Palladium-Catalyzed Amino- and Selenocarbonylation of Unsaturated Carbon-Carbon Bonds

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Statement of Authorship

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Zhusong Cao

Rostock, 11. 10. 2024

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Abstract

Palladium-Catalyzed Amino- and Selenocarbonylation of Unsaturated Carbon-Carbon Bonds

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This dissertation presents the development of several novel palladium-catalyzed carbonylation reactions, namely palladium-catalyzed aminocarbonylation of acetylene and selenocarbonylation of alkenes. First, we developed the palladium-catalyzed hydroaminocarbonylation of acetylene, allowing modular and diverse synthesis of various acrylamides including ibrutinib, osimertinib and other bioactive compounds. Following this work, we disclosed an efficient methodology for the synthesis of *β*-perfluoroalkyl acrylamides by palladium-catalyzed four-component aminocarbonylation of acetylene with amines and perfluoroalkyl iodide. Finally, we turned our attention to the regioselective issue in the palladium-catalyzed carbonylation of alkenes. Using the same catalyst system, we realized regiodivergent carbonylation of alkenes with selenols to give either branched or linear selenoesters in the presence of different amounts of acid.

Palladiumkatalysierte Amino- und Selenocarbonylierung von ungesättigten Kohlenstoff-Kohlenstoff-Bindungen

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In dieser Dissertation wird die Entwicklung mehrerer neuartiger Palladium-katalysierter Carbonylierungsreaktionen vorgestellt, nämlich die Palladium-katalysierte Aminocarbonylierung von Acetylen und die Selenocarbonylierung von Alkenen. Zunächst entwickelten wir die Palladium-katalysierte Hydroaminocarbonylierung von Acetylen, die eine modulare und vielfältige Synthese verschiedener Acrylamide, einschließlich Ibrutinib, Osimertinib und anderer bioaktiver Verbindungen, ermöglicht. Im Anschluss an diese Arbeit wurden neuartige Synthesen von β-Perfluoralkylacrylamiden durch Palladium-katalysierte Vier-Komponenten-Aminocarbonylierung von Acetylen mit Aminen und Perfluoralkyliodiden durchgeführt. Schließlich wurde die Regioselektivität der Palladium-katalysierten Carbonylierung von Alkenen untersucht. Hier gelang es unter Verwendung desselben Katalysatorsystems eine regiodivergente Carbonylierung von Alkenen mit Selenolen zu realisieren, wobei entweder verzweigte oder lineare Selenoester in Gegenwart verschiedener Säuremengen erhalten wurden.

List of abbreviations

Ac	Acetyl
Ar	Aryl
atm	Atmosphere
BINAP	(2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BNPPA	1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate
Bu	Butyl
py^{t}bpx	1,2-Bis((*tert*-butyl(pyridin-2-yl)phosphino)methyl)benzene
Cat.	Catalyst
Co	Cobalt
CO	Carbon monoxide
COD	Cycloocta-1,5-diene
Cu	Copper
Cy	Cyclohexyl
dba	Dibenzylideneacetone
dcpf	1,1'-Bis(dicyclohexylphosphino)ferrocene
DME	Dimethoxyethane
DMF	Dimethylformamide
DPPA	Diphenylphosphinic acid
DPPB	1,4-Bis(diphenylphosphino)butane
dppdtbpf	1-Diphenylphosphino-1'-(di-*tert*-butylphosphino)ferrocene
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
DPPP	1,3-Bis(diphenylphosphino)propane
DPPPen	1,5-Bis(diphenylphosphino)pentane
DPEphos	Bis[(2-diphenylphosphino)phenyl] ether
DTBP	Di-*tert*-butyl peroxide
DTBPMB	1,2-Bis(di-*tert*-butylphosphinomethyl)benzene
DtBPF	1,1'-Bis(di-*tert*-butylphosphino)ferrocene
ect.	Et cetera
equiv.	Equivalent
et al.	Et alii
Et_3N	Triethylamine
h	Hour
H_2	Hydrogen
HOTf	Trifluoromethanesulfonic acid
HPLC	High performance liquid chromatography
i-	*Iso-*
L	Ligand
Me	Methyl
MeCN	Acetonitrile
n-	*Neo-*
Ni	Nickel
mmol	Millimole
MSA	Methanesulfonic acid
Neolephos	2,2'-bis(*tert*-butyl(pyridin-2-yl)phosphanyl)-1,1'-binaphthalene
NMP	*N*-Methyl-2-pyrrolidone
OAc	Acetoxy
O_2	Oxygen
Ph	Phenyl

Pd	Palladium
Pt	Platinum
PPh_3	Triphenylphosphine
psi	Pound per square inch
PTSA/ *p*-TsOH	*p*-Toluenesulfonic acid
Rh	Rhodium
RT	Room temperature
***t*-**	*Tert*-
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TON	Turnover number
RuPhos	Dicyclohexyl(2',6'-diisopropoxy-[1,1'-biphenyl]-2-yl)phosphine
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
2-MeTHF	2-Methyltetrahydrofuran
5-Cl-SA	5-Chlorosalicylic acid

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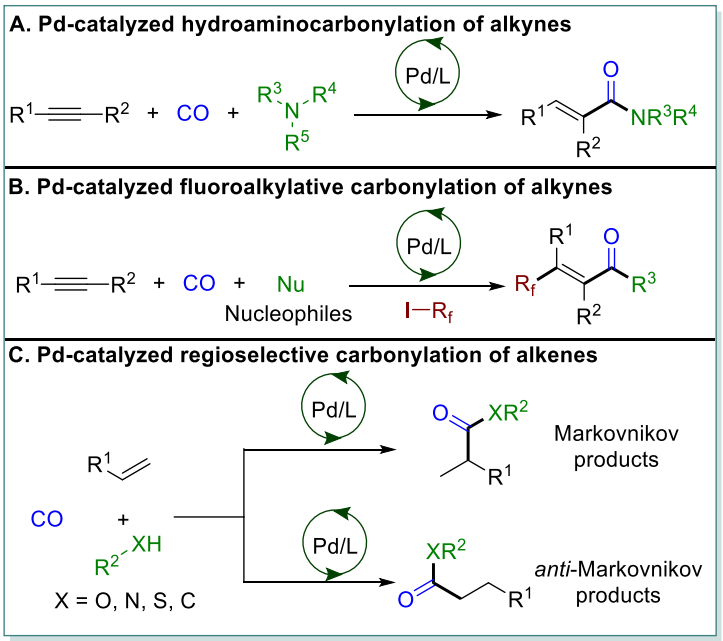
1 Introduction

Alkenes and alkynes are pivotal structural units found in numerous pharmaceuticals, agrochemicals and natural products. Due to their abundance, readily availability and versatile reactivity, alkenes and alkynes have been extensively applied in the organic synthesis.[1] The methodologies that allow their transformation into functional compounds are highly interesting and have received a great deal of attention from chemists. By introducing one or two functional groups into unsaturated carbon-carbon bonds via cleavage of *π*-bonds, molecular diversity and complexity can be effectively achieved from alkene and alkyne scaffolds in a single step.

As another abundant feedstock, carbon monoxide (CO) has been recognized as a potent C1 building block in organic synthesis, enabling straightforward transformations for the rapid synthesis of carbonyl compounds.[2] In particular, transition metal-catalyzed carbonylation reactions belong to the most important industrial processes in the field of homogeneous catalysis.[3] Since the original work of Reppe in the last century,[4] transition metal-catalyzed carbonylation of unsaturated bonds has been widely used as a powerful toolbox for the synthesis of numerous value-added fine chemicals. Compared to cobalt, nickel, rhodium, and other transition metal-based catalysts, palladium complexes often outperformed alternatives in carbonylation reactions due to their high reactivity and selectivity.[5] Hence, in this introduction, the state of the art process on palladium-catalyzed carbonylation of unsaturated carbon-carbon bonds with nucleophiles is present. In particular, three types of carbonylation reactions will be discussed: 1) Palladium-catalyzed hydroaminocarbonylation of alkynes to acrylamides (Scheme 1A); 2) Palladium-catalyzed fluoroalkylative carbonylation of alkynes with amines, which represents an efficient strategy for the synthesis of *β*-perfluoroalkyl-substituted carbonyl compounds (Scheme 1B). 3) Palladium-catalyzed regioselective carbonylation of alkenes with different nucleophiles, which is one of the most challenging and important targets in the carbonylation reactions (Scheme 1C).

