of copper-catalyzed carbonylative cross coupling, therefore it can be an emerging area to investigate. The development of this transformation will certainly promote the development of an unexplored area in copper catalysis in close contact with silicon chemistry. In a related approach, the Wu group in 2020 described a Cu-catalyzed borocarbonylative four component cross-coupling of alkenes **324** with alkyl halides **330** for the synthesis of β-boryl ketones **331**.[274] The reaction is performed with a catalytic system based on 10 mol% of IPrCuCl and 12 mol% of Xantphos under 10 atm of carbon monoxide and using an excess of B_2pin_2 (**322**, 2.0 equiv.). Therefore, it is possible to envision a similar reaction pathway that leads to the preparation of β-silyl ketones **332** by using (dimethylphenylsilyl)boronic acid pinacol ester (**326**, $PhMe_2SiBpin$) as reagent. A plausible catalytic cycle starts with the formation of a $LCuSiMe_2Ph$ complex **II**. Thus, the $LCuSiMe_2Ph$ species **II** is involved in a reaction of silylcupration of the olefin to obtain the intermediate **III**. At this point, an alkyl radical **IV** is generated from the reaction of the copper(I) complex **III** and the alkyl iodide to provide a copper(II) complex **V** with a single electron transfer process. Then, the radical species **IV** undergoes carbonylation to furnish the acyl radical species **VI**, which reacts with the copper(II) complex **V** to form the copper (III) intermediate **VII**. Finally, this species highly reactive **VIII** regenerates the Cu(I) catalyst through a reductive elimination which furnish the desired β-silyl ketone **332**. The preparation of β-silyl ketones is of high interest because also these substrates can be further functionalized with the

[274] Wu, F. P.; Yuan, Y.; Schünemann, C.; Kamer, P. C. J.; Wu, X.F. *Angew. Chem. Int. Ed.* **2020**, *59*, 10451–10455.

Hiyama cross-coupling and the Tamao-Fleming oxidation, thus allowing the preparation of highly functionalized ketones **340** and β-hydroxy ketones **341**, respectively (Scheme 229).

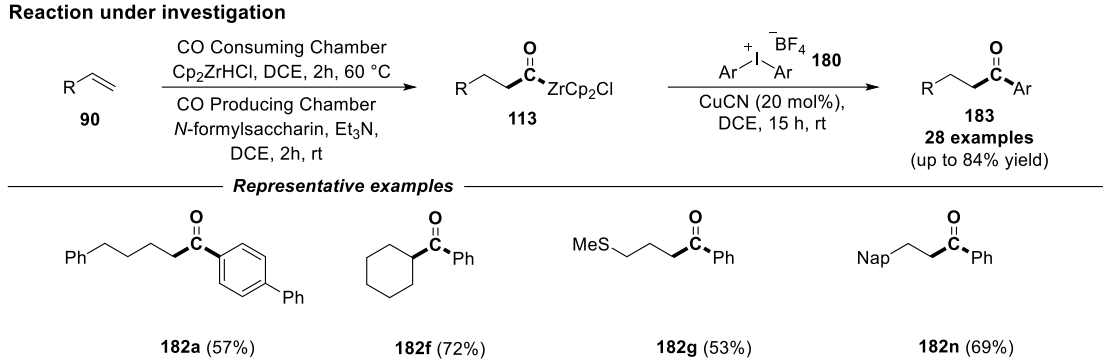


Scheme 229. Copper-catalyzed carbonylative cross-coupling for the preparation of β-silyl ketones.

- **Development of a novel copper-catalyzed carbonylative cross-coupling of acyl zirconium complexes and aryl iodonium salts**

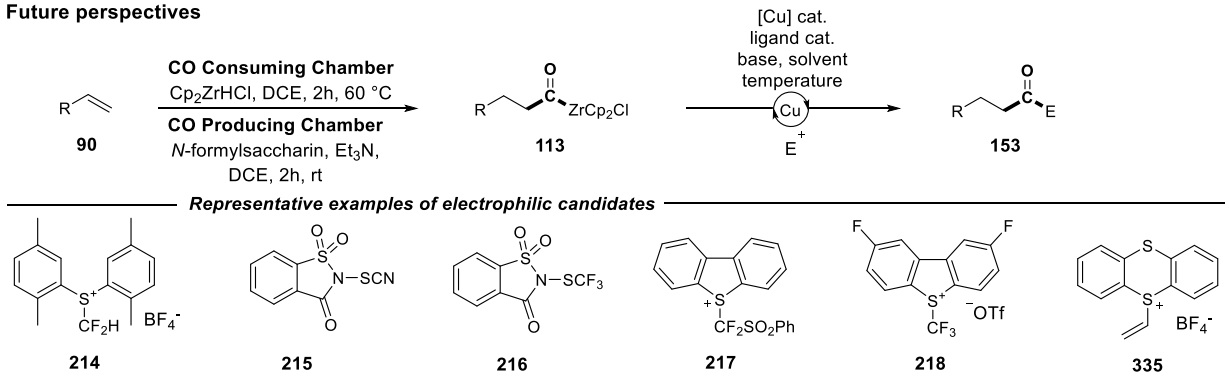
In the second project investigated we have developed an efficient cross-coupling between acylzirconocenes, readily available starting materials conveniently prepared by hydrozirconation of alkenes **90** and a subsequent carbonylation with carbon monoxide, and diaryliodonium tetrafluoroborates **180** (Scheme 230). This procedure enables the synthesis of a broad variety of alkyl-aryl-ketones **183** upon simple catalysis with copper cyanide without the need of additional ligands and only requires a low pressure of carbon monoxide generated *in situ*, in a two-chamber reactor, from *N*-formylsaccharin. In addition to providing a straightforward entry to alkyl-aryl-ketones **183**, it also brings useful insights into the unique reactivity of acylzirconocenes under copper catalysis. Specifically, this work highlights the long-neglected potential of acyl zirconium complexes and allows the execution of carbonylative cross-coupling using an easy to handle and inexpensive two-chamber system. Therefore, the development of this new technology will

certainly stimulate and promote the interest of the scientific community in the development of new and innovative carbonylative cross-couplings using acyl zirconium complexes **113**, an efficient coupling partner neglected for too long. In the future, under similar reaction conditions, it can be envisioned to exploit the reactivity of acyl-zirconocene complexes **113** to prepare additional carbonyl compounds of high synthetic value which are not easy to prepare with the classical methods. In fact, by reacting acylzirconocene chlorides complexes with electrophilic compounds like those described in the Scheme 231, new copper-catalyzed carbonylative cross-coupling reactions could be developed.



Scheme 230. Copper-catalyzed cross-coupling of acylzirconocenes and diaryliodonium salts.

For this purpose, -CF_2H **214**,[275] -SCN **215**,[276] -SCF_3 **216**,[277] -CF_2SO_2Ph **217**, [278] -CF_3 **218**,[279] and –C_2H_3 **335**,[280] (vinyl) moieties may be particularly appealing and might be smoothly incorporated using various electrophilic agents reported in the literature (Scheme 231).

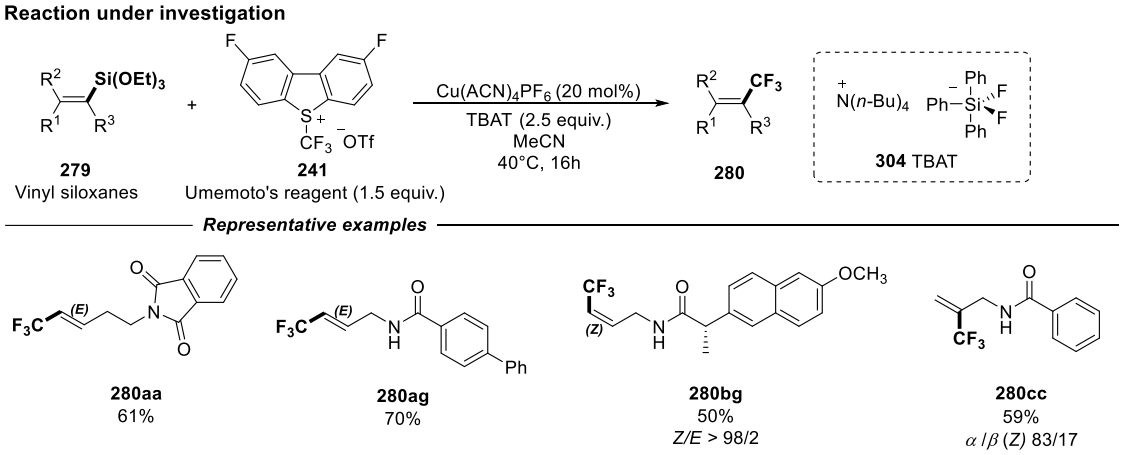


Scheme 231. Copper-catalyzed carbonylative functionalization of alkenes with electrophiles.

[275] Noto, N.; Koike, T.; Akita, M. *Chem. Sci*. **2017**, *8*, 6375–6379.
[276] Wu, D.; Qiu, J.; Karmaker, P. G.; Yin, H.; Chen, F. X. *J. Org. Chem*. **2018**, *83*, 3, 1576–1583.
[277] Xu, C.; Ma, B.; Shen, Q. *Angew. Chem. Int. Ed*. **2014**, *53*, 1–6.
[278] Nobile, E.; Hébert, J.; Castanheiro, T.; Ledoux, A.; Besset, T. *Org. Process Res. Dev*. **2022**, *26*, 8, 2415–2422.
[279] Umemoto, T.; Zhang, B.; Zhu, T.; Zhou, X.; Zhang, P.; Hu, S.; Li, Y. *J. Org. Chem*. **2017**, *15*, 7708–7719.
[280] Juliá, F.; Yan, J.; Paulus, F.; Ritter, T. *J. Am. Chem. Soc.* **2021**, *33*, 12992–12998.

- **Development of a novel copper-catalyzed reaction of trifluoromethylation of vinylsiloxanes**

The last project investigated has been devoted to the development of a novel copper-catalyzed cross-coupling of vinylsiloxanes with the Umemoto's reagent **241** (Scheme 232). The synthesis of trifluoromethylated olefins **280** was carried out via stereodivergent hydrosilylation of terminal alkynes mediated by metal catalysts (Pt, Rh and Ru). Various *trans*, *cis* and 1,1'-disubstituted vinylsiloxanes were prepared and converted into the corresponding trifluoromethylated olefins with good retention of the stereochemistry and under mild reaction conditions. After numerous attempts, it was found out that vinylsiloxanes could be smoothly trifluoromethylation with the Umemoto's reagent when reacting with 20 mol% of $Cu(ACN)_4PF_6$ in presence of TBAT **304** at 40°C in acetonitrile. This procedure enables the synthesis of a broad variety of trifluoromethylated olefins **280** upon simple copper catalysis without the need of additional ligands, under mild reaction conditions and with a good functional group compatibility. In addition to providing a straightforward entry to trifluoromethylated olefins **280**, it also brings useful insights into the unique reactivity of vinyl-copper complex under copper catalysis.



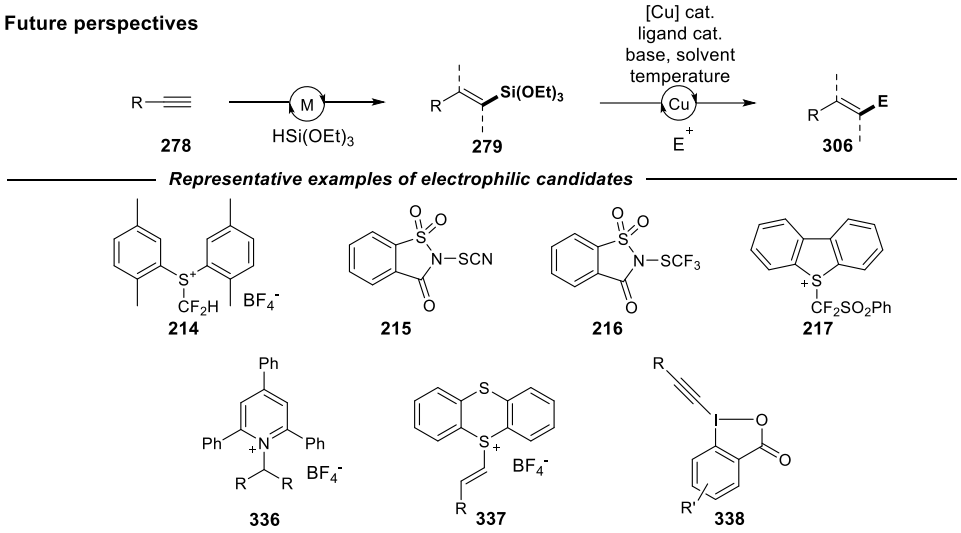
Scheme 232. Copper-catalyzed trifluoromethylation of vinylsiloxanes with the Umemoto's reagent.

Once we optimized the reaction conditions, we then assessed the scope and limitations of our catalytic system. A systematic variation of the identity of the vinyl siloxanes **279** was carried out, which gratifyingly revealed a reasonably wide substrate range. Notably, the trifluoromethylation was carried out on β-(*E*)-vinyl siloxanes, β-(*Z*)-vinyl siloxanes and α-vinyl siloxanes. Through the identified reaction conditions, it was possible to prepare a library of 22 examples of trifluoromethylated olefins with the β-(*E*), β-(*Z*) and α-configuration of the double bond.

In the future, we are interested to apply this methodology to other electrophiles. Indeed, it is possible to imagine the preparation of new functionalized olefins through the reaction of vinylsiloxanes with other electrophiles using copper sources as reaction catalysts. In this way, simply adapting the identified reaction conditions and changing the nature of the electrophiles it will be possible to obtain functionalized olefins of significant synthetic interest. Indeed, via a sequential hydrosilylation followed by a copper-catalyzed cross-coupling, it will be possible to prepare alkenes containing important moieties such as difluoromethyl **214**

(-CF_2H),[281] (phenylsulfonyl)difluoromethyl thiocyanato **215** (-SCN)[282], trifluoromethyl sulphide **216** (-SCF_3)[283] and **217** (-CF_2SO_2Ph)[284], alkyl **336** (R_2CH-)[285], vinyl **337** (RC_2H_2-)[286] and alkynyl **338** (RC_2-)[287] (Scheme 233).

These electrophilic candidates, may be particularly appealing and might be smoothly incorporated using various electrophilic agents already reported in the literature. Definitely, their inert nature makes them the perfect candidates to be used in these transformations with vinyl-siloxanes. Moreover, with the conventional synthetic strategies currently in use, it is difficult to prepare such kind of olefins that contain these fragments.



Scheme 233. Future perspectives for the preparation of functionalized olefins.

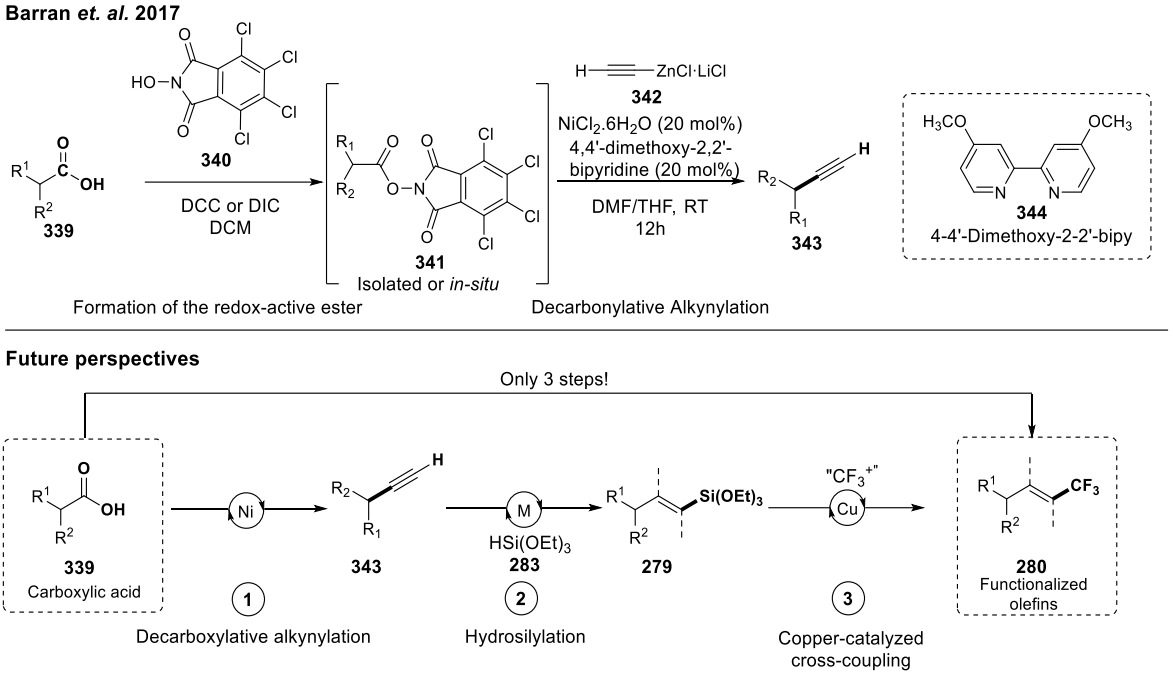
Alternatively, another future perspective is to merge the chemistry of redox active-ester **340** with copper catalysis. Indeed, considering a novel decarboxylative cross-coupling protocol developed by Baran and co-workers in 2017 which affords alkynes **343** from natural and commercially available carboxylic acid **339** is possible to envision an alternative variation of our protocol. The first step of the Baran's protocol is the conversion of the carboxylic acids **339** in the corresponding redox-active esters **341**, which are highly reactive intermediates in organic synthesis. Thereafter, the redox-active esters **313** smoothly follow a decarboxylative alkynylation step utilizing an alkynyl zinc reagent **342**, $NiCl_2 \cdot 6H_2O$ (20 mol%) and 4-4'-dimethoxy-2-2'-bipyridine **344** (Scheme 235).

This new method for the preparation of alkynes **343** is very attractive because it is simple and allow to avoid many additional steps. This is especially true for terminal alkynes, which are frequently accessed from aldehydes. In general, traditional aldehyde homologation reactions have been restricted to the Corey-Fuchs alkynylation,[288] Seyferth-Gilbert homologation and their corresponding modifications (such as the Bestmann-Ohira protocol)[289].

[281] Noto, N.; Koike, T.; Akita, M. *Chem. Sci*. **2017**, *8*, 6375–6379.
[282] Wu, D.; Qiu, J.; Karmaker, P. G.; Yin, H.; Chen, F. X. *J. Org. Chem*. **2018**, *3*, 1576–1583.
[283] Xu, C.; Ma, B.; Shen, Q. *Angew. Chem. Int. Ed*. **2014**, *53*, 1–6.
[284] Nobile, E.; Hébert, J.; Castanheiro, T.; Ledoux, A.; Besset, T. *Org. Process Res. Dev*. **2022**, *8*, 2415–2422.
[285] Plunkett, S.; Basch, C. H.; Santana, S. O.; Watson, M. P. *J. Am. Chem. Soc.* **2019**, *6*, 2257–2262.
[286] Juliá, F.; Yan, J.; Paulus, F.; Ritter, T. *J. Am. Chem. Soc.* **2021**, *33*, 12992–12998.
[287] Fernandez Gonzalez, D.; Brand, J. P.; Waser, J. *Chem. Eur. J.* **2010**, *16*, 9457–9461.
[288] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769–3772.
[289] (a) Hilbert, P; Marmor, S.; Seyferth, D. *J. Org. Chem.* **1971**, *36*, 1379–1386. (b) Weerasooriya, U.; Gilbert, J. C. *J. Org. Chem.* **1982**, *47*, 1837–1845. (c) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564. (d) Müller, S.; Liepold, B.; Roth, G.;

Even though these name reactions have been widely used, they have many drawbacks, such as the need for expensive reagents that are difficult to adapt to complex substrates or situations where a cost-effective production process is required. Furthermore, accessing the aldehyde substrates used in these procedures also necessitates one or more concession steps.

Therefore, combining the protocol for the decarboxylative alkynylation developed by Baran with our method for the copper-catalyzed trifluoromethylation of vinyl-siloxanes **279** will be possible to synthetize, in only three steps, functionalized olefins **280** starting from carboxylic acids **339** (Scheme 234). In this way, we envision to replace time-consuming procedures which a more straightforward pathway based on the use of widely available carboxylic acid **339** as starting materials.



Scheme 234. Future perspectives for the preparation of functionalized olefins.

e) Bestmann, H. J. *Synlett* **1996**, *6*, 521–522. (e) Roth, G. J.; Liepold, B.; Muller, S. G.; Bestmann, H. J. *Synthesis* **2004**, *1*, 59–62.

Experimental Section

General Information

All reactions were carried out in oven-dried glassware under an argon atmosphere employing standard techniques in handling air-sensitive materials.

Diethyl ether and THF were distilled on sodium/benzophenone under an argon atmosphere. 1,2-Dichloroethane was distilled on CaH_2 under an argon atmosphere. Solvents used for work-up were of technical grade. Copper(I) cyanide (99%, extra pure) were respectively purchased from Sigma-Aldrich and used as supplied. Commercial reagents were purchased from Acros, Sigma-Adrich, Fluorochem or TCI and used as received unless stated otherwise.

Reactions were magnetically stirred and monitored by thin layer chromatography using Merck-Kiesegel $60F_{254}$ plates. Flash chromatography was performed with silica gel 60 (particle size 35-70 µm) supplied by Merck. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated.

All ^{1}H and ^{13}C-NMR spectra were recorded in deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) as an internal standard, at ambient temperature on a Bruker DPX 300 MHz Fourier Transform Spectrometer operating at 300 MHz for ^{1}H. Internal reference of δ_H was used for $CDCl_3$. ^{13}C-NMR spectra were recorded at 75 MHz or 100 MHz using $CDCl_3$ (δ_C 77.16) as internal reference. ^{19}F-NMR spectra were recorded at 282 MHz using *bis*[3-(trifluoromethyl)phenyl]methanone (δ_F -62.89) as internal references. ^{31}P-NMR spectra were recorded at 121 or 162 MHz using 85% H_3PO_4 as external reference.

All the spectra were calibrated at δ 0.00 ppm for ^{1}H and δ 77.16 ppm for ^{13}C. Data are presented as follows: chemical shift (in ppm on the δ scale relative to $\delta_{TMS} = 0$), multiplicity *(s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, sept. = septuplet, m = multiplet, br. = broad, app. = apparent)*, coupling constant (*J*/Hz) and integration. IR absorption spectra were recorded as a liquid deposition on a ZnSe crystal on a Shimadzu FTIR 8400 Spectrophotometer from 4000 cm^{-1} to 400 cm^{-1}. High resolution Mass Spectra were obtained from a Thermo Scientific QExactive, with accurate mass reported for the molecular ion or suitable fragment ions. Melting points were recorded on a Stuart Scientific Analogue SMP11.

Reactions were run in an H.E.L. CAT 7 high-pressure reactor and magnetically stirred (Experimental section of Chapter 2).

Reactions were run in a two-chamber glass equipment (COware) purchased from Sigma-Aldrich (Experimental section of Chapter 3). The CO-ware used is ideal for a reaction scale of 0.1-1 mmol (total volume 20 mL).

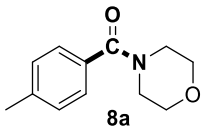
CAUTION: *Carbon monoxide is a highly toxic gas. All manipulations with carbon monoxide must be performed in a well-ventilated fume hood in the presence of a carbon monoxide detector.*

Experimental section of Chapter 2. Copper-catalyzed carbonylative cross-coupling of aryl iodides and amines

General Procedure

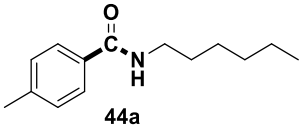
A glass vial containing a PTFE-coated magnetic stirrer was charged with 4-Iodotoluene (109 mg, 0.5 mmol), copper(I) thiophene-2-carboxylate (CuTC) (10 mg, 10 mol%), sodium pentafluorophenolate (124 mg, 0.6 mmol), and Xantphos (58 mg, 0.1 mmol). Anhydrous DMSO (1 mL) and anhydrous morpholine (175 µL, 2.0 mmol) were then added, and the vial was sealed with a PTFE cap and placed in the autoclave. The system was first purged with 10 bar of CO, then pressurized with 10 bar of CO, and stirred at 110 °C for 15h. The autoclave was cooled to room temperature and then gently depressurized. Then, the content of the vial was mixed with DCM (15 mL) and washed with water (15 mL x 3 times) and brine (15 mL x 1 time) in a separatory funnel. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel via injection as silica dust.

Characterization Data



8a

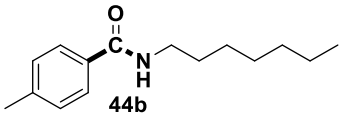
4-Methyl-*N*-morpholinbenzamide 8a. Prepared according to general procedure. Yield: 84% (87 mg, 424 µmol). Slightly yellow solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 60/40; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 3.65 (br s, 8H), 2.34 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 170.6, 140.0, 132.3, 129.1, 127.2, 66.9, 48.3, 42.7, 21.3. This compound has been previously reported.[290]



44a

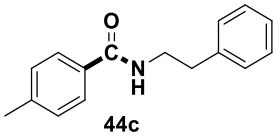
4-Methyl-*N*-hexylbenzamide 44a. Prepared according to general procedure. Yield: 87% (96 mg, 438 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; slightly yellow solid; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.40 (br s, 1H), 3.40 (q., *J* = 7.0 Hz, 2H), 2.36 (s, 3H), 1.57 (quint., *J* = 8.1 Hz, 2H), 1.41 – 1.18 (m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 167.5, 141.6, 132.1, 129.1, 126.9, 40.1, 31.6, 29.7, 26.7, 22.6, 21.4, 14.0. This compound has been previously reported.[291]

[290] Li, J.; Xu, F.; Zhang, Y.; Shen, Q. *J. Org. Chem.* **2009**, *74*, 2575–2577.
[291] Jo, Y.; Ju, J.; Choe, J.; Kwang, H. S.; Lee, S. *J. Org. Chem.* **2009**, *74*, 6358–6361.



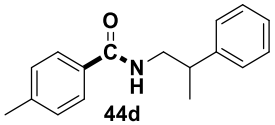
44b

4-Methyl-*N*-heptylbenzamide 44b. Prepared according to general procedure. Yield: 70% (82.2 mg, 352 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; slightly dark yellow solid; **Mp**: 50 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 7.7 Hz, 2H), 6.37 (br s, 1H), 3.40 (q., *J* = 6.8 Hz, 2H), 2.37 (s, 3H), 1.58 (quint., *J* = 7.2 Hz, 2H), 1.35 – 1.22 (m, 8H), 0.87 (t, *J* = 6.8 Hz, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 167.6, 141.7, 132.0, 129.2, 126.9, 40.1, 31.8, 29.7, 29.0, 27.0, 22.6, 21.4, 14.1; **IR** (neat): ν_{max} 3331, 2926, 2858, 2356, 1632 (C=O), 1536, 1507, 1458, 1303, 997, 838, 752, 649 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{15}H_{24}NO$ $[M+H]^+$ 234.1777, found 234.1849.



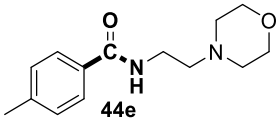
44c

4-Methyl-*N*-(2-phenylethyl)benzamide 44c. Prepared according to general procedure. Yield: 51% (61.1 mg, 255 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; slightly dark yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.40 – 7.28 (m, 2H), 7.28 – 7.05 (m, 5H), 6.09 (br s, 1H), 3.72 (q., *J* = 6.8 Hz, 2H), 2.93 (t, *J* = 6.9 Hz, 2H), 2.38 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 167.7, 141.9, 139.0, 131.8, 129.3, 128.9, 128.7, 126.9, 126.6, 41.2, 35.8, 21.5. This compound has been previously reported.[292]



44d

4-Methyl-*N*-(2-phenylpropyl)benzamide 44d. Prepared according to general procedure. Yield: 58% (74.1 mg, 292 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; slightly dark yellow solid; **Mp**: 65 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.25 (d, *J* = 7.3 Hz, 3H), 7.17 (d, *J* = 7.1 Hz, 2H), 6.13 (br s, 1H), 3.94 – 3.72 (m, 1H), 3.53 – 3.29 (m, 1H), 3.21 – 2.96 (m, 1H), 2.36 (s, 3H), 1.34 (d, *J* = 6.7 Hz, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 167.4, 144.2, 141.7, 131.9, 129.2, 128.8, 127.3, 126.8, 126.8, 46.6, 39.8, 21.4, 19.3; **IR** (neat): ν_{max} 3326, 2959, 1632 (C=O), 1550, 1507, 1405, 1304, 1247, 1189, 1126, 1018, 837, 750, 701 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{17}H_{20}NO$ $[M+H]^+$ 254.1545, found 254.1534.

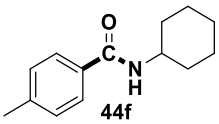


44e

4-Methyl-*N*-(2-morpholinoethyl)benzamide 44e. Prepared according to general procedure. Yield: 65% (80 mg, 322 µmol). Beige solid. Solvent system for flash column chromatography: DCM /MeOH: 96/4; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.2 Hz, 2H), 7.21 (d, *J* = 6.3 Hz, 2H), 6.80 (br s, 1H), 3.70 (t, *J* = 3.6 Hz, 4H), 3.52 (q., *J* = 5.0, 4.0 Hz, 2H), 2.58 (s, 2H), 2.51 – 2.46 (m, 4H), 2.37 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 167.4, 141.8, 131.8, 129.2, 126.9, 67.0, 57.0, 53.4, 36.0, 21.4. This compound has been previously reported.[293]

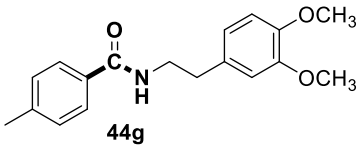
[292] Xing, D.; Xu, X.; Yang, L. *Synthesis.* **2009**, *20*, 3399–3404.

[293] Desmecht, A.; Steenhaut, T.; Pennetreau, F.; Hermans, S.; Riant, O. *Chem. Eur. J.* **2018**, *24*, 12992–13001.