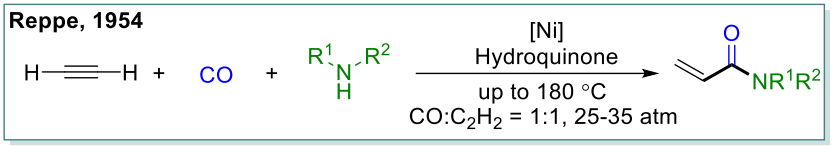


Scheme 1. Pd-catalyzed carbonylation of unsaturated carbon-carbon bonds in this introduction

1.1 Palladium-catalyzed hydroaminocarbonylation of alkynes

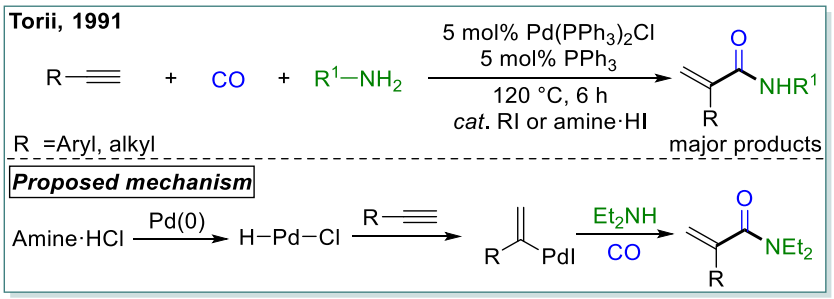
α, *β*-Unsaturated amides (acrylamides) are a valuable class of compounds and determining structural unit, which ubiquitously occur in natural products, pharmaceuticals, and functional materials.[6] Consequently, the development of the efficient synthesis of *α*, *β*-unsaturated amides has attracted much attention over several decades and numerous methods have been developed for the synthesis of these compounds. Nevertheless, the most common methods for the preparation of *α*,*β*-unsaturated amides are based on the substitution or nucleophilic condensation of carboxylic acid derivatives with amines involving the use of stoichiometric amounts of base or condensation reagents, which obviously lead to the formation of significant amount of waste and sometimes face chemoselectivity problems, too.[7] In this regard, the direct synthesis of *α*,*β*-unsaturated amides via transition metal-catalyzed aminocarbonylation of alkynes with amines and CO would be an ideal protocol.

Since the pioneering work of Reppe in the last century,[4] palladium-catalyzed hydroaminocarbonylation of alkynes has been widely used for decades, offering *α*, *β*-unsaturated amides with high atom economy and efficiency. Originally, Reppe and co-workers reported the nickel-catalyzed hydroaminocarbonylation of acetylene in 1954,[8] which proceeds under high pressure and temperature to give acrylamides (Scheme 2).



Scheme 2. Ni-catalyzed hydroaminocarbonylation of acetylene

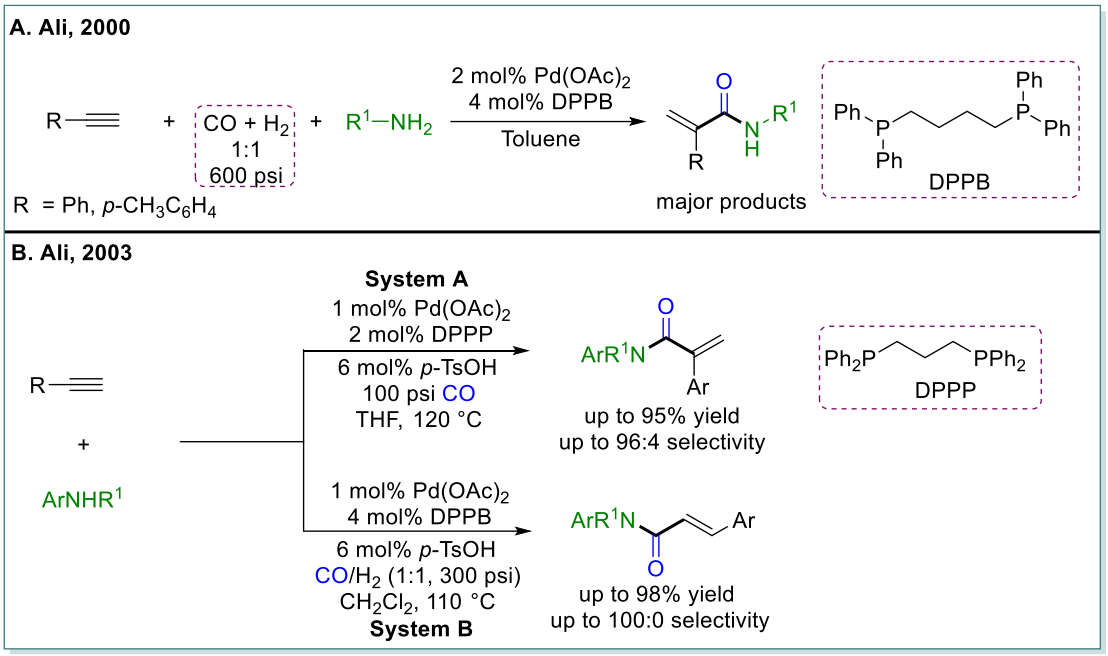
The first catalytic hydroaminocarbonylation of monosubstituted alkynes was developed by Torii and co-workers in 1991.[9] They used $Pd(PPh_3)_2Cl_2$ and PPh_3 as catalyst system in the presence of catalytic amount of organic iodides or amine hydroiodide and obtained the branched *α*,*β*-unsaturated amides as major products (Scheme 3). As a plausible reaction path initial formation of the corresponding alkylammonium iodide was proposed by either the carbonylation of iodobenzene or the reaction of alkyl iodide and diethylamine. Subsequent insertion of alkyne to a palladium hydride species available from Pd(0) and alkylammonium iodide results in the formation of a vinyl palladium complex, which gives the desired product after reacting with CO and amine.



Scheme 3. The first Pd-catalyzed hydroaminocarbonylation of monosubstituted alkynes

Interestingly, the regioselectivity in the hydroaminocarbonylation of alkynes is highly sensitive to the additive, solvent, ligand, and alkyne type. In 2000, Ali and co-workers described the palladium-catalyzed

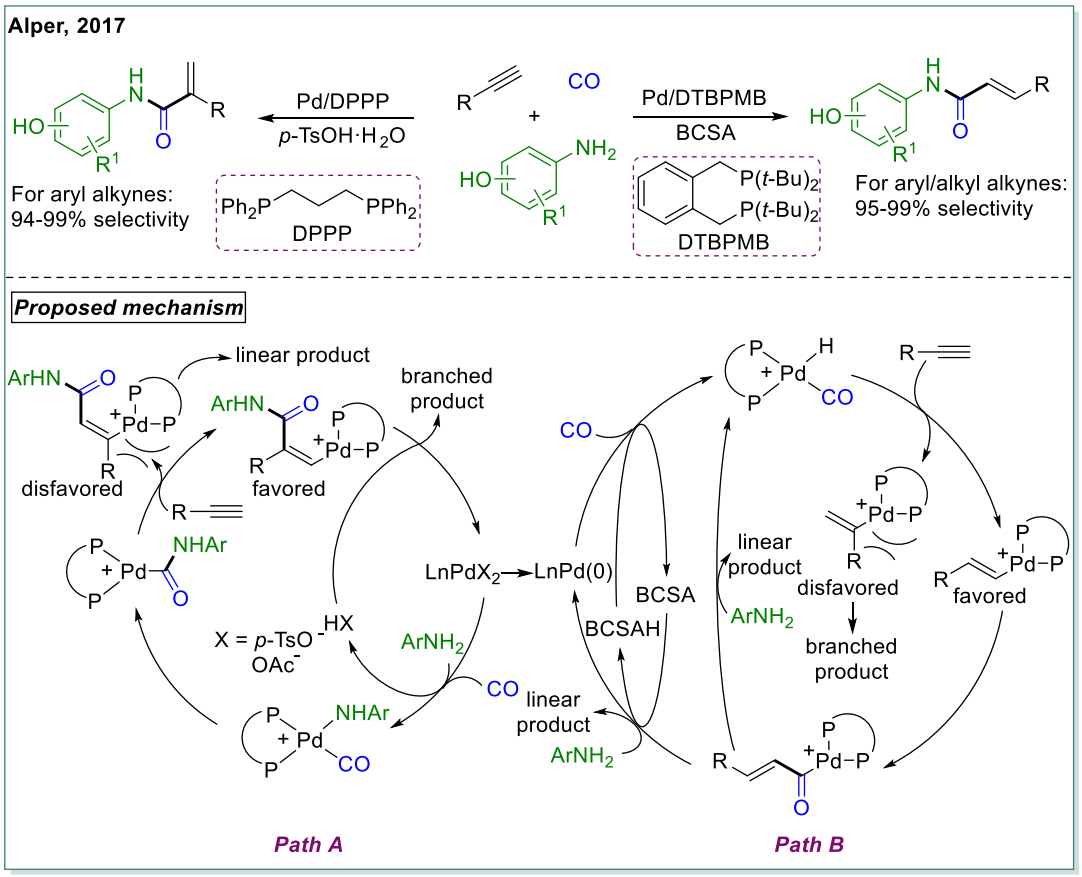
hydroaminocarbonylation of alkynes with amines, providing the branched *α*, *β*-unsaturated amides under syngas conditions (Scheme 4A).[10] The role of H_2 is thought to stabilize the palladium hydride complex. Subsequently, the same group disclosed a palladium-catalyzed regiodivergent hydroamniocarbonylation of terminal alkynes with amines, in which the reversed regioselectivity is successfully achieved employing either the catalytic system A or the system B (Scheme 4B).[11] The system A provided an efficient and simple protocol to produce the branched *α*, *β*-unsaturated amides. The other catalytic system B offered a new route for the synthesis of linear *α*, *β*-unsaturated amides, which were difficult to generate by previous methods.



Scheme 4. Pd-catalyzed regioselective hydroaminocarbonylation of terminal alkynes

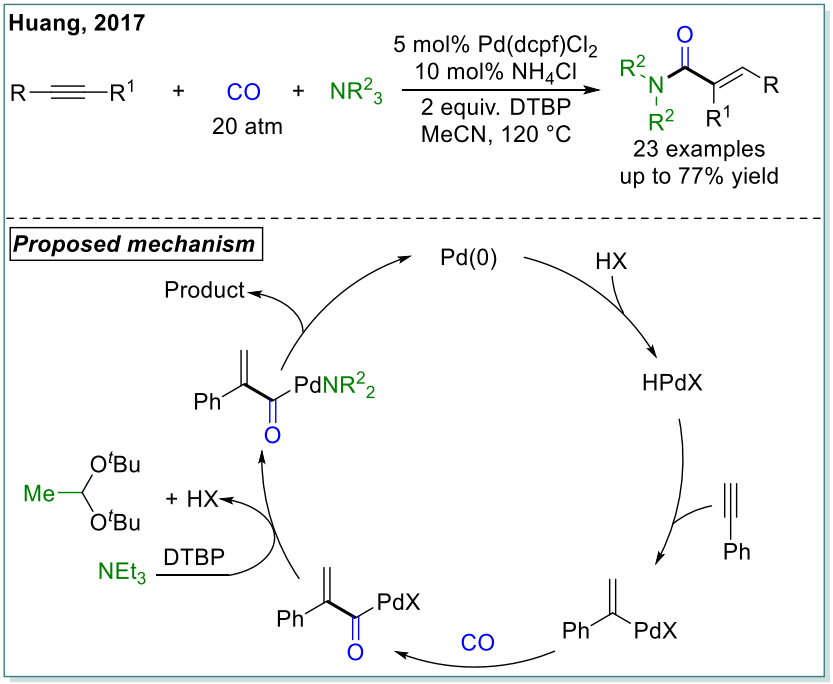
In 2017, Alper and Sha carried out a systematic study of the palladium-catalyzed hydroaminocarbonylation of terminal alkynes with aminophenols, which enabled highly chemo- and regioselective access to *α*, *β*-unsaturated amides (Scheme 5).[12] Based on different ligands and additives, either the linear or branched *α*, *β*-unsaturated amides could be selectively obtained in good to excellent yields. The combination of BCSA (5-chlorosalicylic acid and boronic acid) and 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (DTBPMB) as ligand resulted in linear *α*, *β*-unsaturated amides. On the contrary, the branched isomers could be produced using *p*-TsOH·H_2O as additive and 1,3-bis(diphenylphosphino)propane (DPPP) as ligand. According to mechanistic studies, the authors proposed two pathways to explain the origin of regioselectivity. In the mechanism A (Path A), arylamino palladium species is formed by reacting with arylamine and CO. Followed by coordination and insertion of CO, the arylamino palladium species is converted to arylcarbamoyl palladium species, which reacts with alkyne to generate the favored vinyl palladium species. The resulting palladium species subsequently undergoes protonation with *p*-TsOH·H_2O, hydroxyl or amnio groups to give the branched products. In the other proposed mechanism (path B), the Pd(II) precursor is first reduced in situ to Pd(0) species, which reacts with acid (BCSA) to produce the palladium hydride species. Next, alkyne coordination to palladium hydride species and insertion of alkyne into Pd−H bond furnishes the favored vinyl palladium species, giving the corresponding product via CO insertion and amination of

aminophenol. In both mechanisms *cis*-addition (of Pd and CONHAr or of Pd and H) occurs during the insertion step to offer corresponding isomers.



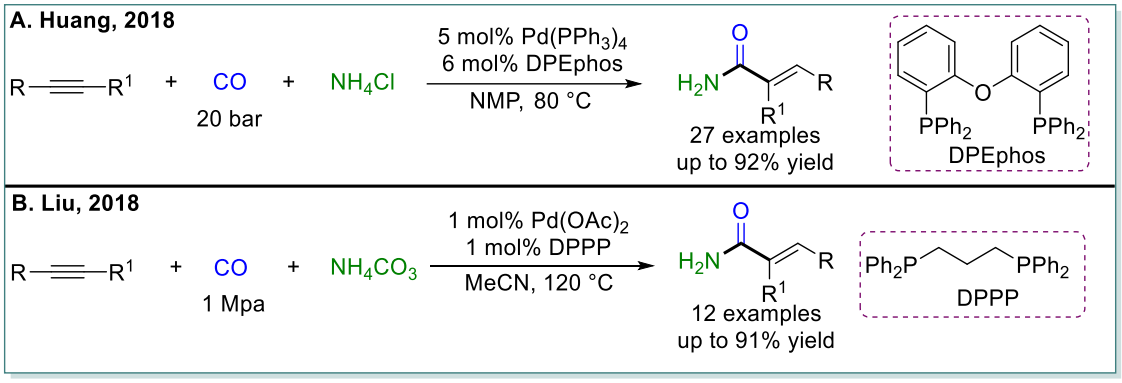
Scheme 5. Ligand- and additive-controlled chemo- and regioselective Pd-catalyzed hydroaminocarbonylation of terminal alkynes with aminophenols

Shortly after, Huang and Gao reported an efficient palladium-catalyzed hydroaminocarbonylation of alkynes with tertiary amines in the presence of DTBP (Scheme 6).[13] A series of *α*, *β*-unsaturated amides were obtained using tertiary amines as amine and proton sources. Apart from terminal alkynes, symmetrical internal alkynes also worked well. And unsymmetrical internal alkyne gave the corresponding product in moderate yield with 4:1 regioselectivity. Based on the basic mechanism studies and previous references, a plausible mechanism for this transformation was proposed by the authors. Initially, Pd(0) and NH_4Cl undergo oxidative addition to afford the palladium hydride species. Alkyne coordination to palladium hydride species is then followed by insertion reaction to furnish the alkenyl palladium species, which undergoes insertion reaction with CO. The resulting acyl palladium intermediate, with cleavage of Et_3N in the presence of DTBP, goes through anion exchange and reductive elimination to provide corresponding product and regenerate the Pd(0) species.



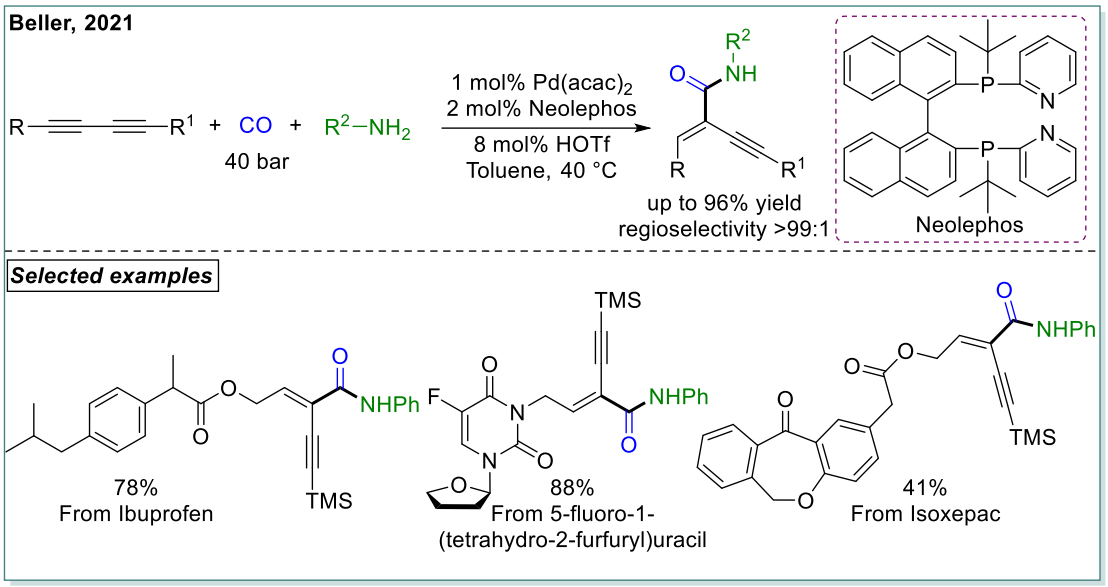
Scheme 6. Pd-catalyzed hydroaminocarbonylation of alkynes with tertiary amines

In 2017, Huang and co-workers exploited ammonium chloride as an amine source to deliver *α*, *β*-unsaturated amides (Scheme 7A).[14] This reaction is compatible with various alkynes and proceeds smoothly on the gram scale with excellent selectivities using 0.05 mol% of catalyst. In the same year, Liu and co-workers described a similar work by applying ammonium bicarbonate as the ammonia surrogate (Scheme 7B).[15] In both cases solid ammonium sources were used instead of stinky gaseous NH_3, exhibiting facile and clean manipulation of these methods.



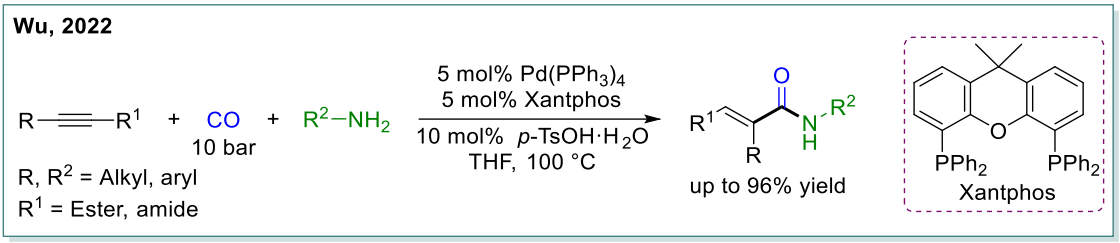
Scheme 7. Pd-catalyzed hydroaminocarbonylation of alkynes with solid ammonium sources

Two years later, our group disclosed a palladium-catalyzed hydroamniocarbonylation of (un)symmetrical 1,3-diynes with advanced Neolephos as ligand, giving a variety of *α*-alkynyl-*α*, *β*-unsaturated amides in good to excellent yields with excellent regio-, chemo-, and stereoselectivities (Scheme 8).[16] The general applicability of this methodology was demonstrated by the versatile modifications of structurally complex molecules and drugs. On a basis of some mechanistic studies and DFT calculations, the intrinsic substituents of substrates and the ligand play the key role in determining the selectivity.