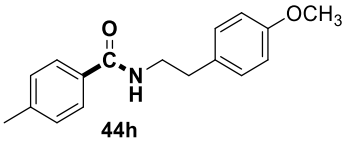
44f

4-Methyl-*N*-cyclohexylbenzamide 44f. Prepared according to general procedure. Yield: 73% (79.4 mg, 365 µmol). Slightly yellow solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 7.4 Hz, 2H), 6.10 (br s, 1H), 4.03 – 3.85 (m, 1H), 2.36 (s, 3H), 2.01 (d, *J* = 3.8 Hz, 1H), 1.98 (d, *J* = 4.1 Hz, 1H), 1.74 (t, *J* = 3.7 Hz, 1H), 1.71 (t, *J* = 3.7 Hz, 1H), 1.63 (dt, *J* = 12.8, 3.7 Hz, 1H), 1.42 (dt, *J* = 11.9, 3.5 Hz, 1H), 1.36 (dt, *J* = 13.1, 3.4 Hz, 1H), 1.28 – 1.14 (m, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 166.6, 141.6, 132.3, 129.1, 126.9, 48.6, 33.2, 25.6, 25.0, 21.4. This compound has been previously reported.[294]



44g

***N*-(3,4-dimethoxyphenethyl)-4-methylbenzamide 44g.** Prepared according to general procedure. Yield: 79% (118 mg, 394 µmol). Slightly yellow solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 60/40; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.73 (d, *J* = 7.9 Hz, 2H), 6.34 (br s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.65 (q., *J* = 6.6 Hz, 2H), 2.85 (t, *J* = 6.9 Hz, 2H), 2.35 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 167.4, 149.1, 147.7, 141.8, 131.8, 131.5, 129.2, 126.8, 120.7, 112.0, 111.4, 55.9, 55.8, 41.3, 35.3, 21.4. This compound has been previously reported.[295]



44h

4-Methyl-*N*-(4-methoxyphenethyl)benzamide 44h. Prepared according to general procedure. Yield: 88% (118 mg, 438 µmol). Slightly dark yellow solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 70/30; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 7.5 Hz, 2H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.56 (br s, 1H), 3.76 (s, 3H), 3.65 (q., *J* = 7.0 Hz, 2H), 2.84 (t, *J* = 7.1 Hz, 2H), 2.36 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 167.5, 158.2, 141.6, 131.8, 131.0, 129.7, 129.1, 126.9, 114.0, 55.2, 41.3, 34.8, 21.4. This compound has been previously reported.[296]

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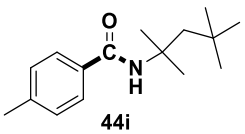
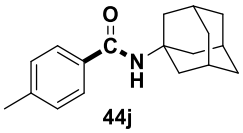


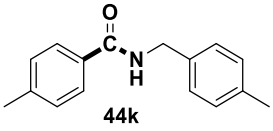
44i

4-Methyl-*N*-(2,4,4-trimethylpentan-2-yl) benzamide 44i. Prepared according to general procedure. Yield: 75% (93 mg, 376 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 90/10; beige solid; **Mp**: 96 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 2H), 5.96 (br s, 1H), 2.37 (s, 3H), 1.85 (s, 2H), 1.51 (s, 6H), 1.03 (s, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 166.9, 141.4, 133.3, 129.2, 126.7, 55.5, 51.8, 31.8, 31.6, 29.4, 21.4; **IR** (neat): ν_{max} 2948, 1640 (C=O), 1518, 1364, 1285, 1226, 995, 860, 836, 754 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{16}H_{26}NO$ $[M+H]^+$ 248.2014, found 248.2007.



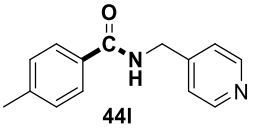
44j

4-Methyl-*N*-(1-adamantyl)benzamide 44j. Prepared according to general procedure. Yield: 40% (52 mg, 193 µmol). White solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 5.78 (br s, 1H), 2.37 (s, 3H), 2.12 (s, 9H), 1.72 (s, 6H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 166.6, 141.4, 133.3, 129.1, 126.8, 52.2, 41.8, 36.5, 29.6, 21.4. This compound has been previously reported.[297]



44k

4-Methyl-*N*-(4-methylbenzyl)benzamide 44k. Prepared according to general procedure. Yield: 82% (98 mg, 409 µmol). Slightly yellow solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 7.7 Hz, 2H), 7.14 (d, *J* = 7.7 Hz, 2H), 6.58 (br s, 1H), 4.57 (d, *J* = 5.0 Hz, 2H), 2.38 (s, 3H), 2.34 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 167.3, 141.9, 137.2, 135.4, 131.6, 129.4, 129.2, 127.9, 127.0, 43.8, 21.5, 21.1. This compound has been previously reported.[298]



44l

4-Methyl-*N*-(pyridin-4-ylmethyl)benzamide 44l. Prepared according to general procedure. Yield: 72% (82 mg, 362 µmol). Solvent system for flash column chromatography: EtOAc; beige solid; **Mp**: 89 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 6.2 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.52 – 7.43 (br s, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 7.14 (s, 2H), 4.53 (d, *J* = 6.1 Hz, 2H), 2.36 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 167.9, 149.8, 148.1, 142.3, 131.0, 129.3, 127.2, 122.4, 42.6, 21.5; **IR** (neat): ν_{max} 3328, 1638 (C=O), 1566, 1507, 1415, 1328, 1291, 1022, 838, 719, 680 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{14}H_{15}N_2O$ $[M+H]^+$ 227.1184, found 227.1180.

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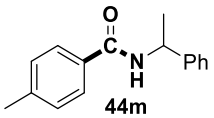
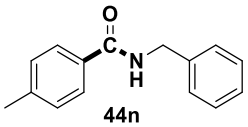


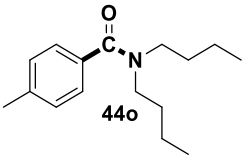
44m

4-Methyl-*N*-(1-phenylethyl)benzamide 44m. Prepared according to general procedure. Yield: 55% (65.4 mg, 273 µmol). Beige solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.41 – 7.30 (m, 4H), 7.29 – 7.22 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.59 (d, *J* = 7.9 Hz, 1H), 5.31 (quint., *J* = 7.1 Hz, 1H), 2.37 (s, 3H), 1.57 (d, *J* = 6.9 Hz, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 166.6, 143.4, 141.8, 131.8, 129.2, 128.7, 127.3, 127.0, 126.3, 49.1, 21.8, 21.4. This compound has been previously reported.[299]



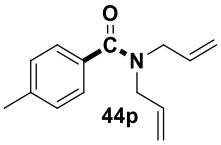
44n

4-Methyl-*N*-benzylbenzamide 44n. Prepared according to general procedure. Yield: 67% (75 mg, 333 µmol). Beige solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 85/15; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 4.5 Hz, 1H), 7.34 – 7.26 (m, 4H), 7.22 (d, *J* = 7.8 Hz, 2H), 6.73 (br s, 1H), 4.62 (d, *J* = 5.7 Hz, 2H), 2.41 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 167.4, 141.9, 138.5, 131.6, 129.2, 128.7, 127.9, 127.5, 127.1, 44.0, 21.4. This compound has been previously reported.[300]



44o

4-Methyl-*N, N*-dibutylbenzamide 44o. Prepared according to general procedure. Yield: 67% (83.4 mg, 337 µmol). Slightly yellow oil. Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 3.47 (s, 2H), 3.19 (s, 2H), 2.33 (s, 3H), 1.61 (s, 2H), 1.46 (s, 2H), 1.37 (s, 2H), 1.12 (s, 2H), 0.95 (s, 3H), 0.77 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 172.0, 139.1, 134.2, 128.9, 126.5, 48.9, 44.6, 30.8, 29.7, 21.3, 20.3, 19.8, 13.9, 13.7. This compound has been previously reported.[301]



44p

***N, N*-diallyl-4-methylbenzamide 44p.** Prepared according to general procedure. Yield: 56% (60 mg, 279 µmol). Slightly yellow solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 2H), 5.85 (s, 1H), 5.74 (s, 1H), 5.25 – 5.11 (m, 4H), 4.10 (s, 2H), 3.84 (s, 2H), 2.35 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 172.0, 139.7, 133.4, 133.0, 129.0, 126.7, 117.6, 50.8, 47.0, 21.4. This compound has been previously reported.[302]

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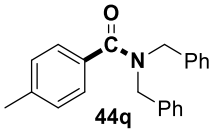
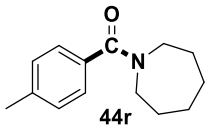


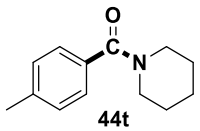
44q

4-Methyl-*N, N*-dibenzylbenzamide 44q. Prepared according to general procedure. Yield: 50% (80 mg, 243 µmol). Beige solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 5H), 7.34 – 7.13 (m, 9H), 4.71 (s, 2H), 4.44 (s, 2H), 2.35 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 172.9, 140.0, 136.9, 136.5, 133.0, 129.2, 128.8, 128.5, 127.7, 127.1, 126.9, 51.7, 47.1, 21.4. This compound has been previously reported.[303]



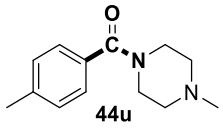
44r

4-Methyl-*N*-azepanbenzamide 44r. Prepared according to general procedure. Yield: 87% (94.5 mg, 435 µmol). Slightly yellow dark oil. Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.7 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 3.66 (br s, 2H), 3.38 (br s, 2H), 2.36 (s, 3H), 1.83 (br s, 2H), 1.59 (br s, 6H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 171.9, 139.1, 134.4, 129.0, 126.5, 49.8, 46.4, 29.6, 27.9, 27.3, 26.5, 21.3. This compound has been previously reported.[304]



44t

4-Methyl-*N*-piperidinbenzamide 44t. Prepared according to general procedure. Yield: 85% (85 mg, 418 µmol). Slightly yellow dark oil. Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 7.6 Hz, 2H), 3.67 (s, 2H), 3.34 (s, 2H), 2.34 (s, 3H), 1.64 (s, 2H), 1.51 (s, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 170.4, 139.3, 133.5, 128.9, 126.8, 48.7, 43.1, 26.4, 25.6, 24.5, 21.3. This compound has been previously reported.[305]



44u

4-Methyl-*N*-(4-Methylpiperazin) benzamide 44u. Prepared according to general procedure. Yield: 60% (64 mg, 293 µmol). Solvent system for flash column chromatography: DCM/CH_3OH: 98/2; yellow solid; **Mp**: 68 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 3.75 (br s, 2H), 3.47 (br s, 2H), 2.40 (br s, 4H), 2.34 (s, 3H), 2.30 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 170.5, 139.8, 132.7, 129.0, 127.1, 54.9, 47.5, 45.9, 41.9, 21.3; **IR** (neat): ν_{max} 2938, 1614 (C=O), 1461, 1436, 1289, 1274, 1140, 1019, 1001, 838, 751 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{13}H_{19}N_2O$ $[M+H]^+$ 219.1497, found 219.1487.

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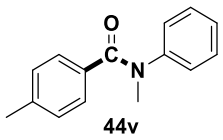
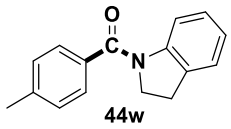


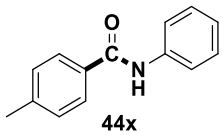
44v

***N*,4-Dimethyl-*N*-phenylbenzamide 44v.** Prepared according to general procedure. Yield: 64% (72 mg, 320 µmol). Beige solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 1H), 7.21 (d, *J* = 8.1 Hz, 3H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 7.1 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 2H), 3.50 (s, 3H), 2.26 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 170.8, 145.3, 139.9, 133.0, 129.2, 129.0, 128.4, 126.9, 126.4, 38.5, 21.4. This compound has been previously reported.[306]



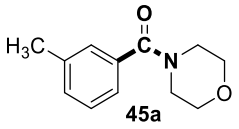
44w

4-Methyl-*N*-indolinbenzamide 44w. Prepared according to general procedure. Yield: 73% (86 mg, 362 µmol). Slightly yellow dark solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.1 Hz, 2H), 7.26 – 7.10 (m, 5H), 7.01 (t, *J* = 7.4 Hz, 1H), 4.10 (t, *J* = 8.2 Hz, 2H), 3.11 (t, *J* = 8.3 Hz, 2H), 2.41 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 169.2, 142.7, 140.7, 134.0, 132.5, 129.2, 127.3, 124.9, 123.9, 117.2, 50.6, 28.1, 21.5. This compound has been previously reported.[307]



44x

4-Methyl-*N*-phenylbenzamide 44x. Prepared according to general procedure. Yield: 64% (67.1 mg, 317 µmol). Beige solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 7.3 Hz, 2H), 7.45 – 7.30 (m, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 2.42 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 165.9, 142.4, 138.2, 132.2, 129.5, 129.1, 127.1, 124.5, 120.3, 21.5. This compound has been previously reported.[308]



45a

3-Methyl-*N*-morpholinbenzamide 45a. Prepared according to general procedure I. Yield: 81% (83 mg, 404 µmol). Slightly yellow dark oil. Solvent system for flash column chromatography: petroleum ether/EtOAc: 50/50; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.23 – 7.14 (m, 2H), 3.78 (s, 6H), 3.47 (s, 2H), 2.37 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.0, 138.5, 134.8, 130.7, 128.4, 127.6, 123.9, 66.8, 48.2, 42.6, 21.3. This compound has been previously reported.[309]

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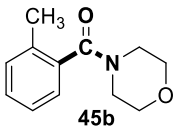
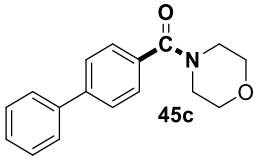


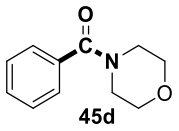
45b

2-Methyl-*N*-morpholinbenzamide 45b. Prepared according to general procedure I. Yield: 63% (65 mg, 317 µmol). Slightly yellow dark oil. Solvent system for flash column chromatography: petroleum ether/EtOAc: 50/50; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 1H), 7.20 (d, *J* = 7.1 Hz, 2H), 7.14 (d, *J* = 7.4 Hz, 1H), 3.81 (d, *J* = 4.4 Hz, 2H), 3.76 (d, *J* = 5.0 Hz, 2H), 3.56 (s, 2H), 3.23 (s, 2H), 2.30 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.1, 135.7, 134.2, 130.5, 129.1, 126.0, 125.9, 67.0, 67.0, 47.3, 41.9, 19.0. This compound has been previously reported.[310]



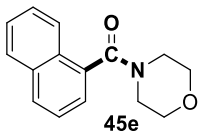
45c

[1,1'-biphenyl]-4-yl(morpholino)methanone 45c. Prepared according to general procedure I. Yield: 81% (108 mg, 404 µmol). Slightly yellow solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 50/50; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 7.0 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 1H), 3.70 (s, 8H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 170.2, 142.8, 140.1, 134.0, 128.9, 127.8, 127.7, 127.2, 127.1, 66.9, 48.2, 42.6. This compound has been previously reported.[311]



45d

Morpholino(phenyl)methanone 45d. Prepared according to general procedure I. Yield: 79% (76 mg, 397 µmol). Slightly yellow dark oil. Solvent system for flash column chromatography: petroleum ether/EtOAc: 50/50; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 5H), 3.68 (s, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.4, 135.3, 129.8, 128.6, 128.5, 127.0, 66.8, 48.2, 42.5. This compound has been previously reported.[312]



45e

Morpholino(naphthalen-2-yl)methanone 45e. Prepared according to general procedure. Yield: 78% (94 mg, 390 µmol). Slightly yellow dark oil. Solvent system for flash column chromatography: petroleum ether/EtOAc: 50/50; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.94 – 7.81 (m, 3H), 7.59 – 7.48 (m, 3H), 7.42 (dd, *J* = 7.0, 1.3 Hz, 1H), 4.10 – 3.97 (m, 1H), 3.96 – 3.88 (m, 1H), 3.87 – 3.80 (m, 2H), 3.63 – 3.41 (m, 2H), 3.29 – 3.14 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 169.5, 133.7, 133.4, 129.5, 129.3, 128.5, 127.1, 126.5, 125.2, 124.6, 123.9, 67.1, 66.9, 47.6, 42.2. This compound has been previously reported.[313]

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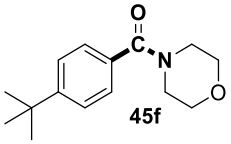
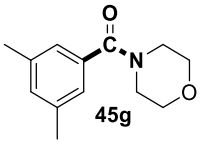


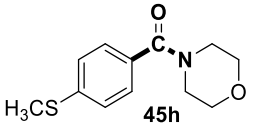
45f

4-*tert*-Butyl-*N*-morpholinbenzamide 45f. Prepared according to general procedure I. Yield: 70% (86 mg, 348 µmol). Slightly yellow dark solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 50/50; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 3.66 (s, 8H), 1.29 (s, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 170.6, 153.1, 132.3, 127.0, 125.4, 66.9, 48.2, 42.6, 34.8, 31.2. This compound has been previously reported.[314]



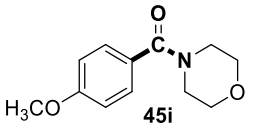
45g

(3,5-Dimethyl-phenyl)-morpholin-4-yl-methanone 45g. Prepared according to general procedure. Yield: 82% (90 mg, 410 µmol). White solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 50/50; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.04 (s, 1H), 6.99 (s, 2H), 3.69 (br s, 8H), 2.32 (s, 6H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 170.8, 138.3, 135.3, 131.4, 124.6, 66.9, 48.2, 42.5, 21.2. This compound has been previously reported.[315]



45h

4-Methylthio-*N*-morpholinbenzamide 45h. Prepared according to general procedure. Yield: 81% (97 mg, 409 µmol). Yellow pale solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 40/60; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 3.66 (s, 8H), 2.47 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 170.1, 141.5, 131.5, 127.8, 125.8, 66.9, 48.1, 42.6, 15.3. This compound has been previously reported.[316]



45i

4-Methoxy-*N*-morpholinbenzamide 45i. Prepared according to general procedure. Yield: 75% (83 mg, 375 µmol). Yellow pale oil. Solvent system for flash column chromatography: petroleum ether/EtOAc: 40/60; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 3.67 (s, 8H); **^{13}C-NMR** (75 MHz, $C_2D_2Cl_4$) δ 169.9, 160.9, 128.8, 127.7, 113.8, 113.8, 66.5, 55.2, 45.5. This compound has been previously reported.[317]

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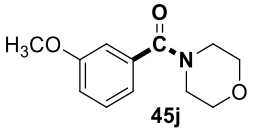
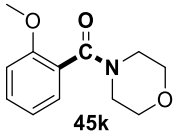


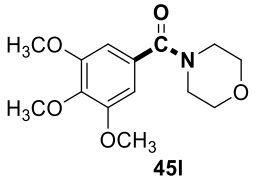
45j

3-Methoxy-*N*-morpholinbenzamide 45j. Prepared according to general procedure. Yield: 63% (70 mg, 316 µmol). Yellow pale oil. Solvent system for flash column chromatography: petroleum ether/EtOAc: 30/70; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.63 (t, *J* = 8.1 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.26 (s, 2H), 4.14 (s, 3H), 3.96 (s, 8H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 170.2, 159.7, 136.6, 129.7, 119.1, 115.6, 112.5, 66.9, 55.4, 48.2, 42.6. This compound has been previously reported.[318]



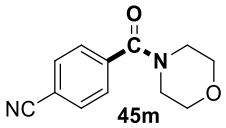
45k

2-Methoxy-*N*-morpholinbenzamide 45k. Prepared according to general procedure. Yield: 33% (37 mg, 167 µmol). Yellow pale oil. Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/80. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.34 (ddd, *J* = 8.3, 7.4, 1.7 Hz, 1H), 7.24 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.98 (td, *J* = 7.5, 0.9 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 3.83 (s, 3H), 3.81 – 3.70 (m, 4H), 3.59 (dt, 2H), 3.25 (dt, *J* = 16.6, 5.1 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 168.0, 155.3, 130.7, 128.2, 125.4, 121.1, 111.0, 67.0, 66.9, 55.6, 47.4, 42.2. This compound has been previously reported.[319]



45l

3,4,5-Trimethoxy-*N*-morpholinbenzamide 45l. Prepared according to general procedure. Yield: 63% (88.6 mg, 315 µmol). Beige solid. Solvent system for flash column chromatography: EtOAc; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.60 (s, 2H), 3.84 (s, 3H), 3.83 (s, 6H), 3.67 (s, 8H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 170.2, 153.4, 139.4, 130.7, 104.4, 66.9, 60.9, 56.3. This compound has been previously reported.[320]



45m

4-Cyano-*N*-morpholinbenzamide 45m. Prepared according to general procedure. Yield: 70% (76 mg, 351 µmol). Beige solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 60/40; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 3.74 (s, 4H), 3.59 (s, 2H), 3.33 (s, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 168.3, 139.6, 132.5, 127.8, 118.0, 113.6, 66.7, 48.0, 42.5. This compound has been previously reported.[321]

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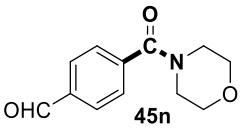
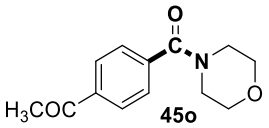


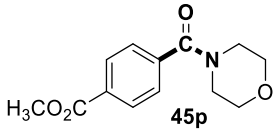
45n

4-(Morpholine-4-carbonyl)benzaldehyde 45n. Prepared according to general procedure. Yield: 46% (48 mg, 219 µmol). Slightly yellow solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/80; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 3.79 (s, 4H), 3.63 (s, 2H), 3.40 (s, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 191.4, 169.1, 141.0, 137.1, 130.0, 127.7, 66.8, 48.1, 42.6. This compound has been previously reported.[322]



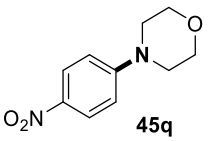
45o

1-(4-(morpholine-4-carbonyl)phenyl)ethan-1-one 45o. Prepared according to general procedure. Yield: 45% (52.3 mg, 224 µmol). Slightly yellow solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/80; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.9 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 2H), 3.77 (s, 4H), 3.60 (s, 2H), 3.39 (s, 2H), 2.60 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 197.3, 169.3, 139.7, 138.0, 128.6, 127.4, 66.8, 48.1, 42.6, 26.7. This compound has been previously reported.[323]



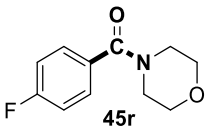
45p

Methyl 4-(morpholine-4-carbonyl)benzoate 45p. Prepared according to general procedure. Yield: 45% (56 mg, 225 µmol). Slightly yellow dark oil. Solvent system for flash column chromatography: petroleum ether/EtOAc: 40/60; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 3.91 (s, 3H), 3.76 (s, 4H), 3.60 (s, 2H), 3.38 (s, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 169.4, 166.3, 139.6, 131.4, 129.9, 127.1, 66.9, 52.4, 48.1, 42.5. This compound has been previously reported.[324]



45q

4-(4-nitrophenyl)morpholine 45q. Prepared according to general procedure. Yield: 85% (88.5 mg, 425 µmol). Yellow solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 70/30; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.1 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 3.85 (t, *J* = 4.9 Hz, 4H), 3.36 (t, *J* = 4.8 Hz, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 155.0, 138.9, 125.9, 112.6, 66.4, 47.1. This compound has been previously reported.[325]



45r

4-Fluoro-*N*-morpholinbenzamide 45r. Prepared according to general procedure. Yield: 71% (74 mg, 354 µmol). Slightly yellow oil. Solvent system for flash column chromatography: petroleum ether/EtOAc: 50/50; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.08 (t, *J* = 8.7 Hz, 2H), 3.63 (s, 8H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 169.5, 164.8, 162.3, 131.4, 131.3, 129.5, 129.4, 115.8, 115.6, 66.9, 48.3, 42.6. This compound has been previously reported.[326]

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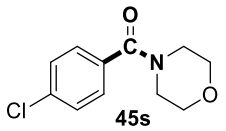
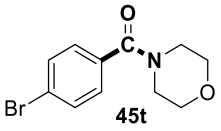


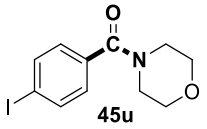
45s

4-Chloro-*N*-morpholinbenzamide 45s. Prepared according to general procedure. Yield: 78% (88 mg, 390 µmol). Slightly yellow solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 50/50; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 3.66 (s, 8H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 169.3, 136.0, 133.6, 128.8, 128.7, 66.8, 48.2, 42.7. This compound has been previously reported.[327]



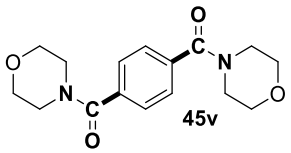
45t

4-Bromo-*N*-morpholinbenzamide 45t. Prepared according to general procedure. Yield: 89% (121 mg, 448 µmol). Slightly yellow dark oil. Solvent system for flash column chromatography: petroleum ether/EtOAc: 60/40; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 3.70 (s, 8H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 169.3, 134.0, 131.7, 128.8, 124.1, 66.7, 47.9, 42.5. This compound has been previously reported.[328]



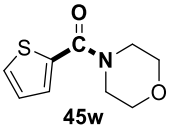
45u

4-Iodo-*N*-morpholinbenzamide 45u. Prepared according to general procedure. Yield: 27% (44.3 mg, 140 µmol). Slightly yellow oil. Solvent system for flash column chromatography: petroleum ether/EtOAc: 50/50; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 3.65 (s, 8H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 169.5, 137.8, 134.7, 128.9, 96.2, 66.8, 48.0, 42.6. This compound has been previously reported.[329]



45v

1,4-phenylenebis(morpholinomethanone) 45v. Prepared according to general procedure. Yield: 89% (135 mg, 443 µmol). Beige solid. Solvent system for flash column chromatography: EtOAc/MeOH: 94/6; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.42 (s, 4H), 3.74 (s, 12H), 3.37 (s, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 169.4, 136.9, 127.4, 66.8, 48.1, 42.6. This compound has been previously reported.[330]



45w

Morpholino(thiophen-2-yl)methanone 45w. Prepared according to general procedure. Yield: 86% (85 mg, 430 µmol). Slightly yellow dark oil. Solvent system for flash column chromatography: petroleum ether/EtOAc: 50/50; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.30 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.05 (dd, *J* = 5.0, 3.6 Hz, 1H), 3.80 – 3.75 (m, 4H), 3.75 – 3.70 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 163.7, 136.6, 129.0, 128.9, 126.8, 66.9, 45.7. This compound has been previously reported.[331]

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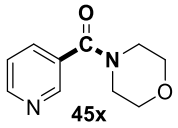
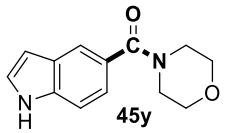


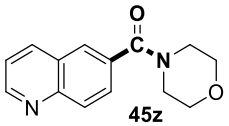
45x

Morpholino(pyridin-3-yl)methanone 45x. Prepared according to general procedure. Yield: 77% (74.1 mg, 385 µmol). Slightly yellow dark oil. Solvent system for flash column chromatography: AcOEt/MeOH: 90/10; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.64 (dd, *J* = 4.8, 1.7 Hz, 2H), 7.73 (dt, *J* = 7.7, 2.0 Hz, 1H), 7.34 (dd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 3.72 (s, 6H), 3.43 (s, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 167.8, 151.0, 148.0, 135.1, 131.2, 123.6, 66.8, 48.2, 42.7. This compound has been previously reported.[332]



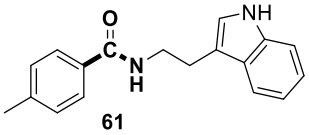
45y

(1H-indol-5-yl)(morpholino)methanone 45y. Prepared according to general procedure. Yield: 57% (65.1 mg, 283 µmol). Beige solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/90; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.73 (s, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.22 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.19 (t, *J* = 2.8 Hz, 1H), 6.55 (s, 1H), 3.72 (s, 8H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 172.3, 136.7, 127.4, 126.3, 125.8, 121.2, 120.3, 111.4, 102.9, 67.0, 48.4, 42.6. This compound has been previously reported.[333]



45z

Morpholino(quinolin-6-yl)methanone 45z. Prepared according to general procedure. Yield: 78% (95 mg, 392 µmol). Slightly yellow dark solid. Solvent system for flash column chromatography: EtOAc; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.15 (dd, *J* = 8.3, 1.8 Hz, 0H), 8.11 (dd, *J* = 8.6, 2.9 Hz, 0H), 7.88 (s, 0H), 7.67 (dq, *J* = 8.6, 1.9 Hz, 1H), 7.42 (dt, *J* = 7.3, 3.6 Hz, 1H), 3.70 (s, 8H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 169.7, 151.7, 148.4, 136.5, 133.4, 130.0, 127.8, 127.8, 127.1, 122.0, 66.8, 48.2, 42.7. This compound has been previously reported.[334]



61

***N*-(2-(1H-indol-3-yl)ethyl)-4-methylbenzamide 61.** Prepared according to general procedure I. Yield: 88% (122 mg, 438 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 50/50; beige solid; **Mp**: 115 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 7.0 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.12 (t, *J* = 7.0 Hz, 1H), 6.99 (s, 1H), 6.45 (t, *J* = 5.7 Hz, 1H), 3.78 (q., *J* = 6.5 Hz, 2H), 3.08 (t, *J* = 6.7 Hz, 2H), 2.37 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 167.7, 141.8, 136.5, 131.7, 129.2, 127.3, 126.9, 122.3, 122.1, 119.3, 118.7, 112.7, 111.5, 40.4, 25.3, 21.4; **IR** (neat): ν_{max} 3282, 1624 (C=O), 1611, 1566, 1507, 1455, 1429, 1323, 1233, 1098, 845, 737, 720, 666 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{18}H_{19}N_2O$ $[M+H]^+$ 279.1497, found 279.1501.