Scheme 8. Pd-catalyzed hydroaminocarbonylation of diynes with amines

More recently, Wu and co-workers described a palladium-catalyzed hydroaminocarbonylation of unsymmetrical internal alkynes to synthesize various *α*, *β*-unsaturated amides (Scheme 9).[17] This method features good regio- and (*E*)-stereoselectivity, broad substrate scope, and good functional group tolerance.



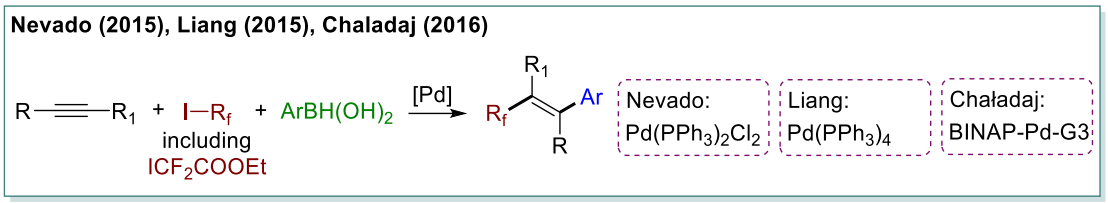
Scheme 9. Pd-catalyzed hydroaminocarbonylation of internal alkynes with amines

1.2 Palladium-catalyzed perfluoroalkylative carbonylation of alkynes

With unique physical and chemical properties, organofluorine chemicals are of importance in many areas such as agrochemicals, pharmaceuticals, and materials,[18] thus attracting attention to the incorporation of these fluorine-containing motifs into the organic scaffolds. As a result, methods to introduce a fluorinated building block into bioactive molecules are plausible ways to modify their biological properties such as reactivity, lipophilicity, and metabolic stability.[19]

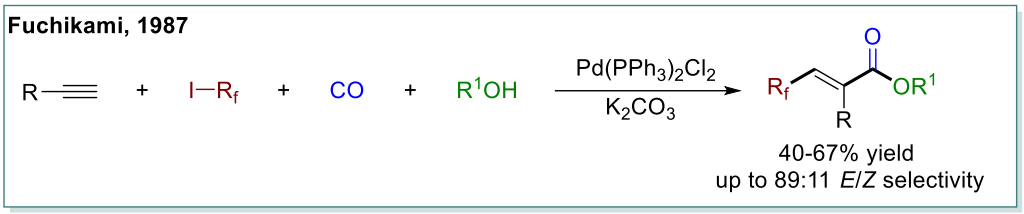
Already in the 1950s, Haszeldine reported the iodoperfluoroalkylation of alkynes via a radical route.[20] Since then, several methods have been developed for the iodoperfluoroalkylation of alkynes through different radical initiators or transition metal catalysts.[21] Among these methods, Ishihara and co-workers disclosed this transformation with palladium as catalyst.[21a] Perfluoroalkyl-substituted vinyl iodides, as corresponding products of a two-component reaction, are useful building blocks. However, such products should be further functionalized by cross-coupling reactions, which make this process more complicated.[22] In this regard, palladium-catalyzed carboperfluoroalkylations of alkynes with perfluoroalkyl iodides (or iodofluoroacetate) and arylboronic acids, were successively reported by

Nevado, Liang, and Chaładaj groups (Scheme 10).[23] This three-component reaction is more straightforward than the two-component reaction to construct perfluoroalkylated trisubstituted alkenes in one step. Furthermore, various *β*-perfluoroalkyl acryloyls were successfully obtained by palladium-catalyzed four-component carbonylation of alkynes, which turns out to be a powerful, step-economic route to synthesize fluorine-containing products directly from readily accessible alkynes and perfluoroalkyl iodides.



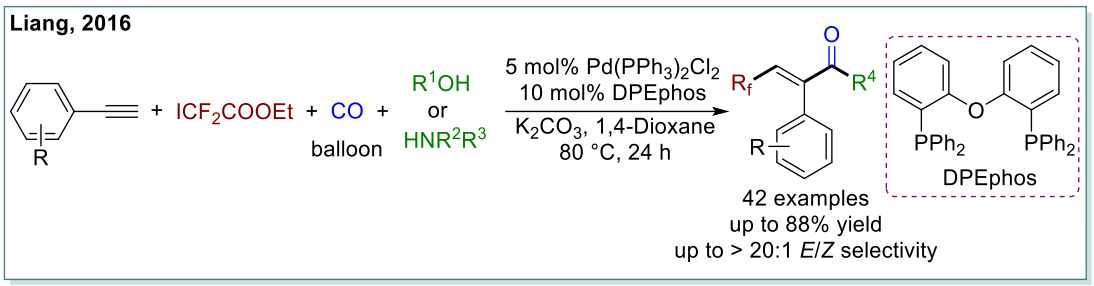
Scheme 10. Pd-catalyzed carboperfluoroalkylation of alkynes with perfluoroalkyl iodides and aryl boronic acids

In 1987, Fuchikami and co-workers described the first palladium-catalyzed four-component carbonylation of terminal alkynes with CO and perfluoroalkyl iodides in alcohols, providing a series of *β*-perfluoroalkyl-substituted alkenoates (Scheme 11).[24] Here, the coordination of CO was thought to prevent *β*-perfluoroalkyl vinylpalladium species from undergoing the reductive elimination with the iodide.



Scheme 11. The first Pd-catalyzed four-component carbonylation of alkynes with alcohols

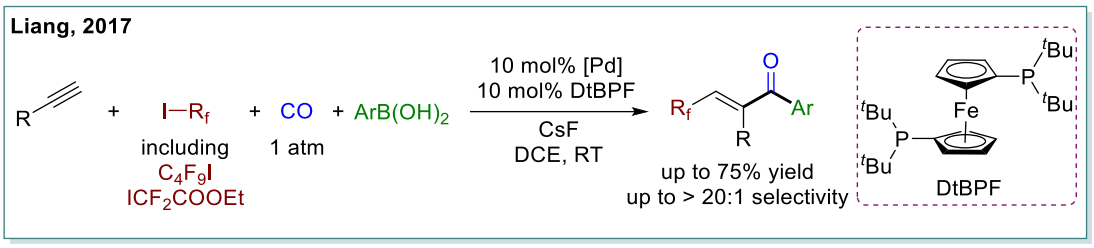
In 2016, Liang and co-workers disclosed a novel, four-component synthetic strategy with alcohol or amines as nucleophiles, affording an array of *β*-difluoroalkyl unsaturated esters/amides with high regioselectivities (Scheme 12).[25] In a single step, two new C-C bonds and one C-O(N) bond are simultaneously forged through this method. The synthetic methodology is characterized by high regioselectivity and a broad substrate scope of alkynes and nucleophiles. The difluoroalkyl radical pathway was suggested to be involved in this process according to preliminary mechanistic studies.



Scheme 12. Pd-catalyzed four-component carbonylation of alkynes with alcohols or amines

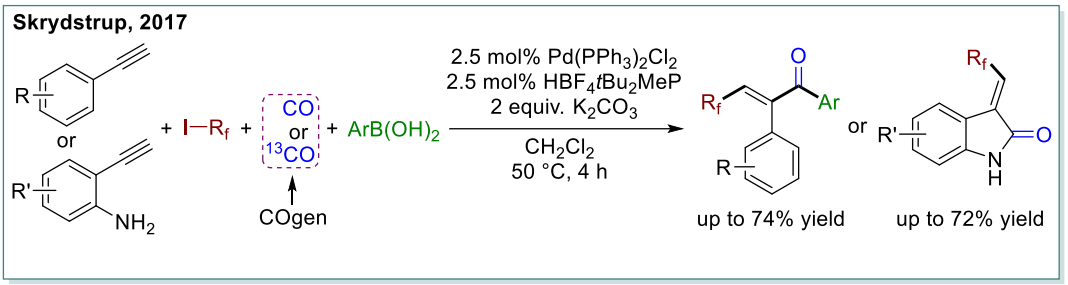
Liang and co-workers reported a palladium-catalyzed carbonylative difluoroalkylation/perfluoroalkylation of alkynes with arylboronic acids in 2017.[26] Using DtBPF as ligand, various alkynes were successfully converted to *β*-difluoroalkyl/perfluoroalkyl enones with excellent *E*-selectivities (Scheme 13). It is worth noting that this transformation readily occurs with 1 atm CO at room temperature.

Interestingly, the reaction rate could be decreased in the absence of CsF, whereas the reaction could be completed in a short time and gave a much higher yield with CsF, implying that CsF plays an important role in increasing the reaction rate, not only as an additive, but also as a base.