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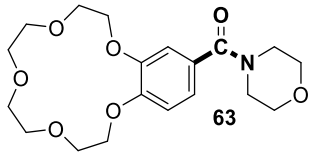
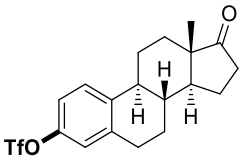


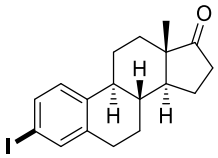
63

Morpholino(2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13]pentaoxacyclopentadecin-15-yl)methanone 63. Prepared according to general procedure I. Yield: 84% (81 mg, 212 µmol). Solvent system for flash column chromatography: AcOEt/MeOH: 90/10; slightly yellow dark oil; **^{1}H-NMR** (400 MHz, 1,1,2,2-Tetrachloroethane-d_2) δ 7.01 (s, 1H), 6.99 (d, *J* = 2.1 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.20 (q., *J* = 4.5 Hz, 4H), 3.92 (dq, *J* = 4.5, 2.4 Hz, 4H), 3.76 (s, 8H), 3.72 – 3.68 (m, 4H), 3.65 – 3.59 (m, 4H); **^{13}C-NMR** (75 MHz, 1,1,2,2-Tetrachloroethane-d_2) δ 169.7, 150.8, 149.2, 128.4, 120.7, 114.5, 114.0, 70.9, 70.5, 70.5, 69.6, 69.4, 69.3, 66.6, 45.5; **IR** (neat): ν_{max} 2923, 2861, 2228, 1626 (C=O), 1514, 1433, 1266, 1224, 1137, 1114, 892, 743, 701, 624 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{19}H_{28}NO_7$ $[M+H]^+$ 382.1866, found 382.1868.



65

3-trifloxy-1,3,5(10)-estratrien-17-one / estronyl triflate 65. Prepared according to general procedure I. Yield: 81% (2.16 mg, 5.39 mmol). White solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.8 Hz, 1H), 7.03 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.99 (d, *J* = 2.7 Hz, 1H), 2.99 – 2.86 (m, 2H), 2.51 (dd, *J* = 18.8, 8.3 Hz, 1H), 2.44 – 2.35 (m, 1H), 2.35 – 2.23 (m, 1H), 2.22 – 2.11 (m, 1H), 2.11 – 2.01 (m, 2H), 2.01 – 1.94 (m, 1H), 1.73 – 1.38 (m, 6H), 0.92 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 220.5, 147.7, 140.4, 139.4, 127.3, 123.6, 121.3, 120.4, 118.4, 117.3, 114.1, 50.5, 47.9, 44.2, 37.8, 35.9, 31.6, 29.5, 26.2, 25.8, 21.7, 13.9. This compound has been previously reported.[335]



66

(*8R*,*9S*,*13S*,*14S*)-3-iodo-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-*17H*-cyclopenta[*a*]phenanthren-17-one 66. Prepared according to general procedure I. Yield: 58% (88 mg, 231 µmol). White solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 50/10; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.3 Hz, 2H), 7.02 (d, *J* = 7.5 Hz, 1H), 2.87 (dd, *J* = 9.2, 3.6 Hz, 2H), 2.55 – 2.46 (m, 1H), 2.42 – 2.33 (m, 1H), 2.28 – 2.21 (m, 1H), 2.21 – 2.10 (m, 1H), 2.09 – 1.88 (m, 3H), 1.76 – 1.55 (m, 2H), 1.55 – 1.30 (m, 4H), 0.91 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 220.7, 139.6, 139.3, 137.8, 134.8, 127.5, 91.3, 50.5, 48.0, 44.3, 37.9, 35.9, 31.6, 29.0, 26.3, 25.6, 21.6, 13.9. This compound has been previously reported.[336]

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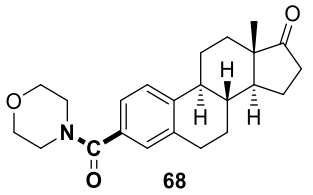
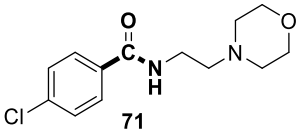


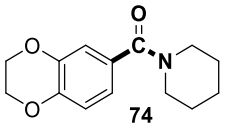
68

(*8R*,*9S*,*13S*,*14S*)-13-methyl-3-(morpholine-4-carbonyl)-6,7,8,9,11,12,13,14,15,16-decahydro-*17H*-cyclopenta[*a*]phenanthren-17-one 68. Prepared according to general procedure I. Yield: 85% (47.2 mg, 128 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/80; slightly yellow pale solid; **Mp**: 140 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.9 Hz, 1H), 7.15 (d, *J* = 5.4 Hz, 2H), 3.69 (s, 8H), 2.99 – 2.88 (m, 2H), 2.51 (dd, *J* = 18.7, 8.7 Hz, 1H), 2.46 – 2.39 (m, 1H), 2.31 (td, *J* = 10.5, 4.3 Hz, 1H), 2.22 – 2.11 (m, 1H), 2.09 – 1.88 (m, 3H), 1.69 – 1.58 (m, 2H), 1.57 – 1.44 (m, 4H), 0.91 (s, 3H); **^{13}C-NMR** (75 MHz, 1,1,2,2-Tetrachloroethane-d_2) δ 219.0, 170.2, 141.7, 136.8, 132.9, 127.5, 124.9, 124.2, 66.6, 50.6, 47.6, 45.3, 44.3, 37.9, 35.5, 31.6, 28.9, 26.1, 25.5, 21.3, 13.7; **IR** (neat): ν_{max} 2932, 1733, 1625 (C=O), 1431, 1272, 1253, 1114, 1027, 914, 839, 744 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$ 368.2226, found 368.2229.



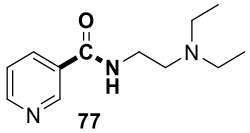
71

4-Chloro-*N*-(2-morpholinoethyl)benzamide / Moclobemide 71. Prepared according to general procedure. Yield: 62% (166 mg, 618 µmol). Beige solid. Solvent system for flash column chromatography: DCM/MeOH: 92/8; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 6.81 (s, 1H), 3.71 (t, *J* = 4.6 Hz, 4H), 3.52 (q., *J* = 5.5 Hz, 2H), 2.58 (t, *J* = 6.0 Hz, 2H), 2.48 (s, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 166.4, 137.7, 133.0, 128.9, 128.4, 67.0, 56.9, 53.4, 36.2. This compound has been previously reported.[337]



74

(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)(piperidin-1-yl)methanone / CX-546 74. Prepared according to general procedure. Yield: 62% (166 mg, 618 µmol). Slightly yellow oil. Solvent system for flash column chromatography: DCM/MeOH: 92/8; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.85 (d, *J* = 9.4 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 4.22 (s, 4H), 3.49 (s, 4H), 1.62 (s, 2H), 1.54 (s, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 169.8, 144.6, 143.3, 129.5, 120.4, 117.1, 116.4, 64.4, 64.3, 48.8, 43.3, 26.0, 24.6. This compound has been previously reported.[338]



77

***N*-(2-(Diethylamino)ethyl)nicotinamide 77.** Prepared according to general procedure. Yield: 72% (80 mg, 362 µmol). Slightly yellow oil. Solvent system for flash column chromatography: AcOEt/MeOH: 50/50; **^{1}H-NMR** (400 MHz, CHLOROFORM-*D*) δ 8.95 (s, 1H), 8.64 (s, 1H), 8.28 – 7.94 (m, 1H), 7.31 (t, *J* = 6.4 Hz, 2H), 3.45 (t, *J* = 5.7 Hz, 2H), 2.63 (q., *J* = 8.0, 7.0 Hz, 2H), 2.58 – 2.48 (m, 4H), 0.99 (q., *J* = 9.2, 8.1 Hz, 6H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 165.4, 152.0, 148.0, 135.0, 130.4, 123.4, 51.2, 46.7, 37.2, 11.8. This compound has been previously reported.[339]

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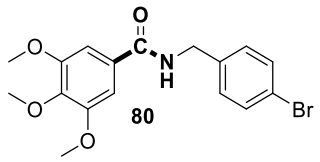
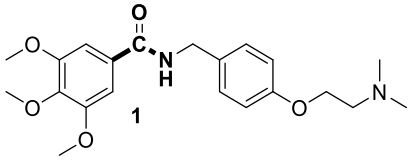
[339] Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 6061–6071.



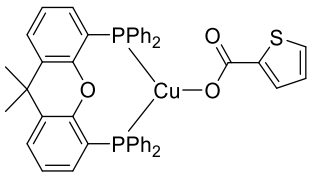
***N*-(4-bromobenzyl)-3,4,5-trimethoxybenzamide 80.** Prepared according to general procedure. Yield: 70% (266 mg, 699 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 50/50; white solid; **Mp**: 161 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.02 (s, 2H), 6.75 (t, *J* = 6.0 Hz, 1H), 4.52 (d, *J* = 5.8 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 6H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 167.2, 153.3, 141.1, 137.5, 131.8, 129.6, 129.6, 121.4, 104.5, 61.0, 56.4, 43.5; **IR** (neat): ν_{max} 3264, 1626 (C=O), 1581, 1536, 1497, 1454, 1411, 1369, 1332, 1234, 1127, 1070, 998, 813, 736 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{17}H_{19}BrNO_4$-$[M+H]^+$ 380.0497, found 380.0490.



***N*-(4-(2-(dimethylamino)ethoxy)benzyl)-3,4,5-trimethoxybenzamide / Tigan 1.** Prepared according to general procedure for the copper-catalyzed cross-coupling of alcohols with aryl halides: An oven-dried screw-cap test tube was charged with CuI (9.5 mg, 0.050 mmol), Me_4Phen (24 mg, 0.10 mmol), aryl halide (1.0 mmol, if solid), Cs_2CO_3 (490 mg, 1.5 mmol), and a magnetic stir bar. The reaction vessel was fitted with a rubber septum. The test tube was evacuated and back-filled with dry argon. Aryl halide (1. 0 mmol, if liquid), and toluene (0.50 mL) were then added by syringe. The rubber septum was removed and the reaction tube was quickly sealed with a Teflon-lined septum. The vessel was immersed in a pre-heated oil bath and stirred vigorously until TLC of the crude reaction mixture indicated that the aryl halide had been completely consumed. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (15 mL), and filtered through a plug of silica, eluting with additional ethyl acetate (30 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography (hexane/ethyl acetate) to provide the desired product.[340] Yield: 60% (60 mg, 154 µmol). Slightly yellow pale solid. Solvent system for flash column chromatography: DCM/MeOH/AcOEt: 5/1/1; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 7.02 (s, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.55 (s, 1H), 4.53 (d, *J* = 5.6 Hz, 2H), 4.06 (t, *J* = 5.7 Hz, 2H), 3.85 (s, 9H), 2.77 (t, *J* = 5.6 Hz, 2H), 2.36 (s, 6H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 167.0, 158.3, 153.2, 141.0, 130.6, 129.9, 129.4, 114.8, 104.5, 65.8, 60.9, 58.2, 56.4, 45.8, 43.7. This compound has been previously reported.[341]

[340] Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284–286.

[341] Lescot, C.; Nielsen, D. U.; Makarov, I. S.; Lindhardt, A. T.; Daasbjerg, K.; Skrydstrup, T. *J. Am. Chem. Soc.* **2014**, *136*, 6142–6147.



82

Cu(Xantphos)TC 82. Prepared according to general procedure reported in literature: to a 100 mL round bottom flask equipped with rubber septum and stir bar was charged with CuTC (1.0 g, 5.25 mmol, 1.0 equiv) and dry acetonitrile (50 mL). The resulting suspension was stirred at 50 °C for 5-10 minutes until all solids dissolved. Xantphos (3.6 g, 5.79 mmol, 1.1 equiv) was added in one portion. Beige precipitate formed immediately at addition of Xantphos. The suspension was stirred at 50 °C for 2 h and then at room temperature overnight. The mixture was filtered and the wet cake was washed with acetonitrile (10 mL), dried under vacuum/nitrogen stream. The product was afforded as a beige powder.[342] Yield: 62% (2.504 g, 3.25 mmol); beige powder; **Mp**: 200 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 3.6, 1.3 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.42 – 7.36 (m, 8H), 7.32 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.23 (d, *J* = 7.3 Hz, 4H), 7.16 (t, *J* = 7.2 Hz, 8H), 7.07 (t, *J* = 7.7 Hz, 2H), 7.00 (dd, *J* = 5.0, 3.6 Hz, 1H), 6.59 (ddd, *J* = 7.7, 4.6, 3.3 Hz, 2H), 1.66 (s, 6H); **^{31}P-NMR** (300 MHz, $CDCl_3$) δ -16.11; **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 168.6, 155.0 (t, *J* = 6.3 Hz), 142.7, 133.9 (t, *J* = 8.3 Hz), 133.5, 131.8 (t, *J* = 17.8 Hz), 131.6, 129.75, 128.5 (t, *J* = 5.0 Hz), 128.4, 127.1, 126.6, 124.6, 120.3 (t, *J* = 14.1 Hz), 35.9, 28.3; **IR** (neat): ν_{max} 1611, 1434, 1405, 1320, 1237, 1095, 793, 750, 697 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{39}H_{32}CuOP_2$ $[M]^+$ 641.1224, found 641.1236.

[342] Huang, J.; Chan, J.; Chen, Y.; Borths, C. J.; Baucom, K. D.; Larsen, R. D.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *11*, 3674–3675.

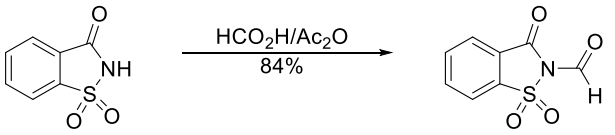
Experimental section of Chapter 3. Copper-catalyzed cross-coupling of acyl zirconium complexes and aryl iodonium salts

Illustration of the applied glassware for the presented work (COware gas reactor)

COware gas reactor. Two glass vials connected with a glass tube to allow gas-transfer.[343] Total volume = 20.0 mL. The system is sealed using a screw cap and a Teflon® coated silicone seal. The CO-ware used is ideal for a reaction scale of 0.1-1 mmol (total volume 20 mL). Glassware under pressure - Warning!

- Glass equipment should always be examined for damages to its surface, which may weaken its strength.
- One must abide to all laboratory safety procedures and always work behind a shield when working with glass equipment under pressure.
- COware is pressure tested to 224 psi, but should under no circumstances be operated above 60 psi (5 bar).

Synthesis of *N*-formylsaccharin (Carbon monoxide surrogate reagent for carbonylation)



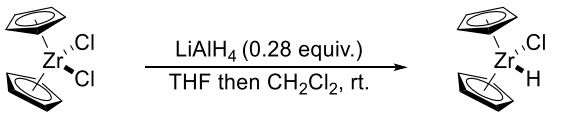
158
(15 € / 100g, Fluorochem)
CAS: 81-07-2

154
N-Formylsaccharin
(70 € / 5g, TCI)

***N*-Formylsaccharin 154**. Prepared according to general procedure reported by Cossy and co-workers.[344] Formic acid (20 mmol, 2 equiv.) and Ac_2O (20 mmol, 2 equiv.) were stirred at 60 °C for 2 h and saccharin (**158**, 1.83 g, 10 mmol, 1 equiv.) was added in one portion. The reaction mixture was stirred for 5 h at 60 °C. Water was added (30 mL), and the white precipitate was filtered to afford pure *N*-formylsaccharin. Yield: 84% (1.77 g, 8.4 mmol). Solvent system for flash column chromatography: DCM/MeOH: 95/10; white solid; **^{1}H-NMR** (300 MHz, CD_3CN) δ (ppm): 9.16 (s, 1H), 8.19 (d, *J* = 7.7 Hz, 1H), 8.14 – 8.07 (m, 2H), 8.04 – 8.00 (m, 1H); **^{13}C-NMR** (75 MHz, CD_3CN) δ (ppm): 157.7, 157.4, 137.9, 137.3, 135.3, 126.0, 124.6, 121.2. This compound has been previously reported.[345]

[343] Demaerel, J.; Veryser, C.; De Borggraeve, W. M. *React. Chem. Eng*. **2020**, *5*, 615–631.
[344] Cochet, T.; Bellosta, V.; Greiner, A.; Roche, D.; Cossy, J. *Synlett*, **2011**, *13*, 1920–1922.
[345] Gehrtz, P. H.; Hirschbecka, V.; Fleischer, I. *Chem. Commun.* **2015**, *51*, 12574–12577.

Synthesis of Schwartz reagent



97
(25 € / 114g, TCI)
CAS: 1291-32-3

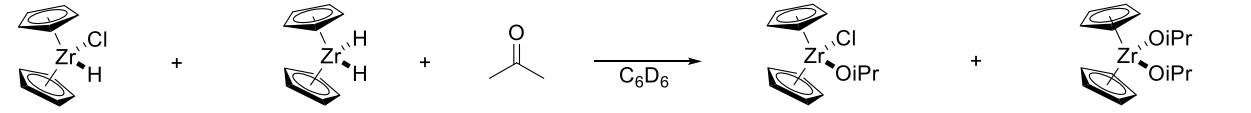
Schwartz's Reagent
98

Schwartz reagent was synthesized according to a modified version of previously reported protocol.[346]

General Procedure

A flame-dried 100 mL flask with Teflon stir bar was charged with zirconocene dichloride (**97**, 23.4 g, 80.0 mmol, 1.0 equiv.), degassed and anhydrous THF (50 mL) was added under argon. $LiAlH_4$ (850 mg, 22.4 mmol, 0.28 equiv.) was dissolved in THF (10 mL) and was transferred into reaction flask slowly (~10-20 min) using a syringe, after addition, the resulting suspension was stirred at the room temperature for 90 min. It was then filtered under air. The white solid was washed on the frit with anhydrous THF (3x15 mL) and anhydrous CH_2Cl_2 (3x15 mL) with stirring. The resulting white solid was dried in vacuum to give a white powder: 15.5-17.8 g, 75-86% yield. The Schwartz reagent **98** was stored in a dry box and kept away from light. **^{1}H-NMR** (300 MHz, C_6D_6) δ 6.02 ppm (s, 10H). **^{13}C-NMR** (75 MHz, C_6D_6) δ 114.1 ppm.

Purity identification of Cp_2ZrHCl: A small sample of the Schwartz' reagent (1 equiv.) is suspended with benzene-d6 in a vial and treated with a known amount of excess acetone (2 equiv.). **NOTE**: Placing the vial within an ultrasonic bath is advised to facilitate a quicker reaction of reduction of acetone with Cp_2ZrHCl. The relative areas of the signal for the mono- and diisopropoxides are determined by ^{1}H-NMR (300 MHz, C_6D_6 integrating the methyl doublets): Cp_2ZrHCl: ~90%:



Schwartz's Reagent, **92**

Bis(cyclopentadienyl) zirconium(IV) dihydride, **98**

(By-product)

99

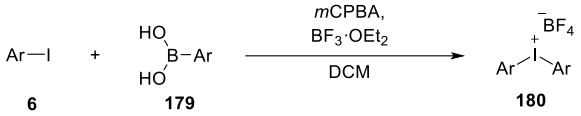
6.07 (s, 10H)
4.09 (septet, 1H)
0.99 (d, 6H).

100

6.17 (s, 10H)
3.90 (septet, 2H)
1.11 (d, 12H).

[346] (a) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Org. Synth.* **1993**, *71*, 77–82. (b) Gao, Y.; Yang, C.; Bai, S.; Liu, X.; Wu, Q.; Wang, J.; Jiang, C.; Qi, X. *Chem*, **2020**, *12*, 675–688.

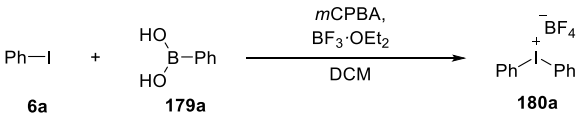
General Procedure for the *one-pot* synthesis of diaryliodonium tetrafluoroborates



6 **179** **180**

m-Chloroperbenzoic acid (81% active oxidant, 61 mg, 0.29 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL). To the solution was added aryl iodide (**6**, 0.26 mmol) followed by $BF_3{\cdot}OEt_2$ (81 µL, 0.65 mmol) at room temperature. The resulting yellow solution was stirred at room temperature for 30 min and then cooled to 0 °C, and arylboronic acid (**179**, 40 mg, 0.29 mmol) was added. After 15 min of stirring at room temperature, the crude reaction mixture was applied on a silica plug (0.8 g) and eluted with CH_2Cl_2 (10 mL) to remove unreacted ArI **6** and *m*-CBA, followed by CH_2Cl_2/MeOH (30 mL, 20:1), to elute the product, leaving any boric acid derivatives on the column. The latter solution was concentrated, and diethyl ether (1 mL) was added to the residue to induce a precipitation of salt, with any iodine(III) intermediates and BF_3 derivatives remaining in solution. (If precipitation is hard to obtain, a small amount of CH_2Cl_2 can be added.) The solution was allowed to stir for 15 min, and then the ether phase was decanted, and the solid was washed twice more with diethyl ether (2 × 1 mL) and then dried *in vacuo* to give pure diaryliodonium tetrafluoroborate salt as a solid.

These compounds have been previously reported and the data were consistent with those already reported in the literature. [325]

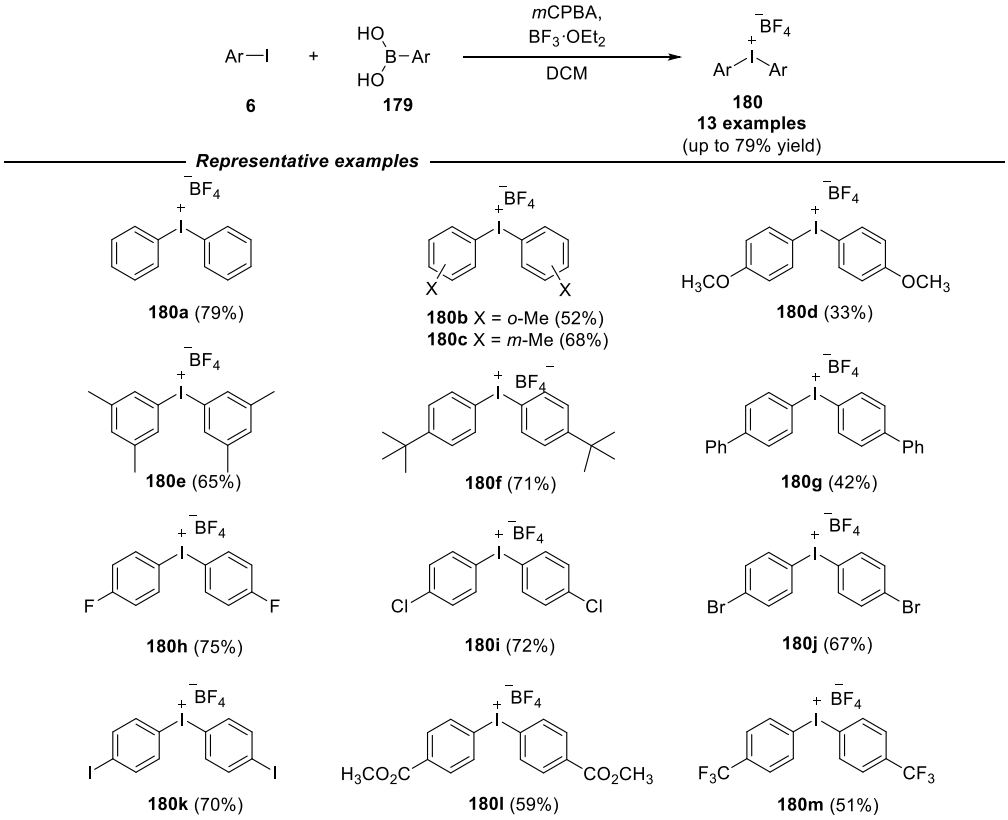


6a **179a** **180a**

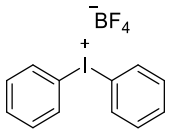
Large-scale synthesis of diphenyliodonium tetrafluoroborate (**180a**). *m*-Chloroperbenzoic acid (81% active oxidant, 640 mg, 3.0 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL). To the solution was added iodobenzene (**6a**, 310 µL, 2.7 mmol) followed by slow addition of $BF_3{\cdot}OEt_2$ (850 µL, 6.8 mmol) at room temperature. The resulting yellow solution was stirred at room temperature for 30 min and then cooled to 0 °C, and phenylboronic acid (**179a**, 370 mg, 3.0 mmol) was added. After 15 min of stirring at room temperature, the crude reaction mixture was applied on a silica plug (6.0 g) and eluted with CH_2Cl_2 (60 mL) followed by CH_2Cl_2/MeOH (120 mL, 20:1). The latter solution was concentrated, and diethyl ether (10 mL) was added to the residue to induce a precipitation. The solution was allowed to stir for 15 min, and then the ether phase was decanted. The solid was washed twice more with diethyl ether (2 × 10 mL) and then dried *in vacuo* to give salt **180a** in 79% yield (784 mg, 2.13 mmol). Analytical data were in agreement with previous reports.[325]

Modified synthesis of electron-rich salts 180d and 180g. *m*-Chloroperbenzoic acid (81% active oxidant, 68 mg, 0.30 mmol) was added to a sealed tube and dissolved in anhydrous CH_2Cl_2 (1 mL). To the solution was added aryl iodide (0.27 mmol), and the reaction mixture was placed in an 80 °C preheated oil bath. After 10 min, the vial was cooled to -78 °C, and a 0 °C mixture of $BF_3{\cdot}OEt_2$ (85 µL, 0.68 mmol) and arylboronic acid 2 (37 mg, 0.30 mmol), dissolved in CH_2Cl_2 (1 mL), was transferred to the cooled reaction mixture through a cannula. The resulting dark solution was stirred for 30 min at -78 °C and brought up to room temperature, and the product was isolated as described in the general procedure. Analytical data were in agreement with previous reports.[325]

Library of diaryliodonium tetrafluoroborates prepared 180a-m

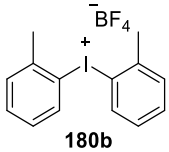


Scheme 149. Library of diaryliodonium tetrafluoroborates prepared.



180a

Diphenyliodonium tetrafluoroborate 180a. Prepared according to large-scale synthesis of diphenyliodonium tetrafluoroborate. Yield: 79% (784 mg, 2.1 mmol). Slightly yellow solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.25 (d, *J* = 8.3 Hz, 4H), 7.67 (t, *J* = 7.5 Hz, 2H), 7.53 (app. t, *J* = 7.7 Hz, 4 H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 135.2, 132.1, 131.8, 116.5; ^{19}F-NMR (282 MHz, DMSO-d_6): δ -147.72, -147.78 (4 F); **ESIHRMS** *m/z* calcd for $C_{12}H_{10}I$ $[M\text{-}BF_4^-]^+$ 280.9822, found 280.9832. This compound has been previously reported and the data were consistent with those already reported in the literature.[347]

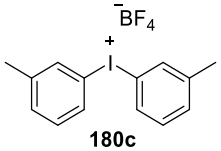


180b

Bis(2-methylphenyl)iodonium tetrafluoroborate 180b. Prepared according to large-scale synthesis of diphenyliodonium tetrafluoroborate. Yield: 52% (556 mg, 1.4 mmol). Slightly white-yellow solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.31 (d, *J* = 7.6 Hz, 2 H), 7.60-7.53 (m, 4 H), 7.33-7.27 (m, 2 H), 2.61 (s, 6 H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 140.6, 137.2, 132.8, 131.6, 129.3, 120.5, 25.0; ^{19}F-NMR (282 MHz, DMSO-d_6): δ -147.78, -147.83 (4 F); ESIHRMS *m/z* calcd for $C_{14}H_{14}I$ $[M\text{-}BF_4^-]^+$ 309.0135, found 309.0132.

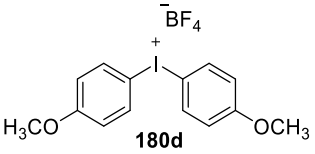
[347] Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem*. **2008**, *73*, 4602–4607.

This compound has been previously reported and the data were consistent with those already reported in the literature.[326]



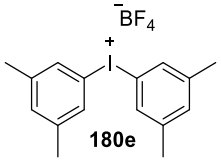
180c

Bis(3-methylphenyl)iodonium tetrafluoroborate 180c. Prepared according to large-scale synthesis of diphenyliodonium tetrafluoroborate. Yield: 68% (727 mg, 1.84 mmol). Pale brown solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.10 (s, 2H), 8.04 (d, *J* = 7.8 Hz, 2H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 2.34 (s, 6H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 141.8, 135.3, 132.7, 132.2, 131.4, 116.1, 20.7; ^{19}F-NMR (282 MHz, DMSO-d_6): δ −147.78, −147.83 (4 F); ESIHRMS *m/z* calcd for $C_{14}H_{14}I$ [M-BF_4^-]$^+$ 309.0140, found 309.0134. This compound has been previously reported and the data were consistent with those already reported in the literature.[348]



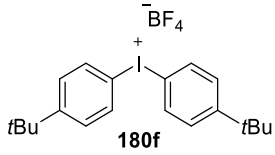
180d

Bis(4-methoxyphenyl)iodonium tetrafluoroborate 180d. Prepared according to modified synthesis of electron-rich salts. Yield: 33% (381 mg, 0.891 mmol). Pale grey solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.12 (d, *J* = 7.2 Hz, 4 H), 7.06 (d, *J* = 7.2 Hz, 4 H), 3.79 (s, 6 H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 161.8, 136.8, 117.3, 105.9, 55.7; ^{19}F-NMR (282 MHz, DMSO-d_6): δ -147.78, -147.84 (4 F); ESIHRMS *m/z* calcd for $C_{14}H_{14}IO_2$ [M-BF_4^-]$^+$ 341.0033, found 341.0029. This compound has been previously reported and the data were consistent with those already reported in the literature.[349]



180e

Bis(3,5-dimethylphenyl)iodonium tetrafluoroborate 180e. Prepared according to large-scale synthesis of diphenyliodonium tetrafluoroborate. Yield: 65% (744 mg, 1.75 mmol). White solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.88 (s, 4H), 7.28 (s, 2H), 2.30 (s, 12H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 141.4, 133.4, 132.4, 115.7, 20.6; ^{19}F-NMR (282 MHz, DMSO-d_6): δ −147.79, −147.84 (4 F); ESIHRMS *m/z* calcd for $C_{16}H_{18}I$ [M-BF_4^-]$^+$ 337.0448, found 337.0442. This compound has been previously reported and the data were consistent with those already reported in the literature.[327]

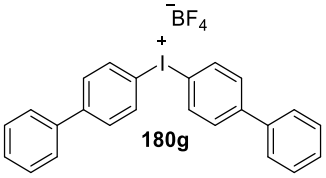


180f

Bis(4-*tert*-butylphenyl)iodonium tetrafluoroborate 180f. Prepared according to large-scale synthesis of diphenyliodonium tetrafluoroborate. Yield: 71% (920 mg, 1.91 mmol). White solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.16 (d, *J* = 8.5 Hz, 4H), 7.54 (d, *J* = 8.5 Hz, 4H), 1.25 (s, 18H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 155.2, 135.0, 128.9, 112.8, 34.9, 30.7; ^{19}F-NMR (282 MHz, DMSO-d_6): δ −147.80, −147.85(4 F); ESIHRMS *m/z* calcd for $C_{20}H_{26}I$ [M-BF_4^-]$^+$ 393.1074, found 393.1067.