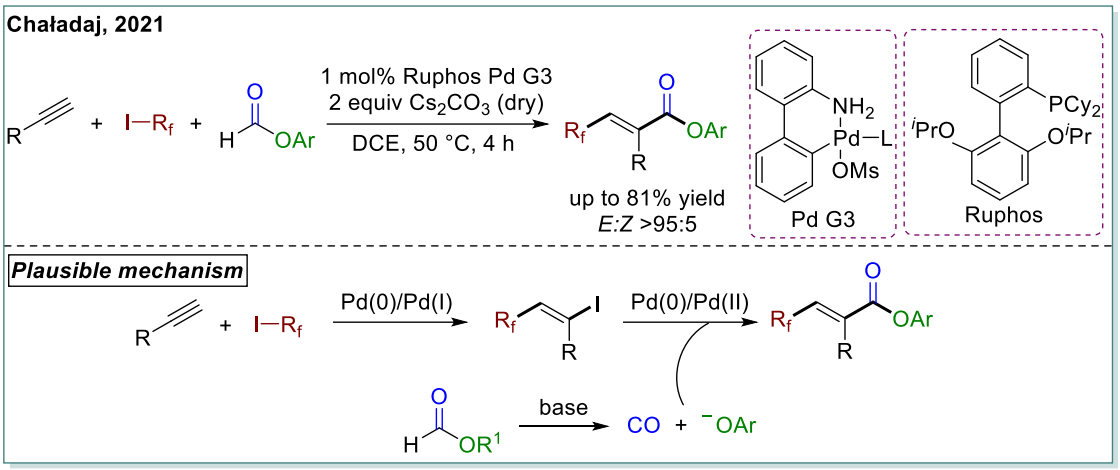
Scheme 13. Pd-catalyzed four-component carbonylation of alkynes with arylboronic acids

In the same year, Skrydstrup and Yin investigated a related study, in which *β*-perfluoroalkyl-substituted enones were prepared by palladium-catalyzed four-component carbonylation of terminal alkynes together with arylboronic acids and perfluoroalkyl iodides in the presence of CO generated *ex situ* (Scheme 14).[27] This process also allowed intramolecular aminocarbonylation to take place, delivering the indolin-2-one framework from 2-aminophenylalkynes. In particular, the critical advantage of two-chamber technology is to synthesize compounds with ^{13}C-isotope labeling.



Scheme 14. Pd-catalyzed four-component carbonylation of alkynes with COgen

The high toxicity of carbon monoxide is one of the constraints that make these processes not easy to handle. In this respect, the development of new carbonylation reactions without carbon monoxide becomes an interesting research topic in organic synthesis, so the multicomponent carbonylation with CO surrogates has been explored at the same time. Recently, Chaładaj and co-workers disclosed a palladium-catalyzed perfluoroalkylative three-component carbonylation of alkynes with formates as CO and nucleophile sources, directly producing a wide range of perfluoroalkyl-substituted *α*, *β*-unsaturated esters with excellent regio- and stereoselectivities (*E*:*Z* >95:5).[28] Detailed control experiments and DFT studies supported the proposed mechanism. This tandem process is thought to be made of two independent palladium-mediated reactions: radical iodoperfluoroalkylation and aryloxycarbonylation, which include processes of Pd(0)/Pd(I) and Pd(0)/Pd(II), respectively (Scheme 15).



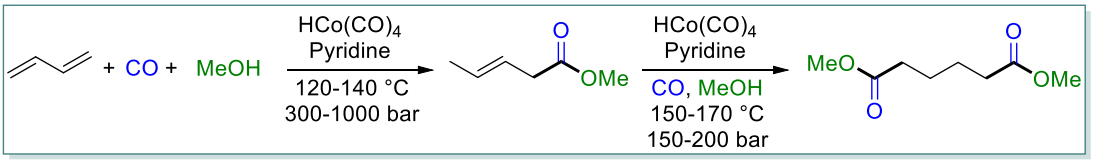
Scheme 15. Pd-catalyzed perfluoroalkylative carbonylation of alkynes with formates as CO surrogate

1.3 Palladium-catalyzed regioselective carbonylation of alkenes with various nucleophiles

As an abundant chemical feedstock, alkenes have been extensively applied in organic synthesis. Recent years have seen an increase in palladium-catalyzed carbonylation of alkenes with different nucleophiles, providing valuable carboxylic acid derivatives in a facile and effective manner.[29] Meanwhile, such carbonylation reactions always offer two regioisomers including linear and branched isomers, which are of great interest for various applications. To this end, the development of regioselective transformations is one of the key goals in this field. Indeed, the complementary methodologies have been established for the hydroformylation, alkoxycarbonylation, hydrocarboxylation, aminocarbonylation and thiocarbonylation of alkenes, which allow the regioselective formation of two regiodivergent products.[30] In general, the regioselectivity of these processes is mainly controlled by applying different types of ligands, metal catalysts, solvents, additives, and so on. Most of the regioselective processes were achieved with palladium as catalyst, thus the related palladium-catalyzed carbonylation reactions are presented here.

1.3.1 Palladium-catalyzed regioselective carbonylation of alkenes with *O*-nucleophiles.

Palladium-catalyzed carbonylation of alkenes with *O*-nucleophiles is a significant method for the synthesis of appealing carboxylic esters and acids. When using alcohols as substrates, the reactions are usually referred to hydroalkoxycarbonylation. In contrast, hydroxycarbonylations are always carried out with water as the nucleophile. These transformations have attracted considerable interest over several decades, applying various transition metals as catalysts such as Pd, Co, Pt, Ni, and Rh, etc.[31] For instance, BASF developed a cobalt-catalyzed two-step carbonylation of 1,3-butadiene and hydrolysis to give adipic acid with an overall selectivity of about 70% through a three-stage process (Scheme 16).[32]

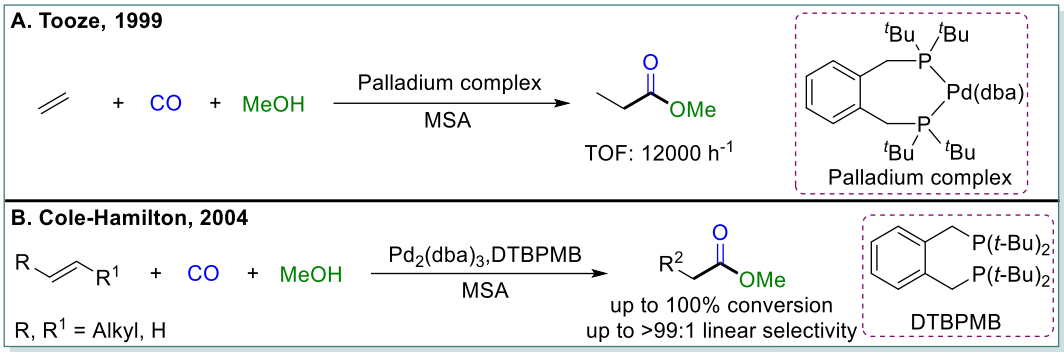


Scheme 16. Co-catalyzed two-step carbonylation of 1,3-butadiene to dimethyl adipate

In the late 1980s, Alper and co-workers developed palladium-catalyzed regioselective hydroalkoxycarbonylation and hydroxycarbonylation of alkenes.[33] In 1989, Alper group disclosed the regiodivergent hydroalkoxycarbonylation of alkenes with formate esters towards linear carboxylic acid esters using palladium(0) complexes with 1,4-bis(diphenylphosphino)butane (DPPB).[33a] Subsequently, the same group reported several hydroxycarbonylation reactions to synthesize linear carboxylic acids with a similar catalyst system (palladium catalyst and DPPB ligand) (Scheme 17).[33b, c]

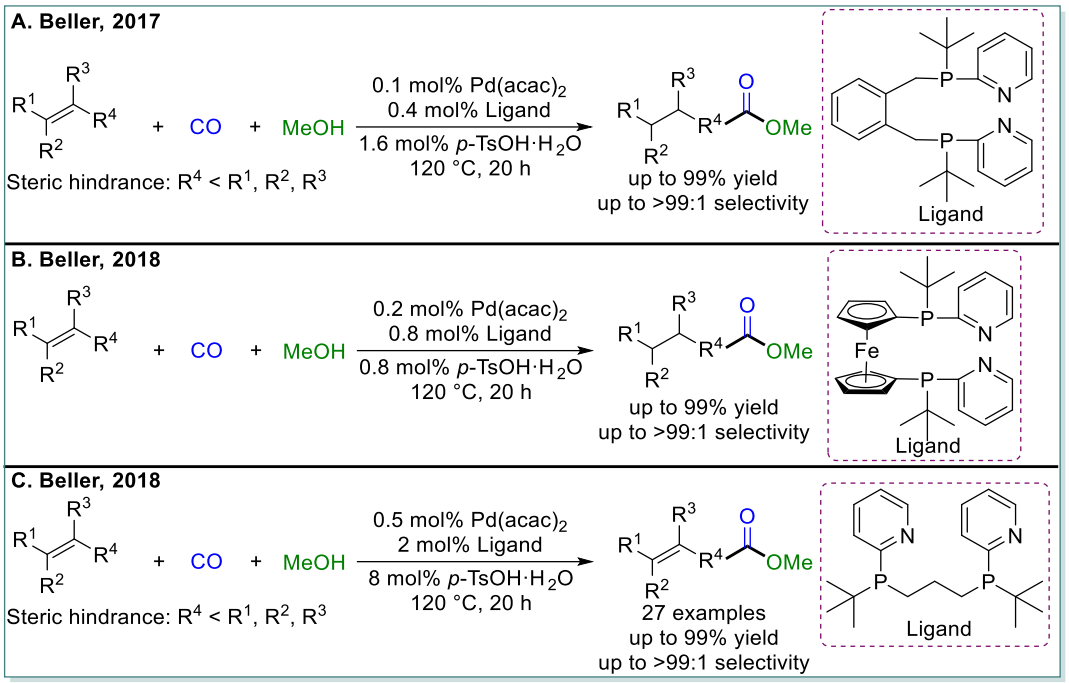
Scheme 17. Pd-catalyzed regioselective hydroalkoxycarbonylation and hydroxycarbonylation of alkenes