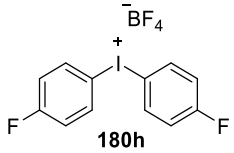
[348] Beaud, R.; Phipps, R. J.; Gaunt, M. J. *J. Am. Chem. Soc*. **2016**, *40*, 13183–13186.
[349] Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem*. **2008**, *73*, 4602–4607.

This compound has been previously reported and the data were consistent with those already reported in the literature.[327]



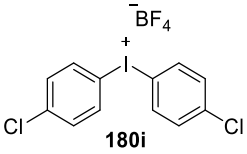
180g

Bis([1,1'-biphenyl]-4-yl)iodonium tetrafluoroborate 180g. Prepared according to large-scale synthesis of diphenyliodonium tetrafluoroborate. Yield: 42% (589 mg, 1.13 mmol). White-grey solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.43 (tt, *J* = 1.3, 7.3 Hz, 1H), 7.50 (tt, *J* = 1.6, 7.6 Hz, 2H), 7.70 (dt, *J* = 1.4, 7.0 Hz, 2H), 7.84 (dt, *J* = 2.0, 8.7 Hz, 2H), 8.35 (dt, *J* = 2.0, 8.7 Hz, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 115.1, 127.0, 128.6, 129.1, 129.8, 135.7, 138.0, 143.6; ^{19}F-NMR (282 MHz, DMSO-d_6): δ −147.80, −147.85(4 F); ESIHRMS *m/z* calcd for $C_{24}H_{18}I$ [M-BF_4^-]$^+$ 433.0453, found 433.0465. This compound has been previously reported and the data were consistent with those already reported in the literature.[350]



180h

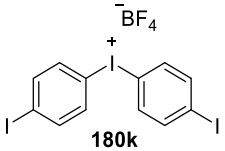
Bis(4-fluorophenyl)iodonium tetrafluoroborate 180h. Prepared according to large-scale synthesis of diphenyliodonium tetrafluoroborate. Yield: 75% (817 mg, 2.02 mmol). White grey solid. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.31 (d, *J* = 8.5 Hz, 2H), 7.41 (t, *J* = 9.0 Hz, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 164.0 (d, *J* = 250.6Hz), 138.0 (d, *J* = 8.8 Hz), 119.3 (d, *J* = 22.5 Hz), 111.2; ^{19}F-NMR (282 MHz, DMSO-d_6): δ –148.3 (d, *J* = 20Hz), –106.6 (q, *J* = 3.8 Hz); ESIHRMS *m/z* calcd for $C_{12}H_8F_2I$ [M-BF_4^-]$^+$ 316.9633, found 316.9630. This compound has been previously reported and the data were consistent with those already reported in the literature.[351]



180i

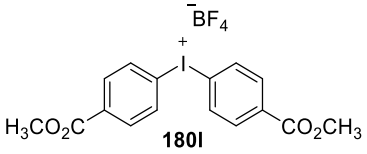
Bis(4-chlorophenyl)iodonium tetrafluoroborate 180i. Prepared according to large-scale synthesis of diphenyliodonium tetrafluoroborate. Yield: 72% (849 mg, 1.94 mmol). White grey solid. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.24 (d, *J* = 9 Hz, 2H), 7.62 (d, *J* = 9 Hz, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 137.5, 137.0, 131.8, 114.7; ^{19}F-NMR (282 MHz, DMSO-d6): δ –148.3 (d, J = 20 Hz); ESIHRMS *m/z* calcd for $C_{12}H_8Cl_2I$ [M-BF_4^-]$^+$ 348.9042, found 348.9041. This compound has been previously reported and the data were consistent with those already reported in the literature.[330]

[350] Lin, D. W.; Masuda, T.; Biskup, M. B.; Nelson, J. D.; Baran, P. S. *J. Org. Chem*. **2011**, *76*, 1013–1030.
[351] Wagner, A. M.; Sanford, M. S. *Org. Lett*. **2011**, *13*, 288–291.



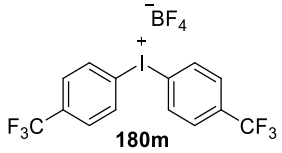
180k

Bis(4-bromophenyl)iodonium tetrafluoroborate 180j. Prepared according to large-scale synthesis of diphenyliodonium tetrafluoroborate. Yield: 67% (946 mg, 1.8 mmol). White grey solid. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.19 – 8.16 (m, 4H), 7.78 – 7.74 (m, 4H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 137.1, 134.7, 126.4, 115.3; ^{19}F-NMR (282 MHz, DMSO-d_6): δ −147.78, −147.83 (4 F); ESIHRMS m/z calcd for $C_{12}H_8I_3$ [M-BF_4^-]$^+$ 532.7755, found 532.7748. This compound has been previously reported and the data were consistent with those already reported in the literature.[352]



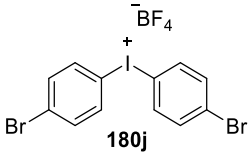
180l

Bis(4-iodophenyl)iodonium tetrafluoroborate 180k. Prepared according to large-scale synthesis of diphenyliodonium tetrafluoroborate. Yield: 70% (1.17 g, 1.89 mmol). White grey solid. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.97 (d, *J* = 9.0 Hz, 2H), 7.89 (d, *J* = 9.0 Hz, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 140.4, 136.8, 116.1, 100.4; ^{19}F-NMR (282 MHz, DMSO-d_6): δ –148.4 (d, *J* = 20 Hz, 4F); ESIHRMS m/z calcd for $C_{16}H_{14}IO_4$ [M-BF_4^-]$^+$ 396.9930, found 396.9932. This compound has been previously reported and the data were consistent with those already reported in the literature.[353]



180m

Bis(4-(ethoxycarbonyl)phenyl)iodonium tetrafluoroborate 180l. Prepared according to large-scale synthesis of diphenyliodonium tetrafluoroborate. Yield: 59% (770 mg, 1.59 mmol). White grey solid. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.39 (d, *J* = 8.5 Hz, 4H), 8.03 (d, *J* = 8.5 Hz, 4H), 4.32 (q, *J* = 7.1 Hz, 4H), 1.30 (t, *J* = 7.1 Hz, 6H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 164.6, 135.6, 133.0, 132.0, 121.4, 61.5, 14.0; ^{19}F-NMR (282 MHz, DMSO-d_6): δ −147.78, −147.84 (4 F); ESIHRMS m/z calcd for $C_{14}H_8F_6I$ [M-BF_4^-]$^+$ 416.9569, found 416.9574. This compound has been previously reported and the data were consistent with those already reported in the literature.[354]

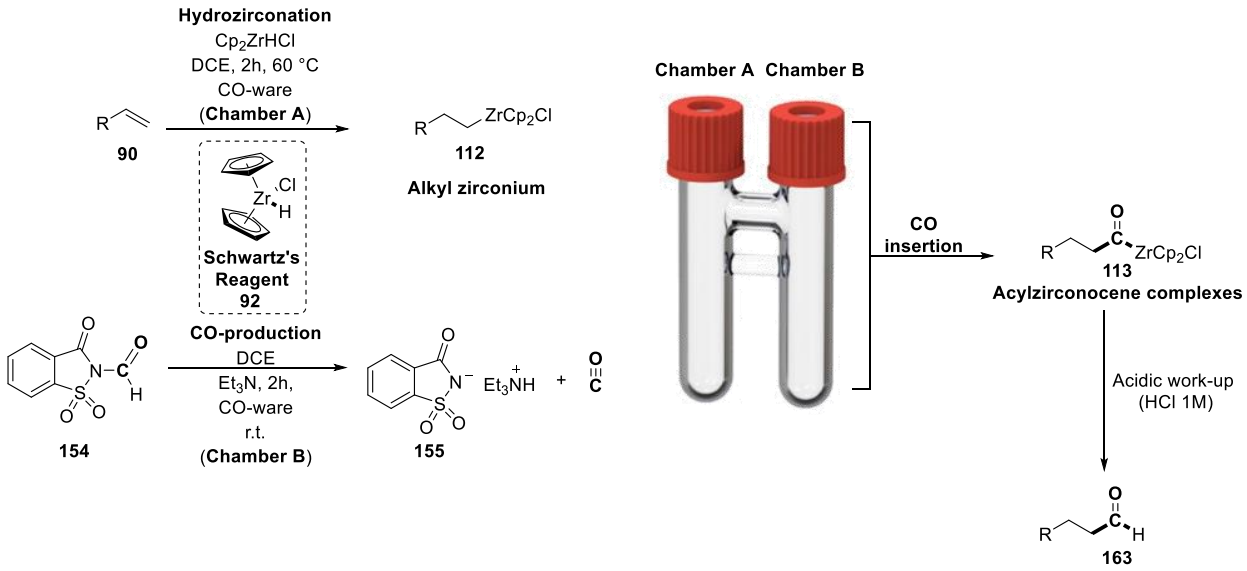


180j

Bis(4-trifluoromethylphenyl)iodonium tetrafluoroborate 180m. Prepared according to large-scale synthesis of diphenyliodonium tetrafluoroborate. Yield: 51% (693 mg, 1.37 mmol). White grey solid. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.51 (d, *J* = 8.0 Hz, 4 H), 7.95 (d, *J* = 8.0 Hz, 4 H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 136.3, 132.1 (q, *J* = 32.3 Hz), 128.6 (q, *J* = 3.5 Hz), 123.4 (q, *J* = 271.5 Hz), 121.0; ^{19}F-NMR (282 MHz, DMSO-d_6): δ -61.25 (6 F, s), - 147.78, -147.83 (4 F); ESIHRMS m/z calcd for $C_{12}H_8Br_2I$ [M-BF_4^-]$^+$ 436.8032, found 436.8017. This compound has been previously reported and the data were consistent with those already reported in the literature.[355]

[352] Beaud, R.; Phipps, R. J.; Gaunt, M. J. *J. Am. Chem. Soc*. **2016**, *40*, 13183–13186.
[353] Wagner, A. M.; Sanford, M. S. *Org. Lett*. **2011**, *13*, 288–291.
[354] Beaud, R.; Phipps, R. J.; Gaunt, M. J. *J. Am. Chem. Soc*. **2016**, *40*, 13183–13186.
[355] Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem*. **2008**, *73*, 4602–4607.

Acid hydrolysis of the acylzirconocene complex for the preparation of the homologated aldehyde



A two-chamber system was loaded as described below:

Chamber A: To chamber A of the two-chamber system was added di(cyclopentadienyl)zirconium(IV) chloride hydride (**92**, 322 mg, 1.25 mmol).

Chamber B: To chamber B of the two-chamber system was added *N*-formylsaccharin (**154**, 600 mg, 2.84 mmol).

The two-chamber system was sealed with the screwcaps fitted with a Teflon® seals and the stabilizers. The COware gas reactor was subjected to three vacuum-nitrogen cycles. Then, anhydrous 1,2-dichloroethane (2 mL) was added to the chamber A containing the Schwartz's reagent **92**, followed by the dropwise addition of the alkene (**90**, 1.25 mmol). The two-chamber system was immersed in an oil bath and the mixtures were stirred at 60 °C for 2 hours. After two hours, the two-chamber reactor was pulled out of the oil bath and in the chamber B was added under argon anhydrous 1,2-dichloroethane (2 mL) and triethylamine (354 μL, 2.5 mmol) dropwise.

NOTE: it is important to carry out a slow addition of triethylamine to avoid the formation of bubbles of CO in the solution that could potentially contaminate the second chamber of the two-chamber system (CO-ware).

After stirring for 2 hours at room temperature, the resulting slightly yellow solution was transferred into a beaker containing a magnetic stir bar, THF (15 mL) and 1M HCl (15 mL) in order to quench the solution of acylzirconocene complex to the corresponding homologated aldehyde. After stirring for 15 minutes over a stirring plate, the solution was extracted with DCM (3×15 mL). The organic phases were combined, washed with brine (2×15 mL), dried over Na_2SO_4 and volatiles were removed under reduced pressure to afford the desired aldehyde as a white solid.

Optimization of the reaction conditions for the preparation of the linear homologated aldehyde

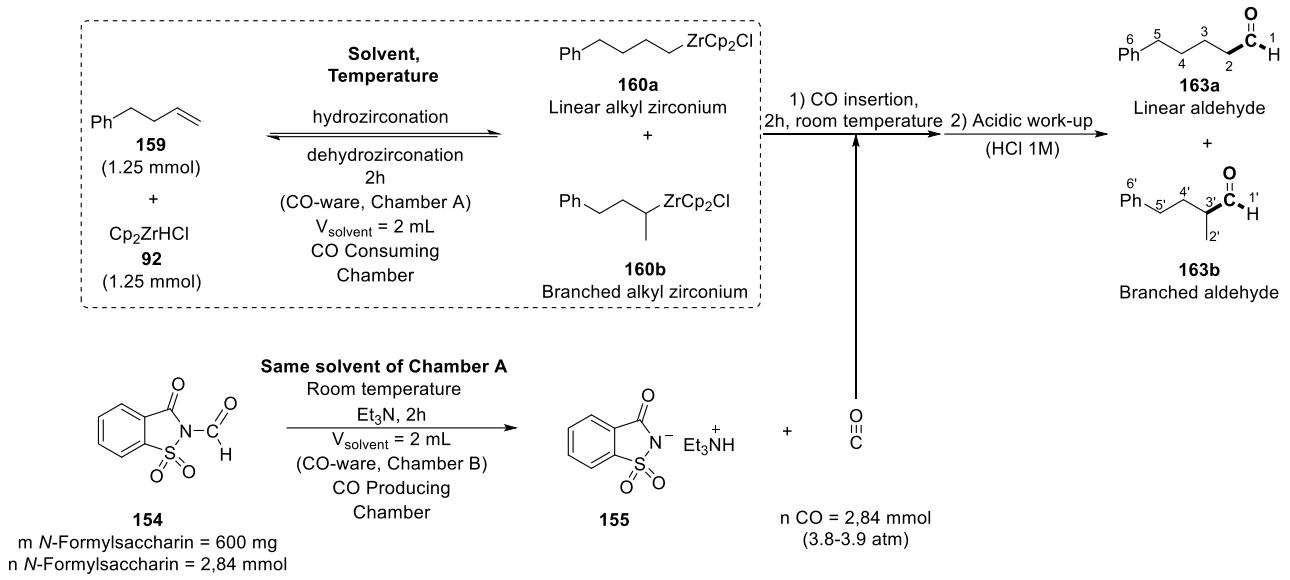
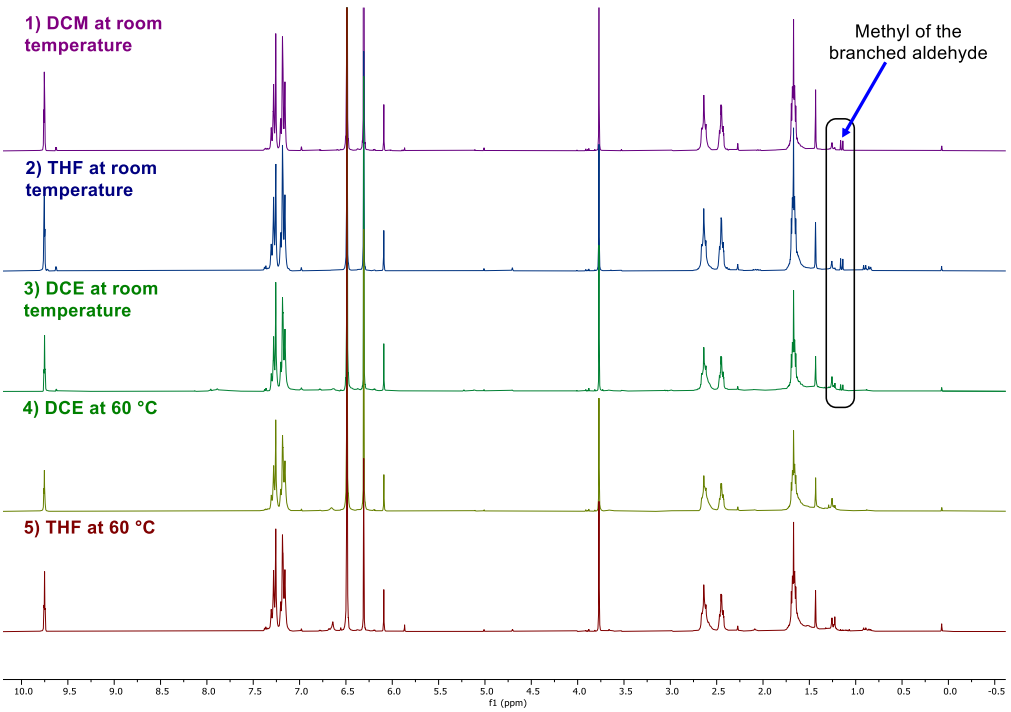


Table and ^{1}H-NMR spectra of the reaction conditions tested for the generation of the acyl-zirconium complex

Entry	Solvent	Temperature	^{1}H-NMR yield of the Linear aldehyde*	^{1}H-NMR yield of the Branched aldehyde*
1	DCM	Room temperature	90%	10%
2	DCE	Room temperature	77%	10%
3	DCE	60 °C	76%	-
4	THF	Room temperature	90%	10%
5	THF	60 °C	76%	-

*The yields were calculated using 1,3,5-trimethoxybenzene as an internal standard.



General Procedure

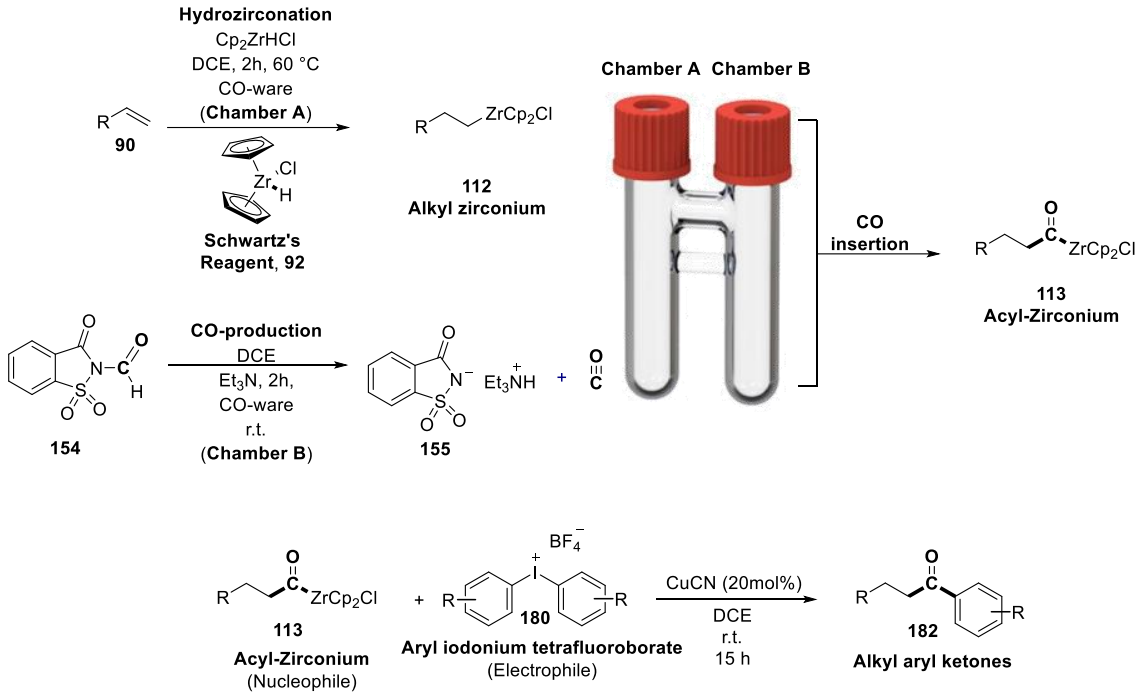


Figure 6. Scheme of the two-chamber gas reactor for the copper-catalyzed carbonylative arylation.

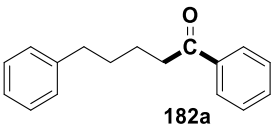
A two-chamber system was loaded as described below:

Chamber A: To chamber A of the two-chamber system was added di(cyclopentadienyl)zirconium(IV) chloride hydride (**92**, 322 mg, 1.25 mmol, 2.5 equiv.).

Chamber B: To chamber B of the two-chamber system was added *N*-formylsaccharin (**154**, 600 mg, 2.84 mmol).

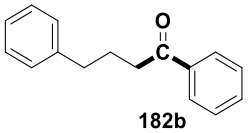
The two-chamber system was sealed with the screwcaps fitted with a Teflon® seals and the stabilizers. The COware gas reactor was subjected to three vacuum-nitrogen cycles. Then, anhydrous 1,2-dichloroethane (2 mL) was added to the chamber A containing the Schwartz's reagent **92**, followed by the dropwise addition of the alkene (**90**, 1.25 mmol, 2.5 equiv.). The two-chamber system was immersed in an oil bath and the mixtures were stirred at 60 °C for 2 hours. After two hours, the two-chamber reactor was pulled out of the oil bath and in the chamber B was added under argon anhydrous 1,2-dichloroethane (2 mL) and triethylamine (354 μL, 2.5 mmol) dropwise. After stirring for 2 hours at room temperature, the resulting slightly yellow solution was transferred *via* a cannula in a Schleck tube containing copper cyanide (10 mg, 0.1 mmol, 20 mol%) and aryl iodonium tetrafluoroborate (**180**, 0.5 mmol, 1 equiv.), previously subjected to three vacuum-nitrogen cycles. Finally, the chamber A of the two-chamber reactor was rinsed with anhydrous 1,2-dichloroethane (3 mL) and added in the Schleck tube. The resulting mixture was stirred at room temperature for 15 hours. The solution was transferred in a flask and the solvent was evaporated under reduced pressure in a rotary evaporator connected with a high vacuum pump. The crude product was purified by flash chromatography to afford the desired product.

Characterization Data



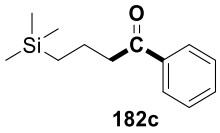
182a

1,5-Diphenylpentan-1-one 182a. Prepared according to general procedure. Yield: 84% (100 mg, 420 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 96/4; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.0 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.30 – 7.24 (m, 2H), 7.18 (d, *J* = 7.1 Hz, 3H), 2.98 (t, *J* = 7.1 Hz, 2H), 2.67 (t, *J* = 7.3 Hz, 2H), 1.87 – 1.60 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 200.3, 142.3, 137.1, 133.0, 128.6, 128.5, 128.4, 128.1, 125.8, 38.5, 35.9, 31.2, 24.1. This compound has been previously reported.[356]



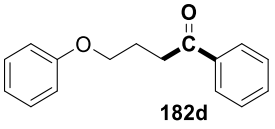
182b

1,4-Diphenylbutan-1-one 182b. Prepared according to general procedure. Yield: 79% (89 mg, 396 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 95/5; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.0 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.36 – 7.26 (m, 2H), 7.23 (d, *J* = 7.4 Hz, 3H), 2.99 (t, *J* = 7.3 Hz, 2H), 2.75 (t, *J* = 7.6 Hz, 2H), 2.11 (quint., *J* = 7.3 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 200.1, 141.8, 137.1, 133.0, 128.6, 128.6, 128.5, 128.1, 126.0, 37.7, 35.3, 25.8. This compound has been previously reported.[357]



182c

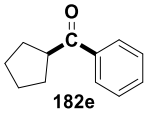
1-phenyl-4-(trimethylsilyl)butan-1-one 182c. Prepared according to general procedure. Yield: 77% (85 mg, 385 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 96/4; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 2.99 (t, *J* = 7.3 Hz, 2H), 1.88 – 1.63 (m, 2H), 0.58 (t, 2H), 0.00 (s, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 200.7, 137.2, 133.0, 128.6, 128.1, 42.4, 19.2, 16.8, -1.6.[358]



182d

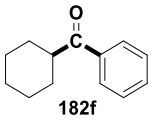
4-Phenoxy-1-phenylbutan-1-one 182d. Prepared according to general procedure. Yield: 67% (81 mg, 337 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 90/10; white solid; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.0 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.35 – 7.20 (m, 2H), 6.96 – 6.86 (m, 3H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.20 (t, *J* = 7.1 Hz, 2H), 2.25 (quint., *J* = 6.0 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 199.7, 159.0, 137.1, 133.1, 129.5, 128.7, 128.1, 120.8, 114.6, 66.9, 35.0, 23.9. This compound has been previously reported.[359]

[356] Dworakowski, K. R.; Pisarek, S.; Hassan, S.; Gryko, D. *Org. Lett*. **2021**, *23*, 9068–9072.
[357] Murphy, J. A.; Commeureuc, A. G. J.; Snaddon, T. N.; McGuire, T. M.; Khan, T. A.; Hisler, K.; Dewis, M. L.; Carling, R. *Org. Lett*. **2005**, *7*, 1427–1429.
[358] Clayden, J.; Watson, D. W.; Chambers, M. *Tetrahedron,* **2005***, 61*, 3195–3203.
[359] Jiao, Ning; Zhu, Yuchao; Zhang, Ziyao; Jin, Rui; Liu, Jianzhong; Liu, Guoquan; Han, Bing. *Angew. Chem. Int. Ed*. **2020**, *59*, 19851–19856.



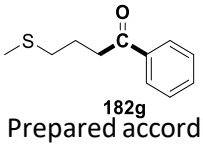
182e

Cyclopentyl(phenyl)methanone 182e. Prepared according to general procedure. Yield: 75% (65 mg, 373 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 96/4; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.0 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 3.71 (quint., *J* = 7.8 Hz, 1H), 1.99 – 1.84 (m, 4H), 1.76 – 1.62 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 202.9, 137.1, 132.8, 128.6, 128.5, 46.4, 30.1, 26.4. This compound has been previously reported.[360]



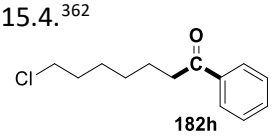
182f

cyclohexyl(phenyl)methanone 182f. Prepared according to general procedure. Yield: 72% (68 mg, 361 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 96/4; slightly yellow solid; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.0 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.3 Hz, 2H), 3.26 (tt, *J* = 11.3, 3.3 Hz, 1H), 1.97 – 1.78 (m, 4H), 1.58 – 1.39 (m, 2H), 1.40 – 1.20 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 204.0, 136.5, 132.8, 128.7, 128.3, 45.8, 29.5, 26.1, 26.0. This compound has been previously reported.[361]



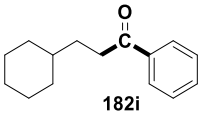
182g

4-(methylthio)-1-phenylbutan-1-one 182g. Prepared according to general procedure. Yield: 53% (52 mg, 267 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc:95/5; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.0 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 3.12 (t, *J* = 7.1 Hz, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 2.11 (s, 3H), 2.06 (t, *J* = 7.1 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 199.7, 137.0, 133.1, 128.7, 128.1, 37.1, 33.8, 23.2, 15.4.[362]



182h

7-chloro-1-phenylheptan-1-one 182h. Prepared according to general procedure. Yield: 67% (75 mg, 335 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 95/5; slightly yellow solid; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.0 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 3.53 (t, *J* = 6.7 Hz, 2H), 2.97 (t, *J* = 7.3 Hz, 2H), 1.86 – 1.69 (m, 4H), 1.55 – 1.32 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 200.3, 137.1, 133.0, 128.7, 128.1, 45.1, 38.4, 32.5, 28.6, 26.8, 24.1.[363]



182i

3-cyclohexyl-1-phenylpropan-1-one 182i. Prepared according to general procedure. Yield: 78% (84 mg, 388 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 96/4; slightly yellow solid; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.0 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 3.02 – 2.89 (m, 2H), 1.80 – 1.55 (m, 7H), 1.37 – 1.11 (m, 4H), 1.03 – 0.82 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 200.8, 137.2, 132.9, 128.6, 128.1, 37.5, 36.2, 33.3, 31.8, 26.6, 26.3. This compound has been previously reported.[364]

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[360] Li, L.; Cai, P.; Guo, Q.; Xue, S. *J. Org. Chem*. **2008**, *73*, 3516–3522**.**

[361] Li, L.; Cai, P.; Guo, Q.; Xue, S. *J. Org. Chem.* **2008**, *73*, 3516–3522.

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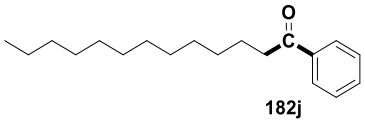
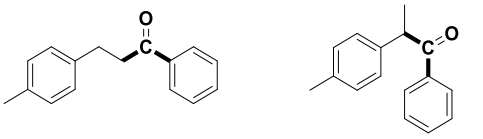


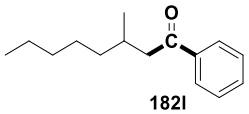
182j

1-phenyltridecan-1-one 182j. Prepared according to general procedure. Yield: 80% (110 mg, 400 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 96/4; white solid; Mp: 38 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.96 (d, *J* = 6.9 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 2.96 (t, *J* = 7.4 Hz, 2H), 1.73 (quint., *J* = 7.4 Hz, 2H), 1.34 (s, 6H), 1.26 (s, 12H), 0.87 (t, *J* = 6.9 Hz, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 200.7, 137.3, 132.9, 128.6, 128.2, 77.1, 38.7, 32.0, 29.8, 29.7, 29.6, 29.6, 29.5, 29.4, 24.5, 22.8, 14.2; **IR** (neat): ν_{max} 2919, 2850, 1683 (C=O), 1597, 1463, 1376, 1263, 1209, 1002, 968, 736, 688, 570 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{19}H_{31}O$ $[M+H]^+$ 275.2375, found 275.2371.