In 1999, Tooze and co-workers reported a highly efficient method to produce methyl propanoate by methoxycarbonylation of ethylene in the presence of a palladium complex modified with the bidentate phosphine ligand bis-(di-*tert*-butylphosphinomethyl) benzene (DTBPMB), and the turnover frequency of this reaction can reach to 12000 h^{-1} (Scheme 18A).[34] Five years later, Cole-Hamilton and co-workers described a highly selective access to linear esters from terminal and internal alkenes using palladium complex and DTBPMB. This reaction worked well via a hydride mechanism, giving linear esters with up to 99.9% selectivity (Scheme 18B).[35]



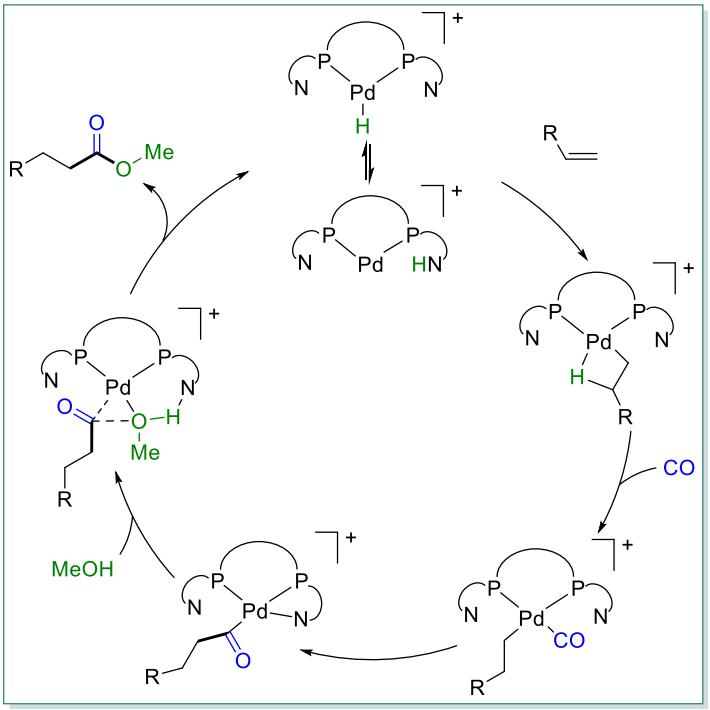
Scheme 18. Pd-catalyzed methoxycarbonylation of alkenes in the presence of DTBPMB

Inspired by the good performances of DTBPMB and 2-pyridinyl diphenylphosphine (2-PyPPh$_2$) in the carbonylation reactions,[36] our group investigated the specific phosphine ligands with a built-in-base function for palladium-catalyzed alkoxycarbonylation and hydroxycarbonylation of alkenes to give corresponding linear products. In 2017, a highly active and efficient catalyst system for methoxycarbonylation of alkenes was disclosed by our group.[37] With a palladium catalyst in the presence of 1,2-bis((*tert*-butyl(pyridin-2-yl)phosphino)methyl)benzene (py^{t}bpx), a variety of linear esters were obtained with high activity and selectivity even from tetra- and tri-substituted alkenes (Scheme 19A). Our group later developed a novel ferrocenyl phosphine as a ligand backbone for palladium-catalyzed methoxycarbonylation of alkenes, even allowing transformation of the less reactive push–pull alkene to react well (Scheme 19B).[38] Following the built-in-base concept, we described a similar ligand 1,3-bis(*tert*-butyl(pyridin-2-yl)phosphino)propane, which also showed the good reactivity and selectivity in the methoxycarbonylation of alkenes (Scheme 19C).[39]



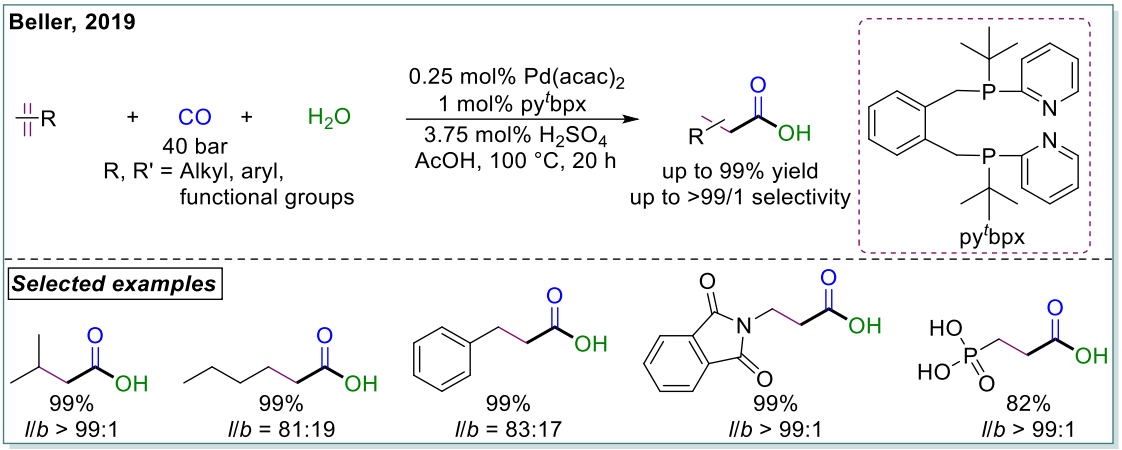
Scheme 19. Pd-catalyzed methoxycarbonylation of alkenes in the presence of built-in-base ligands

On the basis of the experiments and DFT analysis, our group proposed a plausible mechanism for these transformations (Scheme 20).[38] Initially, the palladium complex undergoes protonation, and the proton is in equilibrium between the palladium center and the nitrogen atom of the pyridinyl on the phosphorus ligand. The alkene then coordinates to the above palladium complex, and insertion of alkene furnishes the corresponding alkyl palladium complex, which could be converted to acyl palladium species through CO coordination and insertion. Finally, *N*-assisted aminolysis leads to desired product and regenerates the active catalyst.



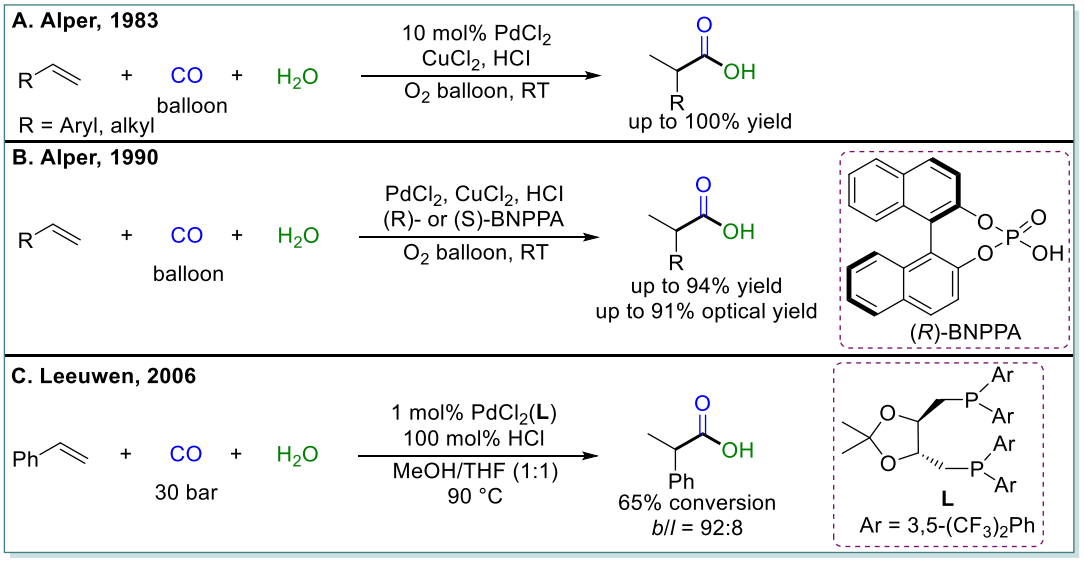
Scheme 20. Proposed mechanism for Pd-catalyzed methoxycarbonylation of alkenes in the presence of built-in-base ligands

In a similar vein, our group subsequently evaluated palladium-catalyzed hydroxycarbonylation of alkenes, regardless of the degree of substitution, offering various carboxylic acids in the presence of our developed ligand py^{t}bpx (Scheme 21).[40] In this case, the stability of the catalyst system is outstanding with >25 recycling runs without measurable loss of activity, the synthetic usability is showcased in the synthesis of the industrially relevant fatty acids.



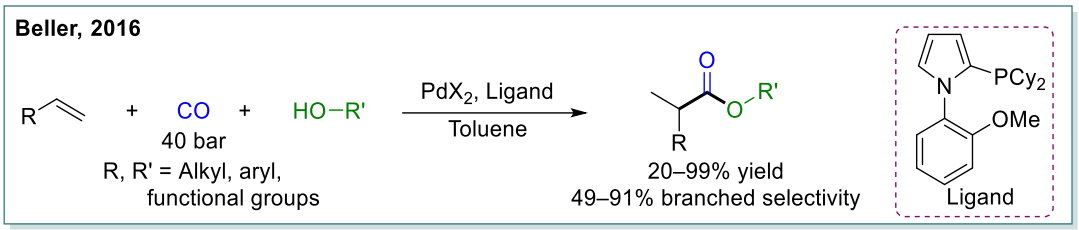
Scheme 21. Pd-catalyzed hydroxycarbonylation of alkenes to linear carboxylic acids in the presence of py^{t}bpx

In contrast to the highly linear (*anti*-Markovnikov)-selective hydroalkoxycarbonylation and hydroxycarbonylation of alkenes, the development of synthetic methods for branched products has occurred at a rather slower pace. In 1983, Alper and co-workers reported an exceedingly mild protocol for achieving the regioselective hydroxycarbonylation of a variety of alkenes (Scheme 22A).[41] With palladium and copper chlorides in the absence of any ligand, the branched products were obtained in moderate to excellent yields. Later, the same group realized asymmetric palladium-catalyzed hydroxycarbonylation of alkenes, enabling the synthesis of the branched and chiral acids in the presence of (*R*)-(-)- or (*S*)-(+)-1,1'-binaphthy-2,2'-diyl hydrogen phosphate (Scheme 22B).[42] In 2006, Van Leeuwen and co-workers developed the hydroxycarbonylation of styrene to deliver branched acid in the presence of a DIOP-type ligand (Scheme 22C). [43]



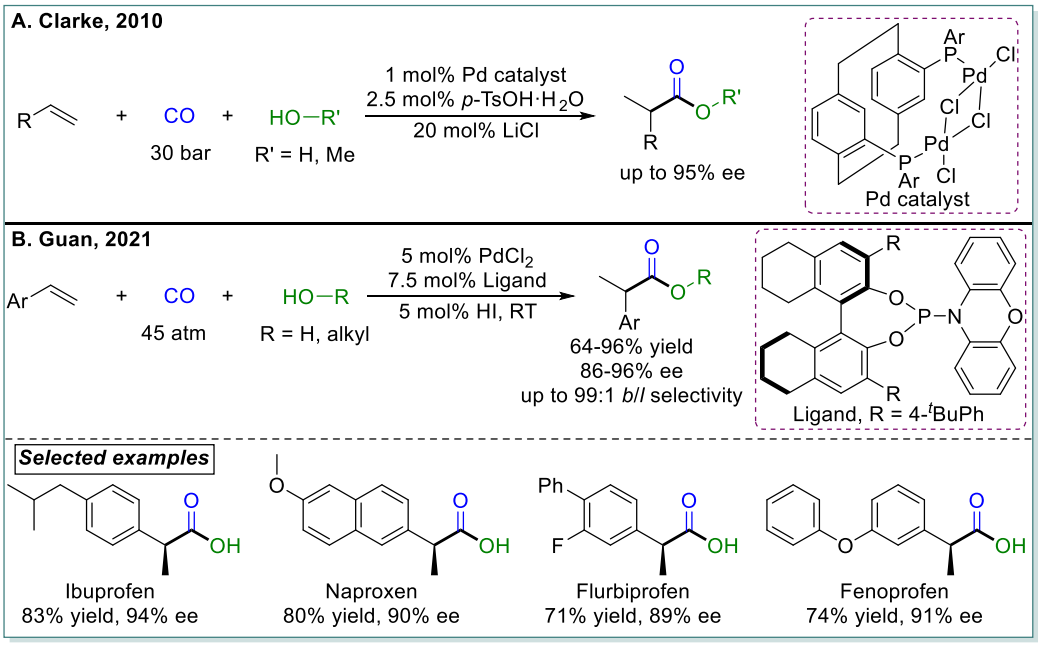
Scheme 22. Pd-catalyzed Markovnikov hydroxycarbonylation of alkenes

In 2016, our group presented a general method for the Markovnikov alkoxycarbonylation of aliphatic olefins (Scheme 23). Applying the specific catalyst system consisting of PdX_2/*N*-phenylpyrrole phosphine (X, halide), this alkoxycarbonylation of alkenes gave a wide range of branched esters with high selectivities (up to 91%).[44]



Scheme 23. Pd-catalyzed Markovnikov hydroalkoxycarbonylation of alkenes in the presence of py^{t}bpx

Further advances in the hydroxycarbonylation and alkoxycarbonylation of alkenes have been demonstrated in the development of enantioselective transformations. In 2010, Clarke and co-workers reported the regio- and enantioselective carbonylation of styrene in the presence of a dipalladium complex treated with the planar-chiral phosphine, delivering the corresponding branched products with high levels of enantioselectivity (Scheme 24A).[45] In 2021, these reactions were expanded by Guan and co-workers, who disclosed a palladium-catalyzed highly enantioselective Markovnikov hydroxycarbonylation and hydroalkoxycarbonylation of vinyl arenes for the synthesis of various chiral acids and esters (Scheme 24B). This novel methodology was successfully applied to synthesize non-steroidal anti-inflammatory drugs such as ibuprofen, naproxen, flurbiprofen, and fenoprofen.[46]



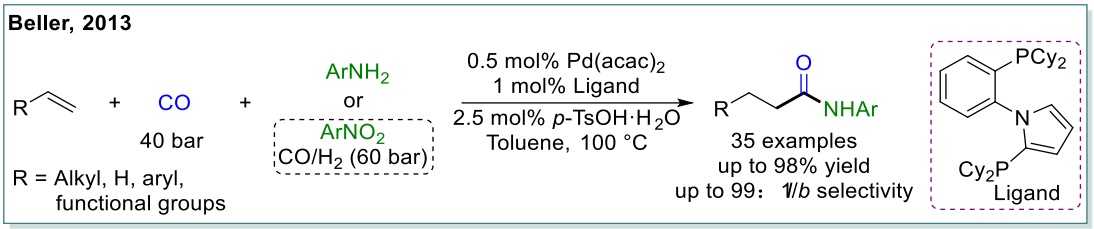
Scheme 24. Pd-catalyzed asymmetrical hydroxycarbonylation and alkoxycarbonylation of alkenes

1.3.2 Palladium-catalyzed regioselective carbonylation of alkenes with *N*-nucleophiles.

The amide group is one of the most fundamental building blocks prevalent in pharmaceuticals, agrochemicals, and materials.[47] Hence, the development of efficient construction of amides, especially with high regioselectivity, is of growing significance in organic synthesis. Not surprisingly, palladium-

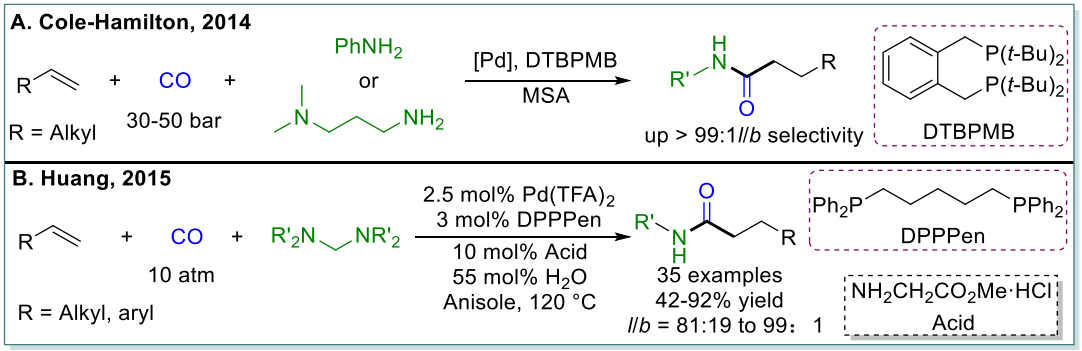
catalyzed regioselective hydroaminocarbonylation has emerged as a popular protocol for the synthesis of amides because of its high step and atom economy.

In 1990s, Alper and co-workers presented a series of palladium-catalyzed intramolecular hydroaminocarbonylation reactions towards six-membered lactams with high selectivity.[48] In 2013, our group described an efficient strategy for the preparation of linear amides via palladium-catalyzed hydroaminocarbonylation of alkenes (Scheme 25).[49] Interestingly, nitroarenes could be directly transformed to the corresponding amides with molecular hydrogen. In this work, using (hetero)aromatic amines, both short- and long-chain terminal olefins provided corresponding amides in good yields with excellent regioselectivities. On the other hand, styrene didn't give a good linear regioselectivity because of the stabilization of the benzylic palladium complex generated during the process. When aliphatic amines such as butyl- or cyclohexylamine were used as substrates, no product was observed due to no formation of the active palladium hydride species in the presence of the more basic aliphatic amines.