182ka (Linear isomer) **182kb** (Branched isomer)

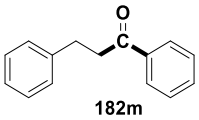
1-phenyl-3-(*p*-tolyl)propan-1-one 182k. Prepared according to general procedure. Yield: 82% (91 mg, 410 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 95/5; slightly yellow oil. Obtained as a mixture of linear and branched isomers in a linear/branched ratio of 75/25 after purification. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.98 (d, *J* = 6.9 Hz, 2.52H, linear + branched isomers), 7.57 (t, *J* = 7.3 Hz, 0.95H, linear isomer), 7.46 (t, *J* = 7.4 Hz, 2.23H, linear + branched isomers), 7.39 (t, *J* = 7.3 Hz, 0.74H, branched isomers), 7.27 – 7.03 (m, 6H, linear + branched isomers), 4.67 (q., *J* = 6.8 Hz, 0.33H, branched isomer), 3.30 (t, *J* = 7.9 Hz, 2H, linear isomer), 3.05 (t, *J* = 7.9 Hz, 2H, linear isomer), 2.34 (s, 3H, linear isomer), 2.30 (s, 1.16H, branched isomer), 1.54 (d, *J* = 6.8 Hz, 0.98H, branched isomer); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 200.5 (branched isomer), 199.4 (linear isomer), 138.6 (branched isomer), 138.3 (linear isomer), 137.0 (linear isomer), 136.6 (branched isomer), 136.6 (branched isomer), 135.7 (linear isomer), 133.1 (linear isomer), 132.8 (branched isomer), 129.8 (branched isomer), 129.3 (linear isomer), 128.8 (branched isomer), 128.7 (linear isomer), 128.5 (branched isomer), 128.4 (linear isomer), 128.1 (linear isomer), 127.7 (branched isomer), 47.6 (branched isomer), 40.7 (linear isomer), 29.8 (linear isomer), 21.1 (linear + branched isomers), 19.6 (branched isomer).[365]



182l

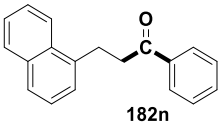
3-Methyl-1-phenyloctan-1-one 182l. Prepared according to general procedure. Yield: 64% (70 mg, 320 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 95/5; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.0 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.3 Hz, 2H), 2.94 (dd, *J* = 15.8, 5.7 Hz, 1H), 2.74 (dd, *J* = 15.7, 8.0 Hz, 1H), 2.22 – 2.10 (m, 1H), 1.36 – 1.18 (m, 8H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.91 – 0.84 (m, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 200.6, 137.6, 132.9, 128.6, 128.2, 46.1, 37.2, 32.1, 29.9, 26.8, 22.7, 20.1, 14.1; **IR** (neat): ν_{max} 2925, 2856, 1684 (C=O), 1597, 1448, 1364, 1281, 1213, 1179, 1002, 750, 689, 660, 602, 571 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{15}H_{23}O$ $[M+H]^+$ 219.1749, found 219.1744.

[365] a) Cui, X.; Zhang, Y.; Shi, F.; Deng, Y. *Chem. Eur. J.* **2011**, *17*, 1021–1028. b) Liu, C.; He, C.; Shi, W.; Chen, M.; Lei, A. *Org. Lett.* **2007**, *9*, 5601–5604.



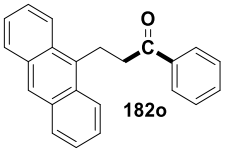
182m

1,3-diphenylpropan-1-one 182m. Prepared according to general procedure. Yield: 75% (79 mg, 375 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 96/4; slightly yellow oil. Obtained as a mixture of linear and branched isomers in a linear/branched ratio of 85/15 after purification. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.0 Hz, 2.32H, linear + branched isomers), 7.54 (t, *J* = 7.3 Hz, 1H, linear isomer), 7.44 (t, *J* = 7.4 Hz, 2.13H, linear isomer), 7.36 (t, *J* = 7.4 Hz, 0.41H, branched isomer), 7.35 – 7.10 (m, 6.63H, linear + branched isomers), 4.67 (q., *J* = 6.9 Hz, 0.17H, branched isomer), 3.29 (t, *J* = 7.9 Hz, 2H, linear isomer), 3.06 (t, *J* = 7.9 Hz, 2H, linear isomer), 1.52 (d, *J* = 6.8 Hz, 0.52H, branched isomer); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 200.1 (branched isomer), 199.0 (linear isomer), 141.3 (branched isomer), 141.1 (linear isomer), 136.7 (linear isomer), 136.3 (branched isomer), 132.9 (linear isomer), 132.6 (branched isomer), 128.8 (branched isomer), 128.6 (branched isomer), 128.4 (linear isomer), 128.4 (linear isomer), 128.3 (branched isomer), 128.3 (linear isomer), 127.9 (linear isomer), 127.6 (branched isomer), 126.7 (branched isomer), 126.0 (linear isomer), 47.7 (branched isomer), 40.3 (linear isomer), 30.0 (linear isomer), 19.3 (branched isomer).[366]



182n

3-(naphthalen-1-yl)-1-phenylpropan-1-one 182n. Prepared according to general procedure. Yield: 69% (90 mg, 345 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 95/5; slightly beige solid; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.3 Hz, 1H), 7.97 (d, *J* = 7.0 Hz, 2H), 7.89 (d, *J* = 9.5 Hz, 1H), 7.79 – 7.71 (m, 1H), 7.59 – 7.40 (m, 7H), 3.56 (t, *J* = 7.0 Hz, 2H), 3.44 (t, *J* = 7.0 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 199.4, 137.4, 136.9, 134.0, 133.2, 131.8, 129.0, 128.7, 128.1, 127.1, 126.2, 126.2, 125.7, 125.7, 123.6, 39.8, 27.3.[367]



182o

3-(anthracen-9-yl)-1-phenylpropan-1-one 182o. Prepared according to general procedure. Yield: 52% (80 mg, 258 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 96/4; slightly yellow solid; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.27 (d, *J* = 8.8 Hz, 2H), 8.04 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.96 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.62 – 7.38 (m, 7H), 4.09 (d, *J* = 8.1 Hz, 2H), 3.47 (d, *J* = 8.0 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 199.5, 136.8, 133.5, 133.3, 131.8, 129.6, 129.5, 128.7, 128.2, 126.3, 126.0, 125.1, 124.1, 77.1, 39.8, 22.1.[368]

[366] a) Kose, O.; Saito, S. *Org. Biomol. Chem.* **2010**, *8*, 896–900. b) Cheon, C. H.; Kanno, O.; Toste, D. F. *J. Am. Chem. Soc.* **2011**, *133*, 13248–13251.

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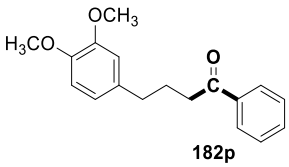
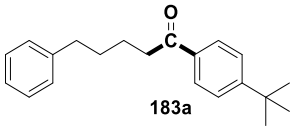


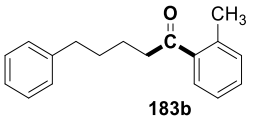
182p

4-(3,4-dimethoxyphenyl)-1-phenylbutan-1-one 182p. Prepared according to general procedure. Yield: 65% (92 mg, 325 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; white solid; Mp: 50 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 6.78 (t, *J* = 8.7 Hz, 1H), 6.73 (d, *J* = 7.3 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.97 (t, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.07 (quint., *J* = 7.4 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 200.3, 149.0, 147.4, 137.1, 134.4, 133.0, 128.6, 128.1, 120.4, 111.9, 111.4, 56.0, 55.9, 37.7, 34.8, 25.9; **IR** (neat): ν_{max} 2937, 1681 (C=O), 1591, 1513, 1448, 1259, 1233, 1141, 1027, 806, 733, 690, 631, 569 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{18}H_{21}O_3$ $[M+H]^+$ 285.1491, found 285.1486.



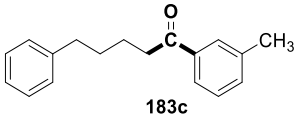
183a

1-(4-(*tert*-butyl)phenyl)-5-phenylpentan-1-one 183a. Prepared according to general procedure. Yield: 75% (100 mg, 375 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 96/4; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.38 – 7.29 (m, 2H), 7.24 (d, *J* = 7.4 Hz, 3H), 3.02 (t, *J* = 7.1 Hz, 2H), 2.73 (t, *J* = 7.3 Hz, 2H), 1.90 – 1.72 (m, 4H), 1.40 (s, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 200.0, 156.7, 142.4, 134.5, 128.5, 128.4, 128.1, 125.8, 125.6, 38.4, 35.9, 35.1, 31.2, 31.2, 24.2.[369]



183b

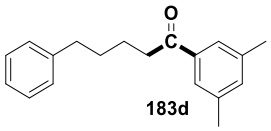
5-phenyl-1-(*o*-tolyl)pentan-1-one 183b. Prepared according to general procedure. Yield: 82% (103 mg, 408 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 95/5; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.0 Hz, 1H), 7.44 – 7.35 (m, 1H), 7.34 – 7.14 (m, 7H), 2.94 (t, *J* = 7.0 Hz, 2H), 2.69 (t, *J* = 7.3 Hz, 2H), 2.51 (s, 3H), 1.87 – 1.56 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 204.6, 142.3, 138.3, 137.9, 132.0, 131.1, 128.5, 128.4, 128.3, 125.8, 125.7, 41.5, 35.9, 31.2, 24.1, 21.3; **IR** (neat): ν_{max} 3025, 2928, 2857, 1682 (C=O), 1601, 1453, 1217, 965, 746, 698, 461 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{18}H_{21}O$ $[M+H]^+$ 253.1592, found 253.1586.



183c

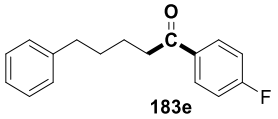
5-phenyl-1-(*m*-tolyl)pentan-1-one 183c. Prepared according to general procedure. Yield: 77% (97 mg, 384 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 95/5; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 7.2 Hz, 2H), 7.22 – 7.14 (m, 2H), 7.10 (d, *J* = 7.3 Hz, 3H), 2.88 (t, *J* = 7.0 Hz, 2H), 2.58 (t, *J* = 7.3 Hz, 2H), 2.32 (s, 3H), 1.89 – 1.55 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 200.5, 142.3, 138.4, 137.2, 133.7, 128.6, 128.5, 128.5, 128.4, 125.8, 125.3, 38.5, 35.9, 31.2, 24.1, 21.4; **IR** (neat): ν_{max} 3029, 2927, 2857, 1682 (C=O), 1603, 1452, 1255, 1157, 1030, 744, 698, 583, 463 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{18}H_{21}O$ $[M+H]^+$ 253.1592, found 253.1586.

[369] Dworakowski, K. R.; Pisarek, S.; Hassan, S.; Gryko, D. *Org. Lett.* **2021**, *23*, 9068–9072.



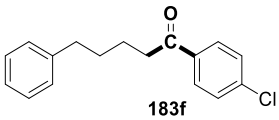
183d

1-(3,5-dimethylphenyl)-5-phenylpentan-1-one 183d. Prepared according to general procedure. Yield: 78% (104 mg, 390 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 95/5; slightly yellow solid; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.45 (s, 2H), 7.28 – 7.14 (m, 2H), 7.09 (d, *J* = 7.2 Hz, 5H), 2.86 (t, *J* = 7.0 Hz, 2H), 2.57 (t, *J* = 7.3 Hz, 2H), 2.27 (s, 6H), 2.00 – 1.53 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 200.7, 142.3, 138.2, 137.3, 134.6, 128.5, 128.4, 125.9, 125.8, 38.5, 35.8, 31.1, 24.1, 21.3.[370]



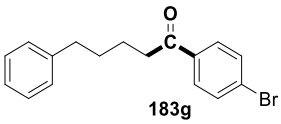
183e

1-(4-fluorophenyl)-5-phenylpentan-1-one 183e. Prepared according to general procedure. Yield: 75% (96 mg, 374 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 96/4; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.87 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.28 – 7.13 (m, 2H), 7.10 (d, *J* = 7.1 Hz, 3H), 7.02 (t, *J* = 8.6 Hz, 2H), 2.85 (t, *J* = 7.0 Hz, 2H), 2.58 (t, *J* = 7.3 Hz, 2H), 2.21 – 1.38 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 198.6, 165.75 (d, *J* = 254.3 Hz), 142.2, 133.5, 133.5, 130.8, 130.6, 128.5, 128.4, 125.8, 115.8, 115.5, 38.4, 35.8, 31.1, 24.0; **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -105.58; **IR** (neat): ν_{max} 2930, 2857, 1683 (C=O), 1596, 1505, 1454, 1409, 1225, 1155, 973, 834, 744, 698, 563, 491 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{17}H_{18}FO$ $[M+H]^+$ 257.1342, found 257.1335.



183f

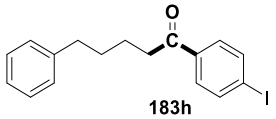
1-(4-chlorophenyl)-5-phenylpentan-1-one 183f. Prepared according to general procedure. Yield: 72% (98 mg, 359 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 96/4; white solid; Mp: 53 °C ; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.28 – 7.17 (m, 2H), 7.11 (d, *J* = 6.0 Hz, 3H), 2.87 (t, *J* = 7.0 Hz, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 1.91 – 1.44 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 199.0, 142.2, 139.4, 135.4, 129.5, 129.0, 128.5, 128.4, 125.9, 38.5, 35.8, 31.1, 24.0; **IR** (neat): ν_{max} 2931, 2857, 1681 (C=O), 1584, 1486, 1452, 1396, 1247, 1196, 1092, 978, 839, 745, 699, 505 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{17}H_{18}{}^{35}ClO$ $[M+H]^+$ 273.1046, found 273.1041.



183g

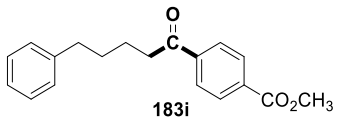
1-(4-bromophenyl)-5-phenylpentan-1-one 183g. Prepared according to general procedure. Yield: 81% (128 mg, 403 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 95/5; slightly yellow solid; Mp: 72 °C ; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.23 – 7.15 (m, 3H), 7.10 (d, *J* = 5.7 Hz, 2H), 2.85 (t, *J* = 6.9 Hz, 2H), 2.58 (t, *J* = 7.2 Hz, 2H), 1.94 – 1.56 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 199.2, 142.2, 135.8, 131.9, 129.6, 128.5, 128.4, 128.1, 125.9, 38.4, 35.8, 31.1, 23.9; **IR** (neat): ν_{max} 3029, 2930, 2857, 1681 (C=O), 1580, 1493, 1394, 1247, 1195, 1070, 1007, 976, 835, 732, 701, 495 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{17}H_{18}{}^{79}BrO$ $[M+H]^+$ 317.0541, found 317.0535.

[370] Zheng, Y.; Xie, P.; Daneshfar, O.; Houk, K. N.; Hong, X.; Newman, S. G. *Angew. Chem. Int. Ed*. **2021**, *133*, 13588–13595.



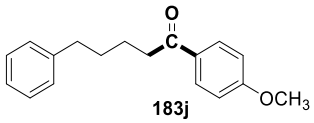
183h

1-(4-iodophenyl)-5-phenylpentan-1-one 183h. Prepared according to general procedure. Yield: 64% (117 mg, 321 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 96/4; slightly yellow solid; Mp: 87 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.36 – 7.16 (m, 3H), 7.11 (d, *J* = 5.4 Hz, 2H), 2.85 (t, *J* = 7.0 Hz, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.13 – 1.53 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 199.6, 142.2, 138.0, 136.3, 129.6, 128.5, 128.4, 125.9, 100.9, 38.4, 35.8, 31.1, 23.9; **IR** (neat): ν_{max} 3025, 2929, 2857, 1681 (C=O), 1577, 1492, 1390, 1248, 1195, 1003, 976, 831, 746, 699, 492 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{17}H_{18}IO$ $[M+H]^+$ 365.0402, found 365.0396.



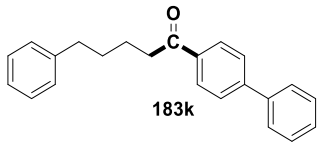
183i

Methyl 4-(5-phenylpentanoyl)benzoate 183i. Prepared according to general procedure. Yield: 64% (95 mg, 320 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 90/10; white solid; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.23 – 7.13 (m, 2H), 7.10 (d, *J* = 7.2 Hz, 3H), 3.86 (s, 3H), 2.92 (t, *J* = 6.9 Hz, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.05 – 1.49 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 199.7, 166.3, 142.2, 140.3, 133.8, 129.9, 128.4, 128.4, 128.0, 125.9, 52.5, 38.8, 35.8, 31.0, 23.8.[371]



183j

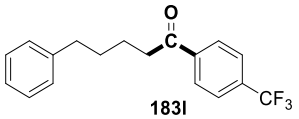
1-(4-methoxyphenyl)-5-phenylpentan-1-one 183j. Prepared according to general procedure. Yield: 67% (90 mg, 335 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 96/4; white solid; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.9 Hz, 2H), 7.24 – 7.14 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 3H), 6.83 (d, *J* = 8.9 Hz, 2H), 3.76 (s, 3H), 2.83 (t, *J* = 7.0 Hz, 2H), 2.57 (t, *J* = 7.3 Hz, 2H), 2.13 – 1.16 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 198.9, 163.4, 142.3, 130.3, 130.2, 128.5, 128.3, 125.8, 113.7, 55.5, 38.1, 35.9, 31.2, 24.3.[372]



183k

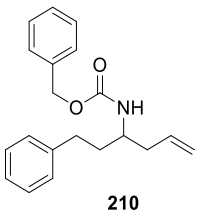
1-([1,1'-biphenyl]-4-yl)-5-phenylpentan-1-one 183k. Prepared according to general procedure. Yield: 57% (90 mg, 286 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 95/5; white solid; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 6.9 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.35 – 7.26 (m, 2H), 7.21 (d, *J* = 7.1 Hz, 3H), 3.03 (t, *J* = 7.1 Hz, 2H), 2.70 (t, *J* = 7.3 Hz, 2H), 2.13 – 1.65 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 200.0, 145.7, 142.3, 140.0, 135.8, 129.0, 128.7, 128.5, 128.4, 128.3, 127.3, 127.3, 125.8, 38.5, 35.9, 31.2, 24.1.[373]

[371] Crawley, M. L.; Phipps, K. M.; Goljer, I.; Mehlmann, F. J.; Lundquist J. T.; Ullrich, J. W.; Yang, C.; Mahaney, E. P. *Org. Lett.* **2009**, *11*, 5, 1183–1185.
[372] Babu, S. A.; Yasuda, M.; Baba, A. *Org. Lett*. **2007**, *9*, 405–408.
[373] Dworakowski, K. R.; Pisarek, S.; Hassan, S.; Gryko, D. *Org. Lett.* **2021**, *23*, 9068–9072.



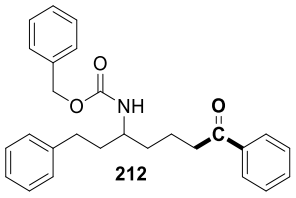
183l

5-phenyl-1-(4-(trifluoromethyl)phenyl)pentan-1-one 183l. Prepared according to general procedure. Yield: 51% (78 mg, 255 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 95/5; slightly yellow solid; Mp: 37 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.45 – 7.15 (m, 2H), 7.11 (d, *J* = 5.9 Hz, 3H), 2.92 (t, *J* = 7.0 Hz, 2H), 2.60 (t, *J* = 7.3 Hz, 2H), 2.02 – 1.51 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 199.2, 142.2, 139.8, 134.4 (q, *J* = 32.6 Hz), 128.5, 128.4, 125.9, 125.7 (q, *J* = 3.8 Hz), 38.8, 35.8, 31.0, 23.8; **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -63.08; **IR** (neat): ν_{max} 3029, 2933, 2861, 1687 (C=O), 1496, 1454, 1409, 1323, 1165, 1125, 1065, 1015, 980, 835, 743, 698, 602, 499 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{18}H_{18}F_3O$ $[M+H]^+$ 307.1310, found 307.1305.



210

Benzyl (1-phenylhex-5-en-3-yl) carbamate 210. Yield: 88% (4.06 g, 13 mmol). Solvent system for flash column chromatography: PE/EtOAc: 90/10; white solid; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 7H), 7.24 – 7.15 (m, 3H), 5.90 – 5.69 (m, 1H), 5.14 (s, 3H), 5.09 (s, 1H), 4.72 (d, *J* = 9.1 Hz, 1H), 3.98 – 3.66 (m, 1H), 2.87 – 2.52 (m, 2H), 2.45 – 2.16 (m, 2H), 1.97 – 1.76 (m, 1H), 1.80 – 1.62 (m, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 156.0, 141.7, 136.7, 134.0, 128.6, 128.5, 128.4, 128.1, 128.1, 126.0, 118.1, 66.6, 50.5, 39.6, 36.5, 32.4. This compound has been previously reported.[374]



212

Benzyl (7-oxo-1,7-diphenylheptan-3-yl)carbamate 212. Following a modified procedure of the general protocol, a two-chamber system of 100 mL was loaded as described below:

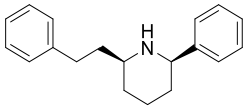
Chamber A: To chamber A of the two-chamber system was added di(cyclopentadienyl)zirconium(IV) chloride hydride (1,29 g, 5.0 mmol, 2.5 equiv.) and the solid alkene (compound **210**, 1.55 g, 5.0 mmol, 2.5 equiv.)

Chamber B: To chamber B of the two-chamber system was added *N*-formylsaccharin (2.0 g, 9.5 mmol).

The two-chamber system was sealed with the screwcaps fitted with a Teflon® seals and the stabilizers. The COware gas reactor was subjected to three vacuum-nitrogen cycles. Then, anhydrous 1,2-dichloroethane (20 mL) was added to the chamber A. The two-chamber system was immersed in an oil bath and the mixtures were stirred at 60 °C for 2 hours. After two hours, the two-chamber reactor was pulled out of the oil bath and in the chamber B was added under argon anhydrous 1,2-dichloroethane (20 mL) and triethylamine (1.3 mL, 9.5 mmol) dropwise. After stirring for two hours at room temperature, the resulting slightly yellow solution was transferred *via* a cannula in a Schleck tube containing 10 mol % of copper cyanide (40 mg, 0.45 mmol) and aryl iodonium tetrafluoroborate (736 mg, 2 mmol, 1 equiv.), previously subjected to three vacuum-nitrogen cycles. Finally, the chamber A of the two-chamber reactor was rinsed with anhydrous 1,2-dichloroethane (30 mL) and added in the Schleck tube. The resulting mixture was stirred at room temperature

[374] Pasunooti, K. K.; Leow, M. L.; Vedachalam, S.; Gorityala, B. K.; X. W. Liu. *Tetrahedron Lett.* **2009**, *50*, 2979–2981.

for 15 hours. The solution was transferred in a flask and the solvent was evaporated under reduced pressure in a rotary evaporator connected with a high vacuum pump. The crude product was purified by flash chromatography to afford the desired product.
Yield: 30% (249 mg, 600 µmol). Solvent system for flash column chromatography: DCM/MeOH: 96/4; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.98 – 7.77 (m, 2H), 7.58 – 7.42 (m, 1H), 7.41 – 7.32 (m, 2H), 7.30 – 6.98 (m, 10H), 5.03 (s, 2H), 4.58 (d, *J* = 9.3 Hz, 1H), 3.96 – 3.49 (m, 1H), 3.25 – 2.76 (m, 2H), 2.70 – 2.44 (m, 2H), 2.09 – 1.60 (m, 4H), 1.57–1.33 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 200.0, 156.3, 141.8, 137.0, 136.7, 133.1, 128.7, 128.6, 128.5, 128.4, 128.1, 128.1, 126.0, 66.7, 51.0, 38.0, 37.3, 34.9, 32.4, 20.3; **IR** (neat): ν_{max} 3335, 3029, 2945, 1684, 1597, 1525, 1449, 1234, 1050, 909, 731, 694, 570, 456 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{27}H_{30}NO_3$ $[M+H]^+$ 416.2226, found 416.2220.



213

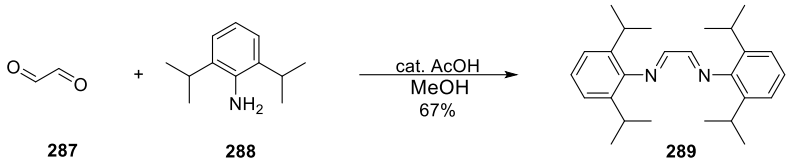
(2S,6R)-2-phenethyl-6-phenylpiperidine 213. Under Ar, substrate **212** (550 mg, 1.32 mmol, 1 equiv.) and 10 mol% of Pd/C (141 mg, 0.132 mmol) were added in sequence to a flame-dried two neck flask. The flask was purged three times with vacuum/H_2 cycle, then EtOH (200 mL) was added. The reaction mixture was stirred overnight under an atmosphere of hydrogen at room temperature. Then, the solution was filtered through celite and the solvent was removed under vacuum. After concentration the crude was purified by flash chromatography to afford the desired product. Yield: 66% (231 mg, 870 µmol). Solvent system for flash column chromatography: DCM/MeOH: 97/3; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 6.7 Hz, 2H), 7.29 – 7.07 (m, 8H), 3.61 (dd, *J* = 11.1, 2.8 Hz, 1H), 2.77 – 2.63 (m, 1H), 2.63 – 2.51 (m, 2H), 1.92 – 1.79 (m, 1H), 1.80 – 1.66 (m, 4H), 1.65 – 1.55 (m, 1H), 1.53 – 1.29 (m, 2H), 1.29 – 1.11 (m, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$): 143.3, 141.8, 128.5, 128.4, 127.6, 127.3, 125.9, 62.4, 57.7, 37.3, 33.6, 32.1, 30.8, 24.9; **IR** (neat): ν_{max} 3031, 2928, 2855, 1456, 1302, 1114, 734, 695, 534, 507, 465 cm^{-1}; **ESIHRMS** *m/z* calcd for $C_{19}H_{24}N$ $[M+H]^+$ 266.1909, found 266.1903. This compound has been previously reported.[375]

[375] Jäkel, M.; Qu, J.; Schnitzer, T.; Helmchen, G. *Chem. Eur. J.* **2013**, *19*, 16746–16755.

Experimental section of Chapter 4. Copper-catalyzed reaction of trifluoromethylation of vinylsiloxanes

Synthesis of Catalysts

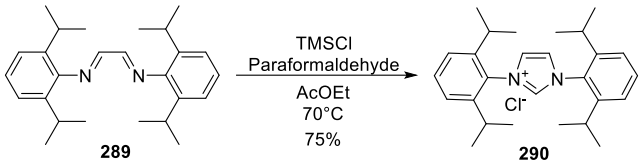
Synthesis of iPr·HCl ligand



287 288 289

1,4-Bis-(2,6-diisopropylphenyl)-1,4-diaza-butadiene 289. A solution of glyoxal (2.8 mL, 40% in water, 0.025 mol, 1.0 equiv) in MeOH (25 mL) was added with vigorous stirring to a warmed (50°C) solution of 2,6-diisopropylaniline (10.47 mL, purity 90%, 0.05 mol, 2.0 equiv) and AcOH (0.05 mL) in MeOH (25 mL). A slightly exothermic reaction commenced. Then, the product started to crystallize after 15 min. The mixture was stirred for 10 h at room temperature, after which the resulting suspension was filtered and the solid product washed with MeOH, until the washing phase remained bright yellow. The product was pre-dried by suction over the filter, then dried to constant weight in high vacuum. The filtrates were collected, evaporated to a volume of 20 mL, and set aside for a second crystallization. Yield: 67% (6.32 g, 0.017 mol). Bright yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 2H), 7.23 – 7.14 (m, 6H), 2.94 (sept, *J* = 6.9 Hz, 4H), 1.21 (d, *J* = 6.9 Hz, 24H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 163.2, 148.1, 136.8, 125.2, 123.3, 28.1, 23.5. This compound has been previously reported and the data were consistent with those already reported in the literature.[376]



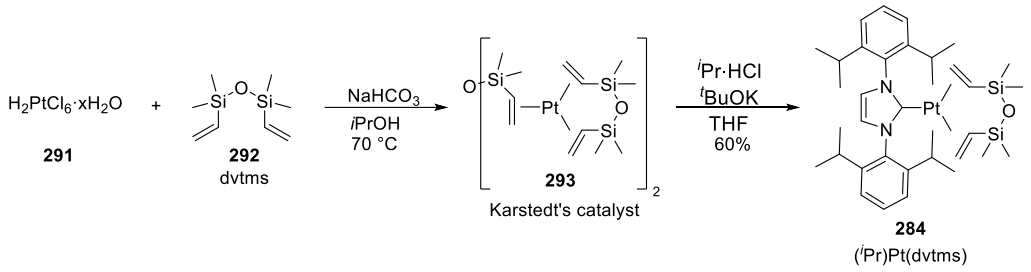
289 290

1,3-Bis-(2,6-diisopropylphenyl)-imidazolium chloride 290. A 250 mL round bottom flask containing EtOAc (120 mL) was heated to 70°C in an oil bath. Diazadiene (**289**, 5.0 g, 13,4 mmol, 1.0 equiv) and paraformaldehyde (0.40 g, 13,5 mmol, 1.01 equiv) were added and the walls washed with EtOAc (5.0 mL). A solution of TMSCl (1.7 mL, 13.4 mmol, 1.0 equiv) in EtOAc (2.0 mL) was added dropwise over 45 min with vigorous stirring, and the resulting yellow suspension stirred for 2 h at 70°C. After cooling to 10°C (ice bath) with stirring, the suspension was filtered and the solid washed with EtOAc and ^{t}BuOMe. The solid was dried to constant weight in an open dish in a well-ventilated oven at 100 °C (1 day). Yield: 75% (4.28 g, 10.1 mol). colourless microcrystalline powder.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.15 (d, *J* = 1.6 Hz, 2H), 7.63 – 7.49 (m, 2H), 7.35 (d, *J* = 7.8 Hz, 4H), 2.45 (sept, *J* = 6.7 Hz, 4H), 1.26 (dd, *J* = 12.6, 6.8 Hz, 24H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 145.1, 138.7, 132.3, 130.0, 126.9, 124.8, 29.2, 24.9, 23.8. This compound has been previously reported and the data were consistent with those already reported in the literature.[333]

[376] Arduengo, A. J.; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999***, 55,* 14523–14534*.*

Synthesis of (iPr)Pt(dvtms), Istvan Marko's catalyst (284)



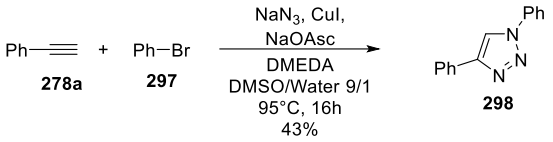
(^{i}Pr)Pt(dvtms) 284. A solution of hexachloroplatinic acid hydrate (40%wt, 271 mg, 0.555 mmol, 1.0 equiv) in isopropanol (4.0 mL) was heated at 70°C for 30 minutes. The heating bath was removed to allow the solution to cool down to room temperature. $NaHCO_3$ (373 mg, 4.44 mmol, 8.0 equiv) was added over 5 minutes and the solution was stirred for 10 minutes. 1,3-Divinyltetramethyldisiloxane (**292**, 1.0 mL, 4.42 mmol, 8.0 equiv) was added, and the resulting solution was stirred at 70°C for 1 hour. The mixture is cooled down to room temperature, is filtrated through a pad of silica gel/Celite/$MgSO_4$ (1/1/1) and eluted with diethyl ether (50 mL). The resulting filtrate was concentrated *in vacuo* to reach a volume of approximately 5 mL, affording the intermediate Karstedt's catalyst. To the above solution was added THF (5.6 mL), 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride (IPr·HCl, **290**, 284 mg, 0.666 mmol, 1.2 equiv) and potassium tert-butoxide (68 mg, 0.67 mmol, 1.2 equiv). The mixture was stirred at room temperature for 1 hour then diluted with water (10 mL). The aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and evaporated *in vacuo*. The resulting crude product was recrystallized from isopropanol overnight. Yield: 60% (258 mg, 0.33 mmol). Pale-yellow crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36 (t, 2H, *J* = 7.8 Hz), 7.21–7.16 (m, 6H), 2.97 (sept, 4H, *J* = 6.7 Hz), 1.79–1.19 (m, 6H), 1.24 (d, 12H, *J* = 6.9 Hz), 1.13 (d, 12H, *J* = 6.9 Hz), 0.13 (s, 6H), –0.76 (s, 6H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 186.1 (t, J_{Pt-C} = 1412.3 Hz), 145.9, 136.8 (t, J_{Pt-C} = 9.8 Hz), 129.5, 124.0 (t, J_{Pt-C} = 42.0 Hz), 123.7, 41.9 (t, J_{Pt-C}= 165.0 Hz, C_{10}), 35.6 (t, J_{Pt-C} = 119.3 Hz), 28.5, 26.0, 22.6, 1.7, –2.2. This compound has been previously reported and the data were consistent with those already reported in the literature.[377]

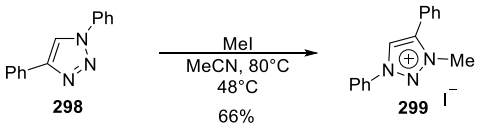
[377] (a) Dierick, S.; Vercruysse, E.; Berthon-Gelloz, G.; Markõ, I. *Chem. Eur. J.* **2015**, *21*, 17073–17078. (b) Berthon-Gelloz, G.; Schumers, J. M.; de Bo, G.; Markó, I. E. *J. Org. Chem.* **2008**, *73*, 4190–4197. (c) de Bo, G.; Berthon-Gelloz, G.; Tinant, B.; Markó, I. E. *Organometallics* **2006**, *25*, 1881–1890.

Synthesis of [Cp*RhI(C,C')-Triaz]rhodium, Alvarez's catalyst (301)

Synthesis of the triazole ligand

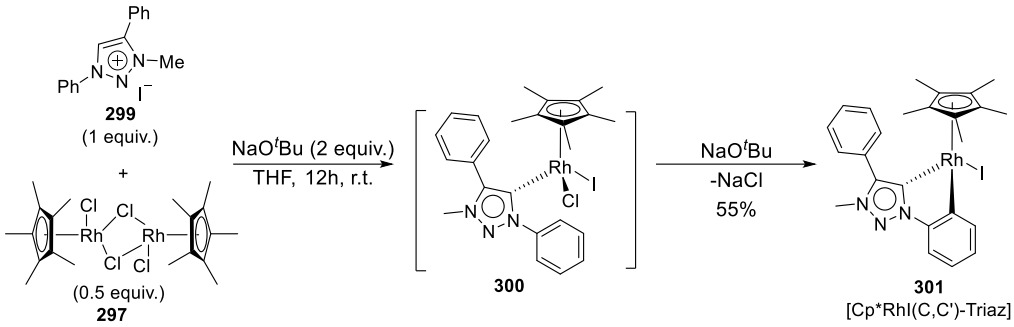


1,4-diphenyl-1H-1,2,3-triazole (298). The halide (**297**) (2.65 mL, 25.0 mmol, 1.0 equiv) and terminal acetylene (**278a**) (2.8 mL, 25.0 mmol, 1.0 equiv) were dissolved in an DMSO/water mixture (100 mL, 9:1). After the addition of sodium azide (3.25 g, 50.0 mmol, 2 equiv), sodium ascorbate (0.5 g, 2.5 mmol, 0.1 equiv), DMEDA (0.53 mL, 5.0 mmol, 0.2 equiv) and copper(I) iodide (0.47 g, 2.5 mmol, 0.1 equiv), the mixture was stirred in a closed Schlenk tube at 95 °C for about 16 hours. The cooled mixture was poured into 50 mL ice water bath. The product was treated with 10 mL NH_4OH (25 %). The aqueous solution was washed three times with 50 mL ethyl acetate. After the organic phase was dried over sodium sulfate, the crude product was concentrated at the rotary evaporator and purified on silica. Yield: 43% (2.37 g, 10.7 mmol). Solvent system for flash column chromatography: DCM, slightly yellowish powder. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.95 – 7.88 (m, 2H), 7.85 – 7.76 (m, 2H), 7.60 – 7.52 (m, 2H), 7.52 – 7.42 (m, 3H), 7.42 – 7.33 (m, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 129.9, 129.0, 128.9, 128.5, 126.0, 120.6, 117.7. This compound has been previously reported and the data were consistent with those already reported in the literature.[378]



3-Methyl-1,4-diphenyl-1,2,3-triazolium iodide (299). 1,4-Diphenyl-1,2,3-triazole (**298**) (0.15 g, 0.68 mmol, 1.0 equiv), MeI (0.63 mL, 10 mmol, 14.7 equiv), and MeCN (10 mL) were added to a 50 mL Schlenk flask. The reaction mixture was stirred at 80°C for 2 days. After the reaction mixture was cooled to room temperature, the solvent was evaporated. The 3-methyl-1,4-diphenyl-1,2,3-triazolium iodide (**299**) was washed with ethyl acetate. Yield: 66% (0.16 g, 0.45 mmol), orange powder. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 9.63 (s, 1H), 8.23 – 8.14 (m, 2H), 8.02 – 7.91 (m, 2H), 7.67 – 7.61 (m, 3H), 7.61 – 7.54 (m, 3H), 4.45 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 144.3, 134.7, 132.1, 132.1, 130.5, 130.2, 129.7, 127.4, 122.1, 121.4, 40.1. This compound has been previously reported and the data were consistent with those already reported in the literature.[379]

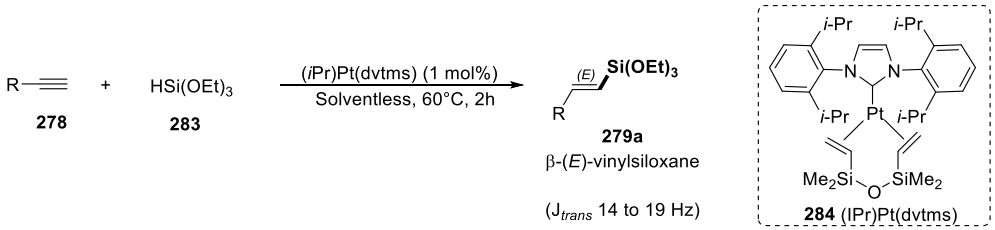
[378] Potratz, S.; Mishra, A.; Bäuerle, P. *Beilstein J. Org. Chem*. **2012**, *8*, 683–692.
[379] Cho, K.; Yang, H. S.; Lee, I. H.; Lee, S. M.; Kim, H. J.; Son, S. U. *J. Am. Chem. Soc.* **2021**, *143*, 4100–4105.



[Cp*RhI(C,C')-Triaz] (301). 1,4-Diphenyl-3-methyl-1,2,3-triazolium iodide (**299**) (100 mg, 0.270 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (**297**) (83.4 mg, 0.135 mmol, 0.5 equiv) and NaO^{t}Bu (51.9 mg, 0.540 mmol, 2.0 equiv) were reacted in anhydrous THF (25 mL) at room temperature for 12 h. After that time, the solution was filtered and then evaporated to dryness under vacuum. The organometallic compound was extracted with CH_2Cl_2 (15 mL), and the resulting dark orange solution was filtered and concentrated to ∼2 mL under reduced pressure. Slow addition of pentane (12 mL) afforded an orange solid which was separated by decantation, washed with pentane (2×3 mL) and dried in vacuum. Recrystallization from dichloromethane/pentane gave the compound as a microcrystalline orange solid. Yield: 55% (46 mg, 0.076 mmol), orange powder. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.92 (d, *J*= 6.1 Hz, 2H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.66 – 7.47 (m, 4H), 7.16 (t, *J* = 6.7 Hz, 1H), 7.04 (t, *J* = 6.9 Hz, 1H), 4.11 (s, 3H), 1.56 (s, 15H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 165.9 (d, $J_{C\text{-}Rh}$ = 55.5), 159.7 (d, $J_{H\text{-}H}$ = 35.8), 145.1 (d, $J_{C–Rh}$ = 3.4), 144.9, 140.2, 131.0, 129.8, 129.0, 128.2, 127.9, 122.5, 113.9, 97.5 (d, $J_{C–Rh}$ = 4.9, C1), 37.3, 10.2. This compound has been previously reported and the data were consistent with those already reported in the literature.[380]

General Procedures

Synthesis of *β-(E)*-vinylsiloxanes

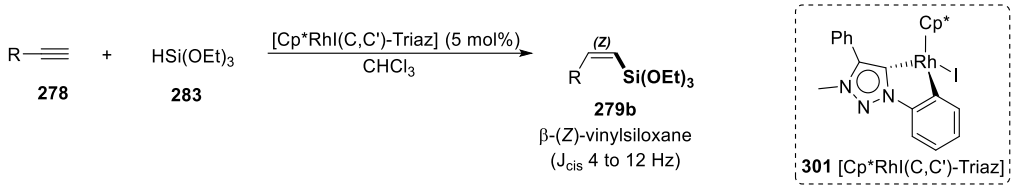


(^{i}Pr)Pt(dvtms) (**302**, 20 mg, 0.01 equiv, 1 mol%) was added to neat triethoxysilane (**283**, 0.62 mL, 3.15 mmol, 1.05 equiv). The solution was stirred at 60°C for 60 minutes. To the resulting yellow solution, it was added the alkyne (**278**, 3.0 mmol, 1.0 equiv.) dropwise and the alkyne-containing flask was rinsed with a minimum amount of anhydrous toluene or DCM (depends on the solubility of the substrate). The solution was stirred at 60°C for 2 hours and monitored by TLC. Thereafter, the reaction mixture was cooled to room temperature and filtered through a pad of silica gel/Celite/$MgSO_4$ (1:1:1 v/v/v), eluting with petroleum ether or diethyl ether (depending on product polarity). The filtrate was concentrated under reduced pressure and the last traces of volatiles were removed under high vacuum to afford the product **279a** as a colorless or light-yellow liquid. If necessary, analytically pure samples of *β-(E)*-vinylsiloxanes can usually be obtained by column chromatography on silica gel.[381]

[380] Sánchez-Page, B.; Munarriz, J.; Jiménez, M. V.; Pérez-Torrente, J. J.; Blasco, J.; Subias, G.; Passarelli, V.; Álvarez, P. *ACS Cat.* **2020**, *10*, 13334–13351.

[381] (a) Dierick, S.; Vercruysse, E.; Berthon-Gelloz, G.; Markõ, I. *Chem. Eur. J.* **2015**, *21*, 17073–17078. (b) Berthon-Gelloz, G.; Schumers, J. M.; de Bo, G.; Markó, I. E. *J. Org. Chem.* **2008**, *73*, 4190–4197. (c) de Bo, G.; Berthon-Gelloz, G.; Tinant, B.; Markó, I. E. *Organometallics* **2006**, *25*, 1881–1890.

Synthesis of *β-(Z)*-vinylsiloxanes



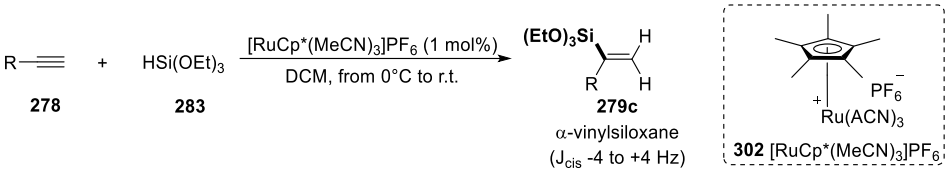
In a Schlenk tube under Ar, [Cp*RhI(C, C')-Triaz] (**301**) (5 mg, 0.0075 mmol, 1 mol%) and the alkyne (**278**, 0.75 mmol, 1.0 equiv) were dissolved in anhydrous $CHCl_3$ (3.75 mL, 0.2M) and treated with triethoxysilane (**283**, 0.15 mL, 0.75 mmol 1.0 equiv.). The resulting mixture was stirred at 60°C for 3 hours and monitored by TLC. Then, the crude reaction mixture was concentrated under reduced pressure and immediately filtered through a short pad of silica gel/Celite/$MgSO_4$ (1/1/1), eluting with petroleum ether or diethyl ether (depending on product polarity). The filtrate was concentrated under reduced pressure and the last traces of volatiles were removed under high vacuum to afford the product as a mixture of β-(*Z*)-isomer and β-(*E*)-isomer. The Alvarez catalyst (**301** is stereoselective for the formation of β-(*Z*)-vinylsiloxanes **279b** as a major product. Analytically pure samples of β-(*Z*)-vinylsiloxanes can be obtained by column chromatography on silica gel. After purification, the desired β-(*Z*)-vinylsiloxane was isolated as a clear, slightly pale yellow oil.[382]

NOTE: In all the cases, the formation of the β-(*Z*)-vinylsiloxanes was confirmed by ^{1}H-NMR analysis evaluating the typical coupling constant which was J_{cis} 4 to 12Hz. The Alvarez catalyst is stereoselective for the formation of β-(*Z*)-vinylsiloxanes as a major product. Traces of the β-(*E*)-stereoisomer can be identified in the NMR spectra as minor by-product with a ratio *Z*/*E* in a range between 99/1 and 65/35. Fortunately, the two stereoisomers are separable through chromatographic purification. Thus, it was possible to isolate only the β-(*Z*)-vinylsiloxanes. Notably, for the preparation of a library of β-(*Z*)-trifluoromethylated olefin we used only the β-(*Z*)-vinylsiloxanes stereochemically pure. The vinylsiloxanes reaction products were unambiguously characterized on the basis of the coupling patterns and constants of vinylic protons in the ^{1}H-NMR spectra and subsequent comparison to literature values.[383] Values for J ranged from 17 to 19 Hz for β-(*E*), 13 to 16 Hz for β-(*Z*), and 1 to 3 Hz for α-vinylsiloxanes.

[382] Sánchez-Page, B.; Munarriz, J.; Jiménez, M. V.; Pérez-Torrente, J. J.; Blasco, J.; Subias, G.; Passarelli, V.; Álvarez, P. *ACS Cat.* **2020**, *10*, 13334–13351.

[383] (a) Jun, C. H.; Crabtree, R. H. *J. Organomet. Chem*. **1993**, *447*, 177−187. (b) Nakamura, S.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2004**, *126*, 11146−11147. (c) Andavan, G. T. S.; Bauer, E. B.; Letko, C. S.; Hollis, T. K.; Tham, F. S. *J. Organomet. Chem*. **2005**, *690*, 5938−5947. (d) Katayama, H.; Taniguchi, K.; Kobayashi, M.; Sagawa, T.; Minami, T.; Ozawa, F. *J. Organomet. Chem*. **2002**, *645*, 192−200.

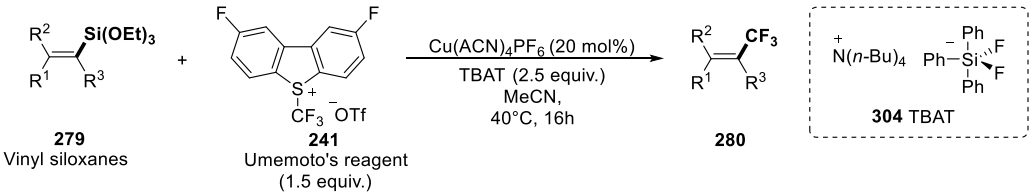
Synthesis of α-vinylsiloxanes



The alkyne (0.174 g, 1.00 mmol), in a flask under Ar, was dissolved in anhydrous CH_2Cl_2 (2mL) and treated with triethoxysilane (203 µL, 1.20 mmol). The flask was cooled to 0 °C, and $Ru(Cp^*)(MeCN)_3PF_6$ (5.0 mg, 0.01 mmol) was added at this temperature. The flask was immediately allowed to warm to ambient temperature and monitored by TLC. The crude reaction mixture was concentrated under reduced pressure and immediately applied to a silica gel column, eluting with petroleum ether or diethyl ether (depending on product polarity). The filtrate was concentrated under reduced pressure and the last traces of volatiles were removed under high vacuum to afford the product as a mixture of α- and β-(*Z*) isomers.

NOTE: The Trost-Ball catalyst (**302**) is stereoselective for the formation of α-vinylsiloxanes (**279c**) as a major product. Traces of the β-(*Z*)-stereoisomer (**279b**) can be identified in the NMR spectra as minor by-product with a ratio α/β-(*Z*) in a range between 82/15 and 88/12. Unfortunately, the two stereoisomers are not separable through chromatographic purification. Thus, it was not possible to isolate the α-vinylsiloxanes stereochemically pure. Notably, for the preparation of α-trifluoromethylated olefin we used the mixture α/β-(*Z*)-vinylsiloxanes.[384]

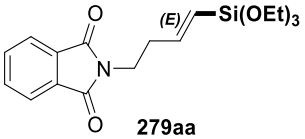
General Procedure: Trifluoromethylation of vinylsiloxanes



A solution of vinylsiloxanes (**279**, 0.40 mmol, 1.0 equiv.) in anhydrous MeCN (2 mL) was transferred to a Schlenck flask containing $Cu(ACN)_4PF_6$ (30 mg, 0.08 mmol, 0.2 equiv., 20 mol%), Umemoto's reagent (**241**, 0.265 g, 0.6 mmol, 1.5 equiv.) and tetrabutylammonium difluorotriphenylsilicate (TBAT, **304**, 0.54 g, 1 mmol, 2.5 equiv.) under argon. The vinylsiloxane-containing flask was rinsed with a minimum amount of anhydrous ACN. The resulting mixture was stirred at 40 °C in an oil bath for 16 hours and monitored by TLC. Thereafter, the mixture was filtrated through a short pad of silica, eluting with dichloromethane or diethyl ether (depending on product polarity). The crude reaction mixture was concentrated under vacuum and the residue was finally purified by flash chromatography over silica gel to afford the desired trifluoromethylated olefin.

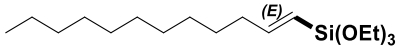
[384] Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc*. **2005**, *127*, 17644–17655.

Characterization Data



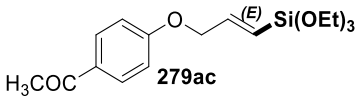
279aa

(*E*)-2-(4-(triethoxysilyl)but-3-en-1-yl)isoindoline-1,3-dione 279aa. Prepared according to general procedure. Yield: 84% (0.91 g, 2.5 mmol). Solvent system for flash column chromatography: DCM/PE: from 10/90 to 60/40; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.85–7.78 (m, 2H), 7.73 – 7.66 (m, 2H), 6.37 (dt, *J* = 18.8, 6.5 Hz, 1H), 5.48 (dt, *J* = 18.7, 1.5 Hz, 1H), 3.81 (t, *J* = 7.0 Hz, 2H), 3.73 (q., *J* = 7.0 Hz, 6H), 2.60 – 2.50 (m, 2H), 1.16 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 168.3, 148.8, 134.0, 132.2, 123.2, 123.0, 58.5, 36.8, 35.5, 18.3.[385]



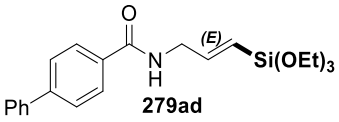
279ab

(*E*)-dodec-1-en-1-yltriethoxysilane 279ab. Prepared according to general procedure. Yield: 99% (0.92 g, 3.0 mmol). Solvent system for flash column chromatography: DCM; colorless oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 6.40 (dt, *J* = 18.8, 6.3 Hz, 1H), 5.38 (dt, *J* = 18.7, 1.6 Hz, 1H), 3.80 (q, *J* = 7.0 Hz, 6H), 2.20 – 2.05 (m, 2H), 1.39 (quint., *J* = 8.1 Hz, 2H), 1.24 (br s, 14H), 1.20 (t, *J* = 7.2 Hz, 9H), 0.84 (d, *J* = 6.9 Hz, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 154.1, 118.9, 58.4, 36.7, 32.0, 29.7, 29.5, 29.4, 29.2, 28.3, 22.7, 18.3, 14.1; **IR** (neat): ν_{max} 2972, 2924, 2854, 1619, 1466, 1389, 1295, 1166, 1101, 1075, 995, 956, 778, 475; **ESIHRMS** *m/z* calcd for $C_{18}H_{39}O_3{}^{28}Si$ $[M+H]^+$ 331.2668, found 331.2663.



279ac

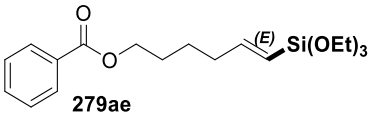
(*E*)-1-(4-((3-(triethoxysilyl)allyl)oxy)phenyl)ethan-1-one 279ac. Prepared according to general procedure. Yield: 76% (0.77 g, 2.3 mmol). Solvent system for flash column chromatography: petroleum ether/DCM: 60/40; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 6.55 (dt, *J* = 19.0, 4.2 Hz, 1H), 5.83 (dt, *J* = 19.0, 1.9 Hz, 1H), 4.66 (dd, *J* = 4.2, 1.9 Hz, 2H), 3.82 (q., *J* = 7.0 Hz, 6H), 2.54 (s, 3H), 1.22 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 196.8, 162.4, 145.7, 130.6, 130.6, 121.9, 114.5, 69.8, 58.7, 26.4, 18.3; **IR** (neat): ν_{max} 2975, 2930, 2891, 1677, 1599, 1508, 1359, 1249, 1168, 1070, 1018, 954, 833,777, 590, 462; **ESIHRMS** *m/z* calcd for $C_{17}H_{27}O_5{}^{28}Si$ $[M+H]^+$ 339.1628, found 339.1619.



279ad

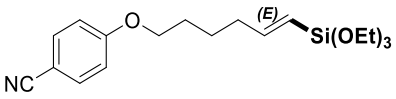
(*E*)-*N*-(3-(triethoxysilyl)allyl)-[1,1'-biphenyl]-4-carboxamide 279ad. Prepared according to general procedure. Yield: 74% (0.89 g, 2.2 mmol). Solvent system for flash column chromatography: DCM/MeOH: 97/3; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.67 – 7.57 (m, 2H), 7.53 – 7.33 (m, 3H), 6.52 (dt, *J* = 18.9, 4.8 Hz, 1H), 6.27 (br s, 1H), 5.68 (dt, *J* = 18.8, 1.8 Hz, 1H), 4.22 (m, 2H), 3.84 (q., *J* = 7.0 Hz, 6H), 1.24 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 167.0, 147.9, 144.5, 140.1, 133.1, 129.0, 128.1, 127.6, 127.4, 127.3, 120.6, 58.7, 44.0, 18.3; **IR** (neat): ν_{max} 3296, 2975, 2887, 1637, 1538, 1485, 1389, 1306, 1164, 1071, 956, 778, 739, 696, 594, 474; **ESIHRMS** *m/z* calcd for $C_{22}H_{30}NO_4{}^{28}Si$ $[M+H]^+$ 400.1944, found 400.1939.

[385] Cornelissen, L.; Lefrancq, M.; Riant, O. *Org. Lett*. **2014**, *16*, 3024–3027.



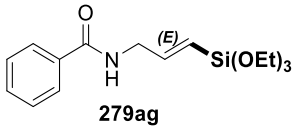
279ae

(*E*)-6-(triethoxysilyl)hex-5-en-1-yl benzoate 279ae. Prepared according to general procedure. Yield: 67% (0.74 g, 2.0 mmol). Solvent system for flash column chromatography: petroleum ether/DCM: 60/40; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.0 Hz, 2H), 7.62 – 7.48 (m, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 6.42 (dt, *J* = 18.8, 6.2 Hz, 1H), 5.45 (dt, *J* = 18.8, 1.6 Hz, 1H), 4.31 (t, *J* = 6.5 Hz, 2H), 3.81 (q., *J* = 7.0 Hz, 6H), 2.23 (q., *J* = 6.0 Hz, 2H), 1.76 (quint., *J* = 8.1 Hz, 2H), 1.60 (quint., *J* = 8.1 Hz, 2H), 1.21 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 166.6, 153.0, 132.9, 130.4, 129.6, 128.4, 119.7, 64.8, 58.5, 36.1, 28.3, 24.8, 18.3; **IR** (neat): ν_{max} 2973, 2927, 2885, 1719, 1619, 1452, 1389,1314, 1270, 1099, 1069, 1026, 996, 955, 776, 710, 463; **ESIHRMS** *m/z* calcd for $C_{19}H_{31}O_5{}^{28}Si$ $[M+H]^+$ 367.1941, found 367.1938.



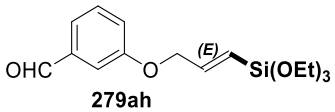
279af

(*E*)-4-((6-(triethoxysilyl)hex-5-en-1-yl)oxy)benzonitrile 279af. Prepared according to general procedure. Yield: 65% (709 mg, 1.95 mmol). Solvent system for flash column chromatography: DCM/MeOH: 97/3; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.41 (dt, *J* = 18.8 Hz, 6.2 Hz, 1H), 5.45 (dt, *J* = 18.7, 1.5 Hz, 1H), 3.98 (t, *J* = 6.3 Hz, 2H), 3.80 (q., *J* = 7.0 Hz, 6H), 2.21 (q., *J* = 7.4 Hz, 2H), 1.79 (quint., *J* = 6.5 Hz, 2H), 1.61 (quint., *J* = 6.5 Hz, 2H), 1.21 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 162.4, 152.9, 134.0, 119.9, 119.3, 115.2, 103.8, 68.1, 58.5, 36.1, 28.5, 24.6, 18.3; **IR** (neat): ν_{max} 2973, 2927, 2883, 2225, 1605, 1508, 1390, 1300, 1257, 1170, 1070, 955, 781, 547, 476; **ESIHRMS** *m/z* calcd for $C_{19}H_{29}N^{23}NaO_4{}^{28}Si$ $[M+Na]^+$ 386.1764, found 386.1758.



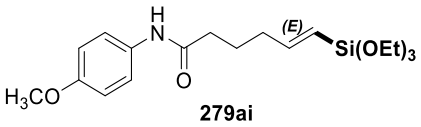
279ag

(*E*)-*N*-(3-(triethoxysilyl)allyl)benzamide 279ag. Prepared according to general procedure. Yield: 81% (0.78 g, 2.4 mmol). Solvent system for flash column chromatography: DCM/petroleum ether: 60/40; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.89 – 7.67 (m, 2H), 7.54 – 7.39 (m, 3H), 6.49 (dt, *J* = 18.8, 4.8 Hz, 1H), 6.31 (br s, 1H), 5.64 (dt, *J* = 18.8, 1.8 Hz, 1H), 4.18 (m, 2H), 3.82 (q., *J* = 7.0 Hz, 6H), 1.22 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 167.4, 147.9, 134.5, 131.6, 128.7, 127.0, 120.4, 58.7, 44.0, 18.3; **IR** (neat): ν_{max} 3319, 2974, 2884, 1640, 1536, 1488, 1389, 1293, 1165, 1071, 956, 776, 693, 594, 460; **ESIHRMS** *m/z* calcd for $C_{16}H_{25}N^{23}NaO_4{}^{28}Si$ $[M+H]^+$ 346.1451, found 346.1445.



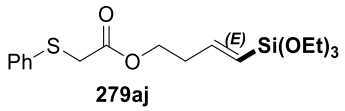
279ah

(*E*)-3-((3-(triethoxysilyl)allyl)oxy)benzaldehyde 279ah. Prepared according to general procedure. Yield: 81% (0.78 g, 2.4 mol). Solvent system for flash column chromatography: petroleum ether/DCM: 60/40; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.48 – 7.42 (m, 2H), 7.42 – 7.34 (m, 1H), 7.20 (dt, *J* = 6.4, 2.8 Hz, 1H), 6.57 (dt, J = 19.0, 4.1 Hz, 1H), 5.85 (dt, *J* = 19.0, 1.9 Hz, 1H), 4.67 (dd, *J* = 4.1, 1.9 Hz, 2H), 3.83 (q., *J* = 7.0 Hz, 6H), 1.22 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 192.1, 159.1, 146.0, 137.9, 130.2, 123.8, 122.2, 121.7, 113.3, 69.9, 58.7, 18.3; **IR** (neat): ν_{max} 2974, 2887, 2731, 1698, 1585, 1485, 1447, 1389, 1260, 1166, 1068, 958, 780, 681, 646, 439; **ESIHRMS** *m/z* calcd for $C_{16}H_{25}O_5{}^{28}Si$ $[M+H]^+$ 325.1471, found 325.1467.



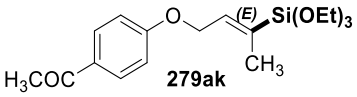
279ai

(*E*)-*N*-(4-methoxyphenyl)-6-(triethoxysilyl)hex-5-enamide 279ai. Prepared according to general procedure. Yield: 69% (789 mg, 2.07 mmol). Solvent system for flash column chromatography: DCM/MeOH: from 100/0 to 96/4; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 9.0 Hz, 2H), 7.32 (br s, 1H), 6.83 (d, *J* = 9.0 Hz, 2H), 6.52 – 6.32 (m, 1H), 5.56 – 5.39 (m, 1H), 3.82 (q., *J* = 7.0 Hz, 6H), 3.77 (s, 3H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.30 – 2.16 (m, 2H), 1.85 (quint., *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 170.9, 156.4, 152.5, 131.1, 121.8, 120.3, 114.1, 77.1, 58.6, 55.5, 36.7, 35.9, 24.1, 18.3; **IR** (neat): ν_{max} 3296, 2975, 2922, 1655, 1603, 1539, 1510, 1412, 1294, 1241, 1168, 1069, 1030, 956, 826, 779, 462; **ESIHRMS** *m/z* calcd for $C_{19}H_{32}NO_5{}^{28}Si$ $[M+H]^+$ 382.2050 , found 382.2043.



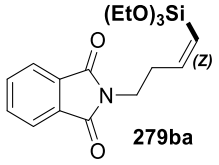
279aj

(*E*)-4-(triethoxysilyl)but-3-en-1-yl 2-(phenylthio)acetate 279aj. Prepared according to general procedure. Yield: 73% (842 mg, 2.19 mmol). Solvent system for flash column chromatography: DCM/MeOH: 96/4; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.50 – 7.37 (m, 2H), 7.35 – 7.17 (m, 3H), 6.35 (dt, *J* = 18.8 Hz, 6.3 Hz, 1H), 5.54 (dt, *J* = 19 Hz, 1.4 Hz, 1H), 4.20 (t, *J* = 6.8 Hz, 2H), 3.82 (q., *J* = 7.0 Hz, 6H), 3.63 (s, 2H), 2.46 (qd, *J* = 6.8, 1.6 Hz, 2H), 1.23 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 169.7, 147.9, 135.1, 130.1, 129.1, 127.1, 122.9, 64.1, 58.6, 36.8, 35.5, 18.3; **IR** (neat): ν_{max} 2973, 2926, 2886, 1733, 1621, 1482, 1440, 1389, 1267, 1070, 988, 956, 776, 739, 690, 474; **ESIHRMS** *m/z* calcd for $C_{18}H_{29}O_5S$ ^{28}Si $[M+H]^+$ 385.1505, found 385.1501.



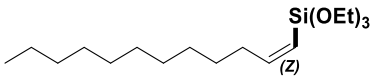
279ak

(*E*)-1-(4-((3-(triethoxysilyl)but-2-en-1-yl)oxy)phenyl)ethan-1-one 279ak. Prepared according to general procedure. Yield: 67% (842 mg, 2.38 mmol). Solvent system for flash column chromatography: petroleum ether/DCM: 60/40; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9 Hz, 2H), 6.96 (d, *J* = 8.9 Hz, 2H), 6.51 (qt, *J* = 6.8, 1.4 Hz, 1H), 4.79 – 4.62 (m, 2H), 3.83 (q., *J* = 7.0 Hz, 6H), 2.54 (s, 3H), 1.84 (d, *J* = 6.8 Hz, 3H), 1.19 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 196.9, 163.1, 145.1, 130.6, 130.3, 129.7, 114.4, 65.6, 58.7, 26.4, 18.3, 15.3; **IR** (neat): ν_{max} 2969, 2927, 2870, 1680, 1600, 1510, 1363, 1253, 1173, 1075, 1025, 960, 840, 779, 597, 452; **ESIHRMS** *m/z* calcd for $C_{18}H_{29}O_5{}^{28}Si$ $[M+H]^+$ 353.1784, found 353.1788.



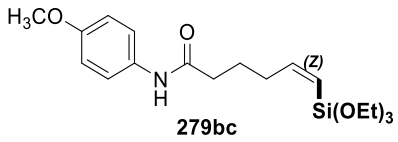
279ba

(*Z*)-2-(4-(triethoxysilyl)but-3-en-1-yl)isoindoline-1,3-dione 279ba. Yield: 87% (0.24 g, 0.65 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 90/10; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.74 – 7.65 (m, 2H), 6.51 (dt, *J* = 14.6, 7.4 Hz, 1H), 5.40 (dt, *J* = 14.3, 1.4 Hz, 1H), 3.79 (t, *J* = 6.8 Hz, 2H), 3.73 (q., *J* = 7.0 Hz, 6H), 2.70 (qd, *J* = 6.9, 1.4 Hz, 2H), 1.16 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 168.3, 149.8, 133.9, 132.3, 123.2, 122.1, 58.4, 37.4, 32.9, 18.2; **IR** (neat): ν_{max} 2974, 2926, 1773, 1709, 1615, 1467, 1436, 1393, 1359, 1297, 1166, 1100, 1070, 1023, 956, 782, 752, 718, 559, 530, 514*;* **ESIHRMS** *m/z* calcd for $C_{18}H_{25}N^{23}NaO_5{}^{28}Si$ $[M+Na]^+$ 386.1400, found 386.1392.



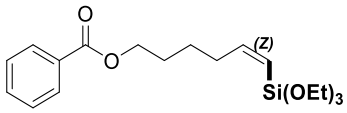
279bb

(*Z*)-dodec-1-en-1-yltriethoxysilane 279bb. Yield: 48% (476 mg, 1.44 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 90/10; colorless oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 6.52 (dt, *J* = 14.2, 7.4 Hz, 1H), 5.29 (dt, *J* = 14.2, 1.3 Hz, 1H), 3.82 (q., *J* = 7.0 Hz, 6H), 2.27 (qd, *J* = 7.6, 1.3 Hz, 2H), 1.45 – 1.33 (m, 2H), 1.34 – 1.26 (m, 14H), 1.23 (t, *J* = 7.0 Hz, 9H), 0.87 (t, *J* = 6.9 Hz, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 155.3, 118.3, 58.3, 34.0, 32.0, 29.7, 29.7, 29.6, 29.5, 29.5, 22.8, 18.3, 14.2; **IR** (neat): ν_{max} 2973, 2924, 2855, 1611, 1466, 1390, 1295, 1166, 1101, 1076, 956, 782, 754, 559, 485; **ESIHRMS** *m/z* calcd for $C_{18}H_{38}{}^{23}NaO_3{}^{28}Si$ $[M+Na]^+$ 353.2488, found 353.2474.



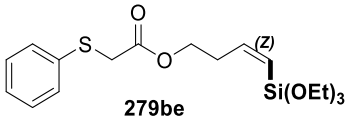
279bc

(Z)-*N*-(4-methoxyphenyl)-6-(triethoxysilyl)hex-5-enamide 279bc. Yield: 61% (698 mg, 1.83 mmol). Solvent system for flash column chromatography: DCM/MeOH: from 100/0 to 96/4; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.78 (br s, 1H), 7.41 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 6.47 (dt, *J* = 14.2, 7.5 Hz, 1H), 5.34 (dt, *J* = 14.2, 1.3 Hz, 1H), 3.81 (q., *J* = 7.0 Hz, 6H), 3.75 (s, 3H), 2.42 – 2.27 (m, 4H), 1.83 (quint., *J* = 7.2 Hz, 2H), 1.21 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 171.4, 156.2, 153.7, 131.4, 121.8, 119.7, 114.0, 58.4, 55.5, 36.8, 33.3, 25.0, 18.2; **IR** (neat): ν_{max} 3296, 2974, 2926, 2887, 1656, 1606, 1541, 1511, 1412, 1298, 1245, 1167, 1101, 1076, 958, 829, 782, 753, 545; **ESIHRMS** *m/z* calcd for $C_{19}H_{32}NO_5{}^{28}Si$ $[M+H]^+$ 382.2050, found 382.2043.



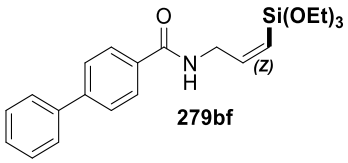
279bd

(*Z*)-6-(triethoxysilyl)hex-5-en-1-yl benzoate 279bd. Yield: 53% (583 mg, 1.59 mmol). Solvent system for flash column chromatography: petroleum ether/DCM: 60/40; colorless oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.61 – 7.49 (m, 1H), 7.43 (t, *J* = 7.4 Hz, 2H), 6.52 (dt, *J* = 14.2, 7.4 Hz, 1H), 5.35 (dt, *J* = 14.2, 1.3 Hz, 1H), 4.33 (t, *J* = 6.5 Hz, 2H), 3.82 (q., *J* = 7.0 Hz, 6H), 2.37 (qd, *J* = 7.5, 1.3 Hz, 2H), 1.92 – 1.74 (m, 2H), 1.64 – 1.53 (m, 2H), 1.23 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 166.7, 154.1, 132.9, 130.6, 129.6, 128.4, 119.4, 65.0, 58.4, 33.4, 28.5, 26.0, 18.3; **IR** (neat): ν_{max} 2973, 2926, 1719, 1610, 1451, 1389, 1314, 1271, 1166, 1069, 955, 781, 710; **ESIHRMS** *m/z* calcd for $C_{19}H_{31}O_5{}^{28}Si$ $[M+H]^+$ 367.1941, found 367.1934.



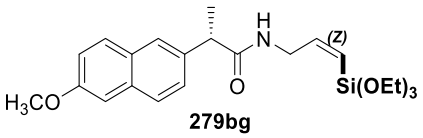
279be

(*Z*)-4-(triethoxysilyl)but-3-en-1-yl 2-(phenylthio)acetate 279be. Yield: 55% (634 mg, 1.65 mmol). Solvent system for flash column chromatography: DCM/MeOH: 96/4; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.33 – 7.27 (m, 2H), 7.25 – 7.19 (m, 1H), 6.41 (dt, *J* = 14.5, 7.3 Hz, 1H), 5.45 (dt, *J* = 14.3, 1.3 Hz, 1H), 4.17 (t, *J* = 6.7 Hz, 2H), 3.81 (q., *J* = 7.0 Hz, 6H), 3.64 (s, 2H), 2.62 (qd, *J* = 6.7, 1.4 Hz, 2H), 1.22 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 169.8, 148.8, 135.1, 130.0, 129.1, 127.1, 122.4, 64.9, 58.5, 36.7, 32.7, 18.3; **IR** (neat): ν_{max} 2974, 2889, 1734, 1615, 1482, 1440, 1280, 1164, 1074, 958, 782, 742, 690; **ESIHRMS** *m/z* calcd for $C_{18}H_{29}O_5{}^{32}S^{28}Si$ $[M+H]^+$ 385.1505, found 385.1498.



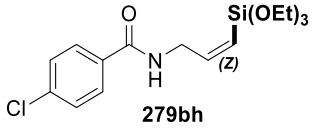
279bf

(*Z*)-*N*-(3-(triethoxysilyl)allyl)-[1,1'-biphenyl]-4-carboxamide 279bf. Yield: 59% (707 mg, 1.77 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: from 90/10 to 80/20; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.79 (m, 2H), 7.71 – 7.57 (m, 4H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.43 – 7.32 (m, 1H), 6.69 (dt, *J* = 14.4, 6.7 Hz, 1H), 5.60 (dt, *J* = 14.4, 1.3 Hz, 1H), 4.29 (ddd, *J* = 6.8, 6.0, 1.2 Hz, 2H), 3.87 (q., *J* = 7.0 Hz, 6H), 1.25 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 166.9, 149.1, 144.3, 140.2, 133.4, 129.0, 128.1, 127.6, 127.3, 122.9, 58.7, 41.4, 18.4; **IR** (neat): ν_{max} 3312, 2973, 2922, 1637, 1536, 1485, 1260, 1076, 959, 854, 784, 746, 696; **ESIHRMS** *m/z* calcd for $C_{22}H_{30}NO_4Si$ $[M+H]^+$ 400.1944, found 400.1936.



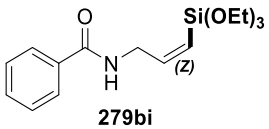
279bg

(S, *Z*)-2-(6-methoxynaphthalen-2-yl)-*N*-(3-(triethoxysilyl)allyl)propanamide 279bg. Yield: 48% (621 mg, 1.44 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: from 90/10 to 60/40; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 3.6 Hz, 1H), 7.68 (d, *J* = 3.9 Hz, 1H), 7.66 – 7.63 (m, 1H), 7.37 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.20 – 7.05 (m, 2H), 6.43 (dt, *J* = 14.4, 6.8 Hz, 1H), 5.83 – 5.68 (br s, 1H), 5.42 (dt, *J* = 14.4, 1.3 Hz, 1H), 3.91 (s, 3H), 3.71 (q., *J* = 7.0 Hz, 6H), 1.59 (d, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 174.0, 157.8, 149.2, 136.6, 133.8, 129.3, 129.1, 127.6, 126.4, 126.2, 122.4, 119.2, 105.7, 58.5, 55.4, 47.1, 41.3, 18.6, 18.2; **IR** (neat): ν_{max} 3300, 2972, 1645, 1606, 1505, 1391, 1264, 1211, 1164, 1073, 1033, 958, 784, 757, 500; **ESIHRMS** *m/z* calcd for $C_{23}H_{34}NO_5{}^{28}Si$ $[M+H]^+$ 432.2206, found 432.2202.



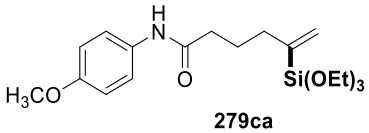
279bh

(*Z*)-4-chloro-*N*-(3-(triethoxysilyl)allyl)benzamide 279bh. Yield: 63% (676 mg, 1.89 mmol). Solvent system for flash column chromatography: DCM/petroleum ether: 60/40; colorless oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 6.66 (dt, *J* = 14.4, 6.6 Hz, 2H), 5.59 (dt, *J* = 14.5, 1.2 Hz, 1H), 4.30 – 4.19 (m, 2H), 3.85 (q., *J* = 7.0 Hz, 6H), 1.23 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 166.2, 148.8, 137.7, 133.1, 128.9, 128.5, 123.0, 58.8, 41.4, 18.3; **IR** (neat): ν_{max} 3308, 2975, 2887, 1638, 1597, 1539, 1487, 1390, 1296, 1166, 1076, 1015, 959, 847, 784, 758; **ESIHRMS** *m/z* calcd for $C_{16}H_{25}{}^{35}ClNO_4{}^{28}Si$ $[M+H]^+$ 358.1241, found 358.1235.



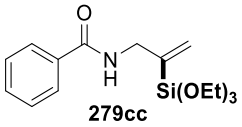
279bi

(*Z*)-*N*-(3-(triethoxysilyl)allyl)benzamide 279bi. Yield: 67% (650 mg, 2.01 mmol). Solvent system for flash column chromatography: DCM/petroleum ether: from 10/90 to 60/40; colorless oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 6.7 Hz, 2H), 7.56 – 7.36 (m, 3H), 6.67 (dt, *J* = 14.4, 6.7 Hz, 1H), 6.62 (br s, 1H), 5.58 (dt, *J* = 14.4, 1.2 Hz, 1H), 4.26 (ddd, *J* = 7.0, 6.0, 1.3 Hz, 2H), 3.85 (q., *J* = 7.0 Hz, 6H), 1.24 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 167.3, 149.1, 134.7, 131.5, 128.6, 127.0, 122.9, 58.7, 41.4, 18.3; **IR** (neat): ν_{max} 3313, 2974, 2926, 1638, 1578, 1535, 1489, 1293, 1075, 959, 787, 693; **ESIHRMS** *m/z* calcd for $C_{16}H_{25}N^{23}NaO_4{}^{28}Si$ $[M+Na]^+$ 346.1451, found 346.1444.



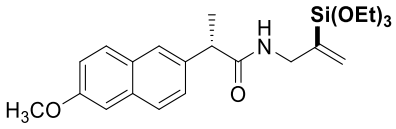
279ca

***N*-(4-methoxyphenyl)-5-(triethoxysilyl)hex-5-enamide 279ca**. Yield: 63% (721 mg, 1.89 mmol). Solvent system for flash column chromatography: DCM/MeOH: from 100/0 to 96/4; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.40 (d, *J* = 9.0 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 5.76 (dt, *J* = 3.0, 1.5 Hz, 1H), 5.68 (dt, *J* = 3.1, 1.0 Hz, 1H), 3.83 (q., *J* = 7.0 Hz, 6H), 3.77 (s, 3H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.24 (t, *J* = 7.4 Hz, 2H), 1.90 (t, *J* = 7.4 Hz, 2H), 1.22 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 171.3, 156.4, 142.9, 131.3, 130.5, 121.8, 114.2, 58.7, 55.6, 37.0, 35.3, 25.0, 18.3; **IR** (neat): ν_{max} 3296, 2979, 2899, 1654, 1600, 1538, 1510, 1243, 1166, 1073, 955, 828, 778, 731, 520, 461; **ESIHRMS** *m/z* calcd for $C_{19}H_{32}NO_5{}^{28}Si$ $[M+H]^+$ 382.2050, found 382.2039.



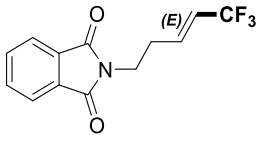
279cc

***N*-(2-(triethoxysilyl)allyl)benzamide 279cc**. Yield: 77% (747 mg, 2.31 mmol). Solvent system for flash column chromatography: DCM/petroleum ether: 60/40; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.83 – 7.73 (m, 2H), 7.56 – 7.36 (m, 3H), 6.81 (br s, 1H), 5.96 (dt, *J* = 2.6, 1.6 Hz, 1H), 5.76 (dt, *J* = 2.6, 1.3 Hz, 1H), 4.19 (dt, *J* = 5.4, 1.4 Hz, 2H), 3.86 (q., *J* = 7.0 Hz, 6H), 1.23 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 167.0, 149.1, 139.4, 134.9, 131.4, 128.5, 127.0, 59.0, 45.6, 18.3; **IR** (neat): ν_{max} 3315, 2974, 2926, 2888, 1642, 1536, 1489, 1389, 1294, 1165, 1071, 956, 780, 693, 471; **ESIHRMS** *m/z* calcd for $C_{16}H_{25}N^{23}NaO_4Si$ $[M+Na]^+$ 346.1451, found 346.1443.



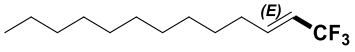
279cb

(S)-2-(6-methoxynaphthalen-2-yl)-N-(2-(triethoxysilyl)allyl)propanamide 279cb. Yield: 47% (609 mg, 1.41 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20 to 60/40; slightly yellow oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 3.6 Hz, 1H), 7.69 (d, *J* = 3.9 Hz, 1H), 7.67 (d, *J* = 1.9 Hz, 1H), 7.39 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.20 – 7.08 (m, 2H), 5.83 (br s, 1H), 5.72 (dt, *J* = 2.6, 1.7 Hz, 1H), 5.60 (dt, *J* = 2.7, 1.4 Hz, 1H), 3.94 (q., *J* = 1.5 Hz, 1H), 3.92 (s, 3H), 3.73 (d, *J* = 1.5 Hz, 1H), 3.71 (d, *J* = 1.5 Hz, 1H), 3.69 (q., *J* = 7.3 Hz, 6H), 1.61 (d, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.0 Hz, 9H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 173.9, 157.8, 149.2, 139.6, 136.7, 133.8, 130.0, 129.3, 127.5, 126.5, 126.2, 119.1, 105.7, 58.7, 55.4, 47.3, 44.6, 18.6, 18.2; **IR** (neat): ν_{max} 3293, 2975, 2930, 2891, 1648, 1605, 1531, 1508, 1389, 1264, 1211, 1162, 1071, 1031, 956, 925, 852, 780, 474; **ESIHRMS** *m/z* calcd for $C_{23}H_{34}NO_5{}^{28}Si$ $[M+Na]^+$ 432.2206, found 432.2198.



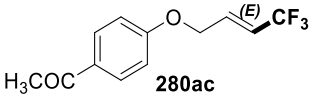
280aa

(*E*)-2-(5,5,5-trifluoropent-3-en-1-yl)isoindoline-1,3-dione 280aa. Prepared according to general procedure. Yield: 61% (66 mg, 240 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 90/10; white solid; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.1 Hz, 2H), 6.37 (dtq, *J* = 16.2, 6.9, 2.1 Hz, 1H), 5.76 – 5.62 (m, 1H), 3.82 (t, *J* = 7.1 Hz, 2H), 2.67 – 2.47 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 168.2, 136.4 (q, $^{3}J_{FC}$ = 6.6 Hz), 134.2, 132.0, 123.5, 122.7 (q, $^{1}J_{FC}$ = 269.0 Hz), 121.1 (q, $^{2}J_{FC}$ = 33.7 Hz), 36.3, 30.7; **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -64.47 (s, *E*-isomer); **IR** (neat): ν_{max} 2945, 1768, 1698, 1680, 1611, 1451, 1398, 1370, 1333, 1274, 1164, 1103, 1045, 1007, 965, 873, 793, 712, 695, 625, 529, 419; **ESIHRMS** *m/z* calcd for $C_{13}H_{11}F_3NO_2$ $[M+H]^+$ 270.0742, found 270.0737.



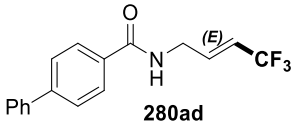
280ab

(*E*)-1,1,1-trifluorotridec-2-ene 280ab. Prepared according to general procedure. Yield: 51% (48 mg, 200 µmol). Obtained as a mixture of *E* and *Z* isomers in a *E*/*Z* ratio of 96/4. Solvent system for flash column chromatography: pentane; colorless oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 6.38 (dtq, *J* = 15.8, 6.7, 2.2 Hz, 1H), 5.60 (dqt, *J* = 15.9, 6.3, 1.6 Hz, 1H), 2.21 – 2.02 (m, 2H), 1.49 – 1.37 (m, 2H), 1.27 (br s, 14H), 0.87 (t, 3H, *J* = 7 Hz); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 141.0 (q, $^{3}J_{FC}$ = 6.5 Hz), 123.30 (q, $^{1}J_{FC}$ = 269.0 Hz), 118.4 (q, $^{2}J_{FC}$ = 33.1 Hz), 32.0, 31.6, 29.7, 29.6, 29.5, 29.4, 29.1, 28.1, 22.8, 14.2; **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -58.08 (s, *Z*-isomer), -63.92 (s, *E*-isomer); **IR** (neat): ν_{max} 2925, 2856, 1681, 1467, 1316, 1271, 1118, 968, 864, 721, 676, 556; **ESIHRMS** *m/z* calcd for $C_{13}H_{24}F_3$ $[M+H]^+$ 237.1830, found 237.1849.



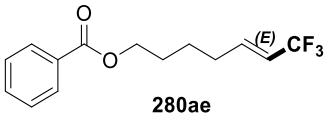
280ac

***(E)*-1-(4-((4,4,4-trifluorobut-2-en-1-yl)oxy)phenyl)ethan-1-one 280ac**. Yield: 70% (68 mg, 280 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 90/10; white solid; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 6.57 (ddq, *J* = 15.8, 4.0, 2.0 Hz, 1H), 6.15 – 5.99 (m, 1H), 4.76 – 4.69 (m, 2H), 2.57 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 196.8, 161.7, 134.2 (q, $^{3}J_{FC}$ = 6.6 Hz), 131.2, 130.8, 122.9 (d, $^{1}J_{FC}$ = 269.5 Hz), 120.0 (q, $^{2}J_{FC}$ = 34.5 Hz), 114.4, 65.7, 26.5; **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -64.51 (s, *E*-isomer); **IR** (neat): ν_{max} 3079, 2926, 2868, 1676, 1600, 1509, 1416, 1360, 1315, 1249, 1174, 1116, 1081, 1023, 958, 834, 594; **ESIHRMS** *m/z* calcd for $C_{12}H_{12}O_2F_3$ $[M+H]^+$ 245.0789, found 245.0784.



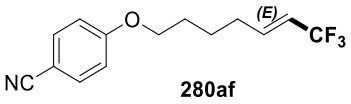
280ad

(*E*)-*N*-(4,4,4-trifluorobut-2-en-1-yl)-[1,1'-biphenyl]-4-carboxamide 280ad. Yield: 70% (85 mg, 280 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 90/10 to 80/20; white solid; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.6 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 6.8 Hz, 2H), 7.47 (t, *J* = 7.2 Hz, 2H), 7.44 – 7.35 (m, 1H), 6.59 – 6.36 (m, 2H), 5.94 – 5.74 (m, 1H), 4.29 – 4.20 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 167.2, 144.9, 139.9, 136.5 (q, $^{3}J_{FC}$ = 6.3 Hz), 132.4, 129.1, 128.2, 127.6, 127.5, 127.3, 122.92 (q, $^{1}J_{FC}$ = 269.5 Hz), 119.7 (q, $^{2}J_{FC}$ = 34.1 Hz), 40.1; **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -64.16 (s, *E*-isomer); **IR** (neat): ν_{max} 3314, 3063, 2930, 1687, 1636, 1535, 1361, 1323, 1270, 1153, 1114, 952, 853, 749, 695; **ESIHRMS** *m/z* calcd for $C_{17}H_{15}F_3NO$ $[M+H]^+$ 306.1106, found 306.1099.



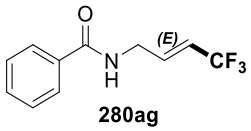
280ae

(*E*)-7,7,7-trifluorohept-5-en-1-yl benzoate 280ae. Yield: 51% (55 mg, 200 µmol). Solvent system for flash column chromatography: toluene; colorless oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 6.9 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 6.39 (m, 1H), 5.65 (m, 1H), 4.34 (t, *J* = 6.4 Hz, 2H), 2.35 – 2.16 (m, 2H), 1.88 – 1.74 (m, 2H), 1.68 – 1.54 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 166.6, 140.1 (q, $^{3}J_{FC}$ = 6.6 Hz), 133.0, 130.4, 129.6, 128.4, 123.13 (q, $^{1}J_{FC}$ = 269.0 Hz), 119.0 (q, $^{2}J_{FC}$ = 33.3 Hz), 64.5, 31.1, 28.2, 24.6; **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -64.00 (s, *E*-isomer); **IR** (neat): ν_{max} 2958, 1717, 1452, 1315, 1269, 1110, 1026, 973, 855, 798, 709, 521; **ESIHRMS** *m/z* calcd for $C_{14}H_{16}F_3O_2$ $[M+H]^+$ 273.1102, found 273.1097.



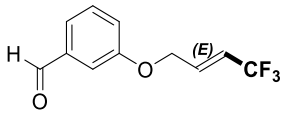
280af

(*E*)-4-((7,7,7-trifluorohept-5-en-1-yl)oxy)benzonitrile 280af. Yield: 64% (70 mg, 259 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 90/10 to 80/20; colorless oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 6.39 (dtq, *J* = 15.8, 6.7, 2.1 Hz, 1H), 5.65 (dqt, *J* = 15.9, 6.3, 1.6 Hz, 1H), 4.01 (t, *J* = 6.2 Hz, 2H), 2.36 – 2.17 (m, 2H), 1.91 – 1.76 (m, 2H), 1.73 – 1.59 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 162.3, 140.0 (q, $^{3}J_{FC}$ = 6.6 Hz), 134.1, 123.1 (q, $^{1}J_{FC}$ = 269.2 Hz), 119.3, 119.0 (q, $^{2}J_{FC}$ = 33.3 Hz), 115.2, 104.0, 67.9, 31.1, 28.4, 24.5; **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -63.98 (s, *E*-isomer); **IR** (neat): ν_{max} 2944, 2225, 1680, 1605, 1569, 1508, 1472, 1301, 1256, 1171, 1112, 1015, 974, 911, 833, 733, 701, 675, 547, 516; **ESIHRMS** *m/z* calcd for $C_{14}H_{14}F_3NO$ $[M+H]^+$ 269.1027, found 270.1103.



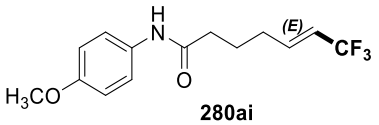
280ag

(*E*)-*N*-(4,4,4-trifluorobut-2-en-1-yl)benzamide 280ag. Prepared according to general procedure. Yield: 67% (61 mg, 270 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 90/10 to 80/20; white solid; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 6.9 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.49 – 7.42 (m, 2H), 6.47 (dtd, *J* = 15.5, 5.2, 2.9 Hz, 2H), 5.89 – 5.70 (m, 1H), 4.27 – 4.14 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 167.6, 136.5 (q, $^{3}J_{FC}$ = 6.3 Hz), 133.8, 132.0, 128.8, 127.1, 122.91 (q, $^{1}J_{FC}$ = 269.3 Hz), 119.7 (q, $^{2}J_{FC}$ = 34.0 Hz), 40.0; **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -64.14 (s, *E*-isomer); **IR** (neat): ν_{max} 3300, 3071, 2930, 1684, 1636, 1535, 1366, 1316, 1263, 1109, 1076, 1038, 958, 862, 801, 692, 667, 415; **ESIHRMS** *m/z* calcd for $C_{11}H_{11}F_3NO$ $[M+H]^+$ 230.0793, found 230.0787.



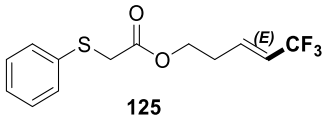
280ah

(*E*)-3-((4,4,4-trifluorobut-2-en-1-yl)oxy)benzaldehyde 280ah. Yield: 53% (49 mg, 210 µmol). Solvent system for flash column chromatography: toluene; colorless oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.56 – 7.46 (m, 2H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.22 (dt, *J* = 7.1, 2.3 Hz, 1H), 6.58 (ddq, *J* = 15.8, 4.0, 2.0 Hz, 1H), 6.16 – 6.01 (m, 1H), 4.76 – 4.68 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 191.9, 158.6, 138.0, 134.4 (q, $^{3}J_{FC}$ = 6.4 Hz), 130.5, 122.94 (q, $^{1}J_{FC}$ = 269.3 Hz), 124.6, 122.1, 119.9 (q, $^{2}J_{FC}$ = 34.3 Hz), 112.7, 65.9; **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -64.49 (s, *E*-isomer); **IR** (neat): ν_{max} 2926, 2858, 2734, 1696, 1586, 1485, 1447, 1386, 1310, 1256, 1115, 1074, 1027, 959, 866, 781, 680, 646, 615, 558, 439; **ESIHRMS** *m/z* calcd for $C_{11}H_{10}F_3O_2$ $[M+H]^+$ 231.0633, found 231.0583.



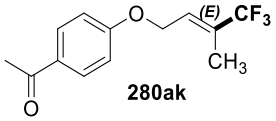
280ai

(*E*)-7,7,7-trifluoro-N-(4-methoxyphenyl)hept-5-enamide 280ai. Yield: 60% (69 mg, 240 µmol). Solvent system for flash column chromatography: toluene/EtOAc: from 100/0 to 90/10; white solid; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.38 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.35 (dtq, *J* = 15.8, 6.7, 2.2 Hz, 1H), 5.62 (dqt, *J* = 15.9, 6.4, 1.6 Hz, 1H), 3.77 (s, 3H), 2.32 (t, *J* = 7.4 Hz, 2H), 2.26 – 2.14 (m, 2H), 1.84 (quint., *J* = 7.1 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 170.6, 156.5, 139.7 (q, $^{3}J_{FC}$ = 6.5 Hz), 130.9, 123.0 (q, $^{1}J_{FC}$ = 269.2 Hz), 122.0, 119.2 (q, $^{2}J_{FC}$ = 33.3 Hz), 114.2, 55.5, 36.2, 30.8, 23.7; **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -64.08 (s, *E*-isomer); **IR** (neat): ν_{max} 3295, 2949, 1652, 1597, 1540, 1513, 1466, 1414, 1355, 1328, 1298, 1241, 1177, 1114, 1080, 1032, 966, 829, 694, 520; **ESIHRMS** *m/z* calcd for $C_{14}H_{17}F_3NO_2$ $[M+H]^+$ 288.1211, found 288.1201.



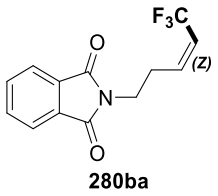
125

(*E*)-5,5,5-trifluoropent-3-en-1-yl 2-(phenylthio)acetate 280aj. Yield: 62% (72 mg, 248 µmol). Solvent system for flash column chromatography: toluene/diethyl ether: 96/4; colorless oil; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 6.8 Hz, 2H), 7.37 – 7.21 (m, 3H), 6.29 (dtq, *J* = 15.8, 6.7, 2.1 Hz, 1H), 5.75 – 5.58 (m, 1H), 4.20 (t, *J* = 6.4 Hz, 2H), 3.65 (s, 2H), 2.50 – 2.39 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 169.7, 135.9 (q, $^{3}J_{FC}$ = 6.6 Hz), 134.8, 130.2, 129.2, 127.3, 122.7 (q, $^{1}J_{FC}$ = 270.8 Hz), 121.1 (q, $^{2}J_{FC}$ = 33.8 Hz), 63.2, 36.6, 30.7; **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -64.34 (s, *E*-isomer); **IR** (neat): ν_{max} 2968, 2917, 1735, 1683, 1584, 1482, 1439, 1319, 1274, 1116, 1086, 1024, 969, 858, 740, 690, 474; **ESIHRMS** *m/z* calcd for $C_{13}H_{14}F_3O_2S$ $[M+H]^+$ 291.0667, found 291.0616.



280ak

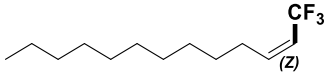
(*E*)-1-(4-((4,4,4-trifluoro-3-methylbut-2-en-1-yl)oxy)phenyl)ethan-1-one 280ak. Yield: 52% (54 mg, 208 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 90/10; white solid; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.99 – 7.87 (m, 2H), 6.95 (dd, *J* = 11.1, 8.9 Hz, 2H), 5.87 – 5.59 (m, 1H), 4.76 – 4.54 (m, 2H), 2.54 (s, 3H), 1.82 (dq, *J* = 7.3, 2.5 Hz, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 196.8, 162.3, 136.9 (q, *J* = 5.8 Hz), 130.6, 129.3, 125.8 (q, *J* = 29.3 Hz), 124.9, 123.7 (q, $^{1}J_{FC}$ = 271.0 Hz), 114.4, 64.0, 26.4, 13.6; **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -66.80 (s, *E*-isomer); **IR** (neat): ν_{max} 2941, 1675, 1599, 1508, 1358, 1314, 1249, 1173, 1117, 1005, 956, 834, 591, 504; **ESIHRMS** *m/z* calcd for $C_{13}H_{14}F_3O_2$ $[M+H]^+$ 259.0946, found 259.0972.



280ba

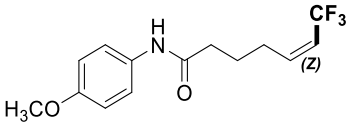
(*Z*)-2-(5,5,5-trifluoropent-3-en-1-yl)isoindoline-1,3-dione 280ba. Yield: 61% (66 mg, 244 µmol). Obtained as a mixture of *Z* and *E* isomers in a *Z*/*E* ratio of 92/8. Solvent system for flash column chromatography: petroleum ether/EtOAc: 90/10; white solid. The signals reported are of the majority stereoisomer. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.5, 3.1 Hz, 2H, *Z*-isomer), 7.71 (dd, *J* = 5.5, 3.1 Hz, 2H, *Z*-isomer), 6.04 (dt, *J* = 11.6, 7.8 Hz, 1H, *Z*-isomer), 5.79 – 5.57 (m, 1H, *Z*-isomer), 3.83 (t, *J* = 6.6 Hz, 2H, *Z*-isomer), 2.94 – 2.61 (m, 2H, *Z*-isomer); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 168.3 (*Z*-isomer), 138.5 (q, $^{3}J_{FC}$ = 5.4 Hz, *Z*-isomer), 134.1 (*Z*-isomer), 132.0 (*Z*-isomer), 123.0 (q, $^{1}J_{FC}$ = 269.0 Hz, *Z*-isomer), 123.4 (*Z*-isomer), 121.1 (q, $^{2}J_{FC}$ = 33.6 Hz, *Z*-isomer), 36.6 (*Z*-isomer), 27.9 (*Z*-isomer); **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -58.28 (s, *Z*-isomer); **IR** (neat): ν_{max}

2944, 1774, 1710, 1417, 1395, 1362, 1228, 1118, 1024, 720, 530; **ESIHRMS** *m/z* calcd for $C_{13}H_{11}F_3NO_2$ $[M+H]^+$ 270.0742, found 270.0735.



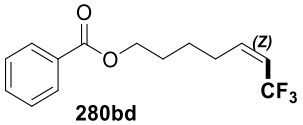
280bb

(*Z*)-1,1,1-trifluorotridec-2-ene 280bb. Yield: 32% (30 mg, 127 µmol). Obtained as a mixture of *Z* and *E* isomers in a *Z*/*E* ratio of 85/15. Solvent system for flash column chromatography: pentane; colorless oil. The signals reported are of the majority stereoisomer. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 5.99 (dt, *J* = 11.6, 7.9 Hz, 1H, *Z*-isomer), 5.68 – 5.48 (m, 1H, *Z*-isomer), 2.37 – 2.21 (m, 2H, *Z*-isomer), 1.48 – 1.38 (m, 2H, *Z*-isomer), 1.28 (s, 14H, *Z*-isomer), 0.88 (t, *J* = 6.9 Hz, 3H, *Z*-isomer); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 142.3 (q, $^3J_{FC}$ = 5.3 Hz, *Z*-isomer), 122.5 (q, $^1J_{FC}$ = 271.6 Hz, *Z*-isomer), 117.3 (q, $^2J_{FC}$ = 33.3 Hz, *Z*-isomer), 31.0 (*Z*-isomer), 28.7 (*Z*-isomer), 28.6 (*Z*-isomer), 28.5 (*Z*-isomer), 28.4 (*Z*-isomer), 28.2 (*Z*-isomer), 28.0 (*Z*-isomer), 27.5 (*Z*-isomer), 21.8 (*Z*-isomer), 13.2 (*Z*-isomer); **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -58.08 (s, *Z*-isomer); **IR** (neat): ν_{max} 2923, 2855, 1466, 1256, 1109; **ESIHRMS** *m/z* calcd for $C_{13}H_{24}F_3$ $[M+H]^+$ 237.1830, found 237.1845.



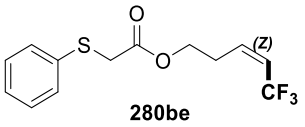
280bc

(*Z*)-7,7,7-trifluoro-N-(4-methoxyphenyl)hept-5-enamide 280bc. Yield: 56% (64 mg, 224 µmol). Obtained as a mixture of *Z* and *E* isomers in a *Z*/*E* ratio of 83/17. Solvent system for flash column chromatography: toluene/EtOAc: from 100/0 to 90/10; colorless oil. The signals reported are of the majority stereoisomer. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.57 (br s, 1H, *Z*-isomer), 7.37 (d, *J* = 9.1 Hz, 2H, *Z*-isomer), 6.82 (d, *J* = 9.0 Hz, 2H, *Z*-isomer), 5.96 (dt, *J* = 11.6, 7.9 Hz, 1H, *Z*-isomer), 5.74 – 5.51 (m, 1H, *Z*-isomer), 3.76 (s, 3H, *Z*-isomer), 2.42 – 2.35 (m, 2H, *Z*-isomer), 2.31 (t, *J* = 7.6 Hz, 2H, *Z*-isomer), 1.95 – 1.68 (m, 2H, *Z*-isomer); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 170.7 (*Z*-isomer), 156.5 (*Z*-isomer), 142.0 (q, $^3J_{FC}$ = 5.4 Hz, *Z*-isomer), 131.0 (*Z*-isomer), 123.3 (q, $^1J_{FC}$ = 269.0 Hz, *Z*-isomer), 122.1 (*Z*-isomer), 119.2 (q, $^2J_{FC}$ = 33.3 Hz, *Z*-isomer), 114.1 (*Z*-isomer), 55.5 (*Z*-isomer), 36.4 (*Z*-isomer), 27.9 (*Z*-isomer), 24.5 (*Z*-isomer); **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -57.94 (s, *Z*-isomer); **IR** (neat): ν_{max} 3293, 2941, 1655, 1603, 1538, 1509, 1413, 1236, 1170, 1111, 1033, 973, 827, 701, 520; **ESIHRMS** *m/z* calcd for $C_{14}H_{17}F_3NO_2$ $[M+H]^+$288.1211, found 288.1202.



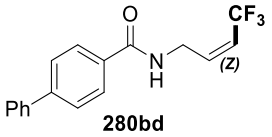
280bd

(*Z*)-7,7,7-trifluorohept-5-en-1-yl benzoate 280bd. Yield: 45% (49 mg, 180 µmol). Obtained as a mixture of *Z* and *E* isomers in a *Z*/*E* ratio of 91/9. Solvent system for flash column chromatography: toluene; colorless oil. The signals reported are of the majority stereoisomer. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.0 Hz, 2H, *Z*-isomer), 7.62 – 7.50 (m, 1H, *Z*-isomer), 7.51 – 7.38 (m, 2H, *Z*-isomer), 6.00 (dt, *J* = 11.6, 7.8 Hz, 1H, *Z*-isomer), 5.75 – 5.53 (m, 1H, *Z*-isomer), 4.34 (t, *J* = 6.4 Hz, 2H, *Z*-isomer), 2.55 – 2.12 (m, 2H, *Z*-isomer), 1.88 – 1.76 (m, 2H, *Z*-isomer), 1.69 – 1.57 (m, 2H, *Z*-isomer); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 166.7 (*Z*-isomer), 142.4 (q, $^3J_{FC}$ = 5.3 Hz, *Z*-isomer), 135.1 (*Z*-isomer), 134.1 (*Z*-isomer), 130.4 (*Z*-isomer), 129.6 (*Z*-isomer), 128.5 (*Z*-isomer), 123.0 (q, $^1J_{FC}$ = 271.0 Hz, *Z*-isomer), 119.1 (q, $^2J_{FC}$ = 33.1 Hz, *Z*-isomer), 64.6 (*Z*-isomer), 28.3 (*Z*-isomer), 28.1 (*Z*-isomer), 25.5 (*Z*-isomer); **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -56.99 (s, *Z*-isomer); **IR** (neat): ν_{max} 2955, 1718, 1452, 1315, 1271, 1115, 1027, 972, 805, 710, 517; **ESIHRMS** *m/z* calcd for $C_{14}H_{16}F_3O_2$ $[M+H]^+$ 273.1102, found 273.1093.



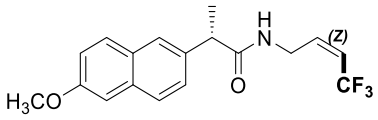
280be

(*Z*)-5,5,5-trifluoropent-3-en-1-yl 2-(phenylthio)acetate 280be. Yield: 43% (50 mg, 172 µmol). Obtained as a mixture of *Z* and *E* isomers in a *Z*/*E* ratio of 90/10. Solvent system for flash column chromatography: toluene/diethyl ether: 96/4; colorless oil. The signals reported are of the majority stereoisomer. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 2H, *Z*-isomer), 7.32 – 7.18 (m, 3H, *Z*-isomer), 5.87 (dt, *J* = 11.7, 7.6 Hz, 1H, *Z*-isomer), 5.64 (dqt, *J* = 11.8, 8.3, 1.7 Hz, 1H, *Z*-isomer), 4.16 (t, *J* = 6.4 Hz, 2H, *Z*-isomer), 3.62 (s, 2H, *Z*-isomer), 2.65 – 2.51 (m, 2H, *Z*-isomer); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 169.7 (*Z*-isomer), 137.7 (q, $^{3}J_{FC}$ = 5.4 Hz, *Z*-isomer), 134.9 (*Z*-isomer), 130.2 (*Z*-isomer), 129.2 (*Z*-isomer), 127.2 (*Z*-isomer), 123.1 (q, $^{1}J_{FC}$ = 271.0 Hz, *Z*-isomer), 120.9 (q, $^{2}J_{FC}$ = 33.6 Hz, *Z*-isomer), 63.7 (*Z*-isomer), 36.6 (*Z*-isomer), 27.8 (*Z*-isomer); **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -58.50 (s, *Z*-isomer); **IR** (neat): ν_{max} 2964, 1735, 1672, 1584, 1482, 1440, 1418, 1272, 1218, 1118, 1025, 740, 690; **ESIHRMS** *m/z* calcd for $C_{13}H_{14}F_3O_2S$ $[M+H]^+$ 291.0667, found 291.0616.



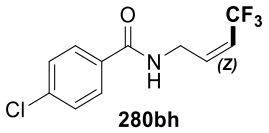
280bd

(*Z*)-*N*-(4,4,4-trifluorobut-2-en-1-yl)-[1,1'-biphenyl]-4-carboxamide 280bd. Yield: 55% (67 mg, 219 µmol). Obtained as a mixture of *Z* and *E* isomers in a *Z*/*E* ratio of 98/2. Solvent system for flash column chromatography: petroleum ether/EtOAc: 90/10 to 80/20; white solid. The signals reported are of the majority stereoisomer. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 2H, *Z*-isomer), 7.67 (d, *J* = 8.0 Hz, 2H, *Z*-isomer), 7.61 (d, *J* = 7.4 Hz, 2H, *Z*-isomer), 7.55 – 7.35 (m, 3H, *Z*-isomer), 6.45 (br s, 1H, *Z*-isomer), 6.17 (dt, *J* = 11.4, 6.8 Hz, 1H, *Z*-isomer), 5.76 (quint., *J* = 9.2 Hz, 1H, *Z*-isomer), 4.64 – 4.26 (m, 2H, *Z*-isomer); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 167.3 (*Z*-isomer), 144.8 (*Z*-isomer), 140.0 (*Z*-isomer), 138.9 (q, $^{3}J_{FC}$ = 5.1 Hz, *Z*-isomer), 135.2 (*Z*-isomer), 132.6 (*Z*-isomer), 129.0 (*Z*-isomer), 128.2 (*Z*-isomer), 127.6 (*Z*-isomer), 127.4 (*Z*-isomer), 127.3 (*Z*-isomer), 123.0 (q, $^{1}J_{FC}$ = 271.0 Hz, *Z*-isomer), 120.2 (q, $^{2}J_{FC}$ = 34.2 Hz, *Z*-isomer), 37.5 (*Z*-isomer); **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -58.39 (s, *Z*-isomer); **IR** (neat): ν_{max} 3285, 1630, 1537, 1487, 1417, 1276, 1230, 1112, 852, 760, 700, 631; **ESIHRMS** *m/z* calcd for $C_{17}H_{15}F_3NO$ $[M+H]^+$ 306.1106, found 306.1098.



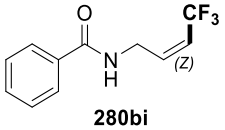
280bg

(S, *Z*)-2-(6-methoxynaphthalen-2-yl)-N-(4,4,4-trifluorobut-2-en-1-yl)propanamide 280bg. Yield: 50% (67 mg, 195 µmol). Obtained as a mixture of *Z* and *E* isomers in a *Z*/*E* ratio of 98/2. Solvent system for flash column chromatography: petroleum ether/EtOAc: 90/10 to 80/20; white solid. The signals reported are of the majority stereoisomer. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.71 (t, *J* = 8.2 Hz, 2H, *Z*-isomer), 7.65 (d, *J* = 1.8 Hz, 1H, *Z*-isomer), 7.36 (dd, *J* = 8.5, 1.9 Hz, 1H, *Z*-isomer), 7.17 (dd, *J* = 8.8, 2.5 Hz, 1H, *Z*-isomer), 7.13 (d, *J* = 2.6 Hz, 1H, *Z*-isomer), 5.89 (dt, *J* = 11.7, 6.5 Hz, 1H, *Z*-isomer), 5.81 – 5.71 (m, 1H, *Z*-isomer), 5.69 – 5.49 (m, 1H, *Z*-isomer), 4.14 – 3.99 (m, 2H, *Z*-isomer), 3.92 (s, 3H, *Z*-isomer), 3.70 (quint., *J* = 7.1 Hz, 1H, *Z*-isomer), 1.60 (d, *J* = 7.2 Hz, 3H, *Z*-isomer); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 174.6 (*Z*-isomer), 157.9 (*Z*-isomer), 139.2 (q, $^{3}J_{FC}$ = 5.1 Hz, *Z*-isomer), 136.1 (*Z*-isomer), 133.9 (*Z*-isomer), 129.3 (*Z*-isomer), 129.0 (*Z*-isomer), 127.8 (*Z*-isomer), 126.3 (*Z*-isomer), 126.2 (*Z*-isomer), 122.9 (q, $^{1}J_{FC}$ = 271.0 Hz, *Z*-isomer), 120.0 (q, $^{2}J_{FC}$ = 34.3 Hz, *Z*-isomer), 119.4 (*Z*-isomer), 105.7 (*Z*-isomer), 55.4 (*Z*-isomer), 46.9 (*Z*-isomer), 37.2 (*Z*-isomer), 18.5 (*Z*-isomer); **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -58.68 (s, *Z*-isomer); **IR** (neat): ν_{max} 3299, 1648, 1607, 1544, 1418, 1265, 1214, 1162, 1115, 1028, 856, 814, 475; **ESIHRMS** *m/z* calcd for $C_{18}H_{19}F_3NO_2$ $[M+H]^+$ 338.1368, found 338.1359.



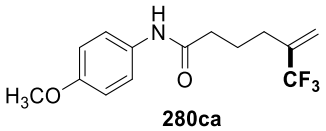
280bh

(*Z*)-4-chloro-*N*-(4,4,4-trifluorobut-2-en-1-yl)benzamide 280bh. Yield: 57% (60 mg, 228 µmol). Obtained as a mixture of *Z* and *E* isomers in a *Z*/*E* ratio of 98/2. Solvent system for flash column chromatography: petroleum ether/EtOAc: 90/10 to 80/20; white solid. The signals reported are of the majority stereoisomer. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.6 Hz, 2H, *Z*-isomer), 7.40 (d, *J* = 8.6 Hz, 2H, *Z*-isomer), 6.54 (br s, 1H, *Z*-isomer), 6.12 (dt, *J* = 11.7, 6.7 Hz, 1H, *Z*-isomer), 5.73 (dqt, *J* = 12.2, 8.6, 1.8 Hz, 1H, *Z*-isomer), 4.31 (m, 2H, *Z*-isomer); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 166.7 (*Z*-isomer), 138.6 (q, ^{3}J = 5.1 Hz, *Z*-isomer), 138.2 (*Z*-isomer), 132.3 (*Z*-isomer), 129.0 (*Z*-isomer), 128.5 (*Z*-isomer), 122.94 (q, $^{1}J_{FC}$ = 271.0 Hz, *Z*-isomer), 120.2 (q, ^{2}J = 34.3 Hz, *Z*-isomer), 37.5 (*Z*-isomer); **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -58.39 (s, *Z*-isomer); **IR** (neat): ν_{max} 3400, 3010, 2986, 1634, 1596, 1537, 1487, 1420, 1316, 1274, 1221, 1149, 1106, 1092, 1014, 844, 712; **ESIHRMS** *m/z* calcd for $C_{11}H_{10}ClF_3NO$ $[M+H]^+$ 264.0403, found 264.0396.



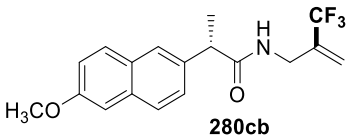
280bi

(*Z*)-*N*-(4,4,4-trifluorobut-2-en-1-yl)benzamide 280bi. Yield: 58% (53 mg, 232 µmol). Obtained as a mixture of *Z* and *E* isomers in a *Z*/*E* ratio of 98/2. Solvent system for flash column chromatography: petroleum ether/EtOAc: 90/10 to 80/20; white solid. The signals reported are of the majority stereoisomer. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 6.8 Hz, 2H, *Z*-isomer), 7.63 – 7.36 (m, 3H, *Z*-isomer), 6.34 (br s, 1H, *Z*-isomer), 6.16 (dt, *J* = 11.7, 6.8 Hz, 1H, *Z*-isomer), 5.83 – 5.67 (m, 1H, *Z*-isomer), 4.41 – 4.26 (m, 2H, *Z*-isomer); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 167.6 (*Z*-isomer), 138.9 (q, $^{3}J_{FC}$ = 5.2 Hz, *Z*-isomer), 134.0 (*Z*-isomer), 131.9 (*Z*-isomer), 128.8 (*Z*-isomer), 127.0 (*Z*-isomer), 123.0 (q, $^{1}J_{FC}$ = 271.0 Hz, *Z*-isomer), 120.2 (q, $^{2}J_{FC}$ = 34.2 Hz, *Z*-isomer), 37.5 (*Z*-isomer); **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -58.41 (s, *Z*-isomer); **IR** (neat): ν_{max} 3304, 2924, 1637, 1579, 1532, 1417, 1275, 1232, 1161, 1112, 691; **ESIHRMS** *m/z* calcd for $C_{11}H_{11}F_3NO$ $[M+H]^+$ 230.0793, found 230.0788.



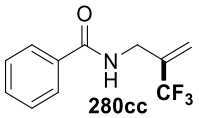
280ca

***N*-(4-methoxyphenyl)-5-(trifluoromethyl)hex-5-enamide 280ca**. Yield: 32% (37 mg, 128 µmol). Obtained as a mixture of α and *Z* isomers in a α/*Z* ratio of 80/20. Solvent system for flash column chromatography: toluene/EtOAc: from 100/0 to 90/10; white solid. The signals reported are of the majority stereoisomer. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 9.0 Hz, 3H, α-isomer), 7.23 (br s, 1H, α-isomer), 6.84 (d, *J* = 9.0 Hz, 2H, α-isomer), 5.71 (d, *J* = 1.8 Hz, 1H, α-isomer), 5.37 (d, *J* = 1.4 Hz, 1H, α-isomer), 3.78 (s, 3H, α-isomer), 2.37 (t, *J* = 7.4 Hz, 2H, α-isomer), 2.29 (t, *J* = 7.7 Hz, 2H, α-isomer), 1.95 (quint., *J* = 7.9 Hz, 2H, α-isomer); **^{13}C-NMR** (75 MHz, $CDCl_3$): 170.4 (α-isomer), 156.6 (α-isomer), 137.7 (q, $^{2}J_{FC}$ = 33.1 Hz, α-isomer), 130.9 (α-isomer), 123.8 (q, $^{1}J_{FC}$ = 273.0 Hz, α-isomer), 121.9 (α-isomer), 118.4(q, $^{3}J_{FC}$ = 6.5 Hz, α-isomer), 114.2 (α-isomer), 55.6 (α-isomer), 36.3 (α-isomer), 28.8 (α-isomer), 23.3 (α-isomer); **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -68.57 (s, α-isomer); **IR** (neat): ν_{max} 3291, 2943, 2839, 1655, 1606, 1511, 1413, 1245, 1166, 1120, 1036, 829, 521; **ESIHRMS** *m/z* calcd for $C_{14}H_{17}F_3NO_2$ $[M+H]^+$ 288.1211, found 288.1202.



280cb

(*S*)-2-(6-methoxynaphthalen-2-yl)-*N*-(2-(trifluoromethyl)allyl)propanamide 280cb. Yield: 53% (72 mg, 212 μmol). Obtained as a mixture of α and *Z* isomers in a α/*Z* ratio of 85/15. Solvent system for flash column chromatography: petroleum ether /EtOAc: 80/20; white solid. The signals reported are of the majority stereoisomer. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.73 (t, *J* = 8.3 Hz, 2H, α-isomer), 7.67 (d, *J* = 1.9 Hz, 1H, α-isomer), 7.36 (dd, *J* = 8.5, 1.9 Hz, 1H, α-isomer), 7.17 (dd, *J* = 8.8, 2.5 Hz, 1H, α-isomer), 7.13 (d, *J* = 2.5 Hz, 1H, α-isomer), 5.67 (q., *J* = 1.3 Hz, 1H, α-isomer), 5.54 (br s, 1H, α-isomer), 5.34 (q., *J* = 1.5 Hz, 1H, α-isomer), 3.98 (t, *J* = 7.1 Hz, 2H, α-isomer), 3.93 (s, 3H, α-isomer), 3.74 (q., *J* = 7.2 Hz, 1H, α-isomer), 1.62 (d, *J* = 7.2 Hz, 3H, α-isomer); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 174.4 (α-isomer), 158.0 (α-isomer), 136.0 (α-isomer), 135.1 (q, $^{2}J_{FC}$ = 29.2 Hz, α-isomer), 134.0 (α-isomer), 129.3 (α-isomer), 129.1 (α-isomer), 127.9 (α-isomer), 126.4 (α-isomer), 126.2 (α-isomer), 123.1 (q, $^{1}J_{FC}$ = 273.9 Hz, α-isomer), 119.6 (q, $^{3}J_{FC}$ = 5.5 Hz, α-isomer), 119.5 (α-isomer), 105.8 (α-isomer), 55.5 (α-isomer), 47.2 (α-isomer), 38.4 (α-isomer), 18.3 (α-isomer); **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -67.68 (s, α-isomer); **IR** (neat): ν_{max} 3289, 2937, 1648, 1605, 1543, 1504, 1389, 1320, 1264, 1212, 1170, 1114, 1030, 925, 853, 808, 698, 473; **ESIHRMS** *m/z* calcd for $C_{18}H_{19}F_3NO_2$ $[M+H]^+$ 338.1368, found 338.1361.



280cc

***N*-(2-(trifluoromethyl)allyl)benzamide 280cc**. Yield: 59% (54 mg, 236 μmol). Obtained as a mixture of α and *Z* isomers in a α/*Z* ratio of 83/17. Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; white solid. The signals reported are of the majority stereoisomer. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 6.9 Hz, 2H, α-isomer), 7.59 – 7.46 (m, 1H, α-isomer), 7.48 – 7.41 (m, 2H, α-isomer), 6.40 (br s, 1H, α-isomer), 5.85 (q., *J* = 0.9 Hz, 1H, α-isomer), 5.66 (quint., *J* = 1.4 Hz, 1H, α-isomer), 4.26 (d, *J* = 6.1 Hz, 2H, α-isomer); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 167.5 (α-isomer), 135.1 (q, $^{2}J_{FC}$ = 29.3 Hz, α-isomer), 134.0 (α-isomer), 132.0(α-isomer), 128.8 (α-isomer), 127.0 (α-isomer), 123.3 (q, $^{1}J_{FC}$ = 273.7 Hz, α-isomer), 120.5 (q, $^{3}J_{FC}$ = 5.5 Hz, α-isomer), 38.9 (α-isomer); **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -67.57 (s, α-isomer); **IR** (neat): ν_{max} 3324, 1639, 1541, 1492, 1423, 1319, 1151, 1114, 952, 691, 640; **ESIHRMS** *m/z* calcd for $C_{11}H_{11}F_3NO$ $[M+H]^+$ 230.0793, found 230.0787.