Scheme 25. Pd-catalyzed hydroaminocarbonylation of alkenes with arylamines to linear amides

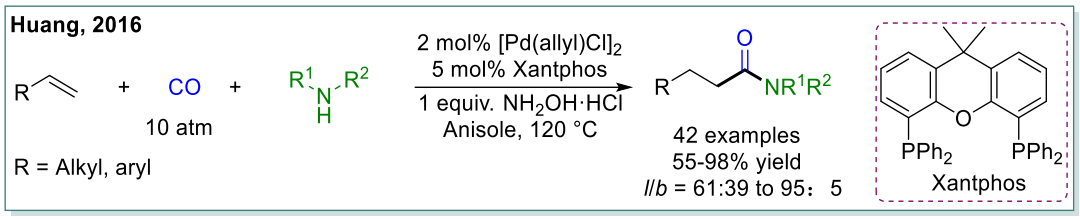
One year later, Cole-Hamilton and co-workers also developed a catalyst system (Pd/DTBPMB) to catalyze hydroaminocarbonylation of alkenes (Scheme 26A), offering linear amides from the long-chain olefins and unsaturated esters with limited amines (aniline and 3-dimethylamino-1-propylamine).[50] To overcome the basicity barrier imparted by aliphatic amines, a novel palladium-catalyzed system for the hydroaminocarbonylation of alkenes with aminals was reported by Huang and co-workers in 2015 (Scheme 26B). The reaction proceeded smoothly and afforded a variety of *N*-alkyl linear amides in moderate to good yields with high regioselectivities. According to authors' hypothesis, *N*-alkyl amine sources were formed from aminals that underwent C-N bond cleavage and hydrolysis.[51]



Scheme 26. Pd-catalyzed hydroaminocarbonylation of alkenes towards linear amides

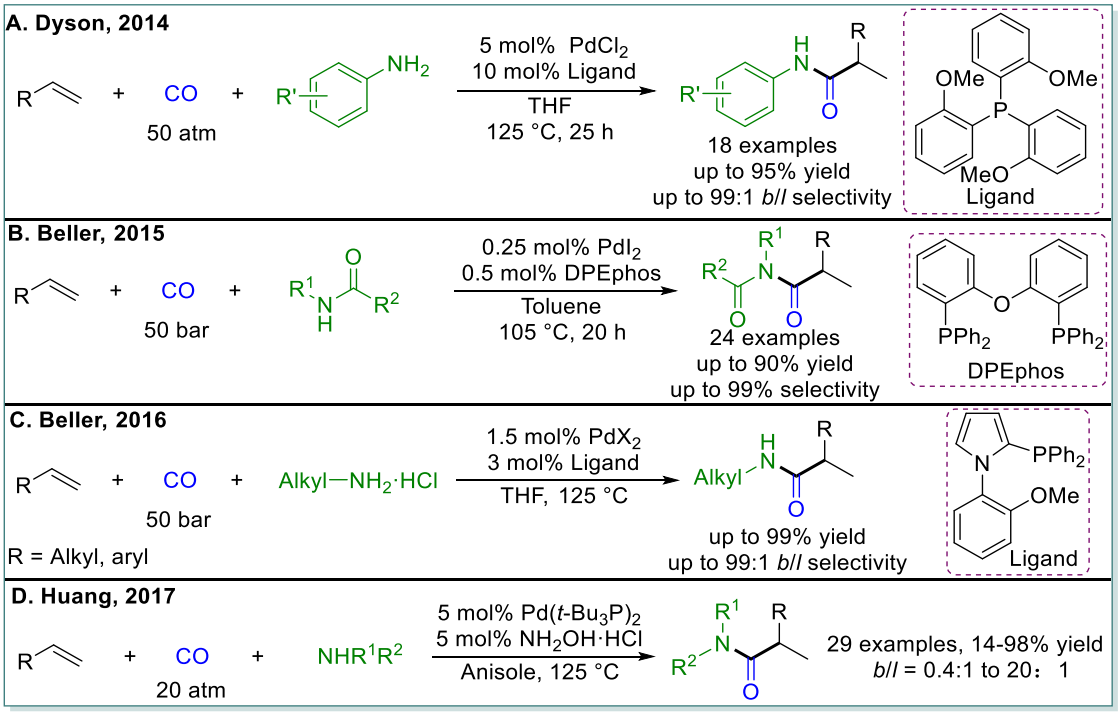
In a subsequent study, Huang and co-workers significantly extended the scope of this process using the $[Pd(allyl)Cl]_2$ and Xantphos. Both aliphatic and aromatic amines were converted to linear amides with good selectivities under a CO atmosphere (Scheme 27).[52] Meanwhile, $NH_2OH·HCl$ was found to be an

effective basicity mask to overcome the basicity barrier imparted by aliphatic amines and promote the desired reaction.



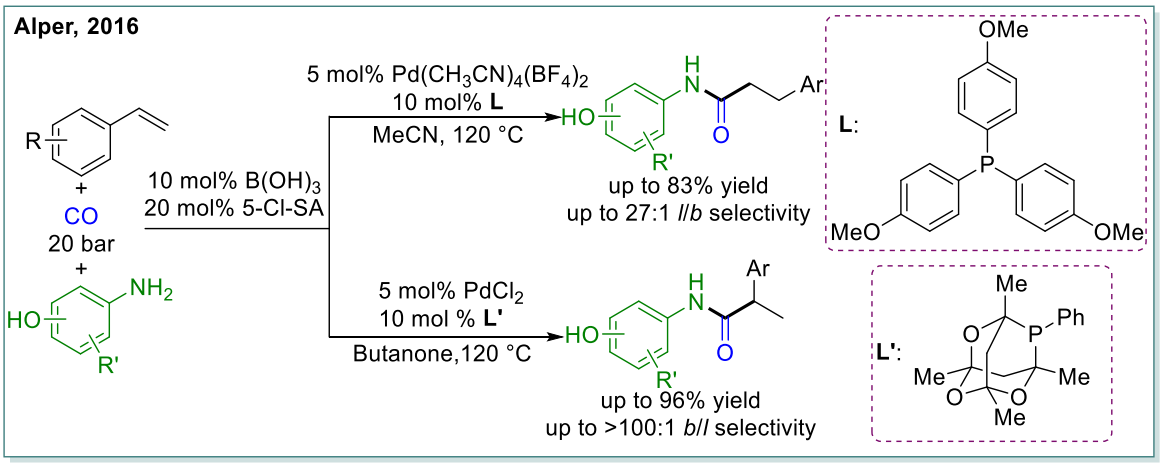
Scheme 27. Pd-catalyzed hydroaminocarbonylation of alkenes with alkyl- and arylamines to linear amides

In 2014, a straightforward synthesis of branched *N*-aryl amides via the palladium-catalyzed hydroaminocarbonylation of alkenes with CO and amines was described by Dyson and co-workers (Scheme 28A).[53] A variety of aromatic amines were efficiently transformed to branched amides in good yields and usually with high regioselectivities. Notably, the reaction performed well with a commercially available bulky monophosphine ligand in the absence of acid, base or any other promoters. Later, a direct and efficient strategy for the preparation of imides from simple alkenes and amides was developed by our group (Scheme 28B).[54] Employing PdI_2 as precatalyst and DPEphos as ligand, a wide range of imides were prepared in good yields with high branched selectivities. In 2016, our group reported palladium-catalyzed hydroaminocarbonylation of alkenes with aliphatic amines (Scheme 28C).[55] Using PdX_2 (X = halide) as precatalyst in the presence of 2-phosphino-substituted pyrrole ligand, various branched amides were generally obtained in good yields (up to 99 %) with high regioselectivities (up to 99:1). In analog to our work above, Huang and co-workers used Pd(*t*-$Bu_3P)_2$ as an efficient ligand for the hydroaminocarbonylation of aromatic alkenes. In the presence of hydroxylamine hydrochloride, both aliphatic and aromatic amines gave the branched amides with desired regioselectivities (Scheme 28D).[56]



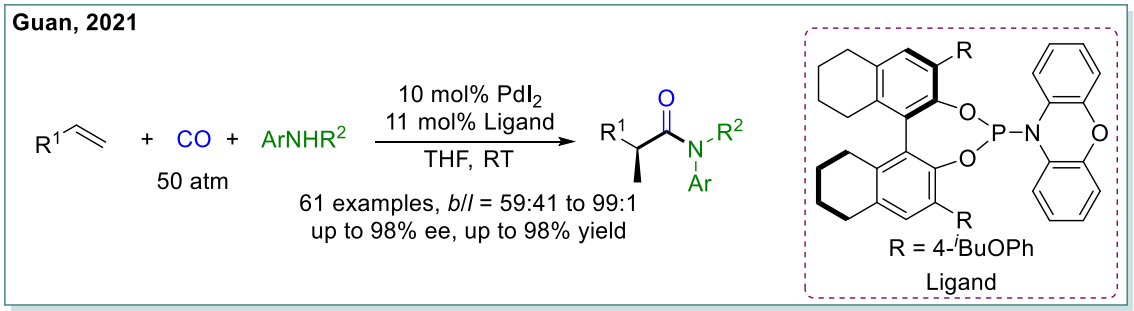
Scheme 28. Pd-catalyzed hydroaminocarbonylation of alkenes to branched amides (or imides)

Interestingly, Alper and co-workers developed ligand-controlled regiodivergent hydroaminocarbonylation of styrenes with aminophenols in the presence of same additives, offering either linear or branched amides depending on the choice of ligand (Scheme 29).[57] In this regard, the reaction with tris(4-methoxyphenyl)phosphine afforded linear products in good yields (up to 83%) with high regioselectivities (up to 27:1). In contrast, linear amides were obtained in high yields (up to 96%) with high selectivities (up to >100:1) applying 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane. Preliminary mechanistic studies showed that ligands appear to be a critical factor in achieving high regioselectivity in this process.



Scheme 29. Pd-catalyzed regiodivergent hydroaminocarbonylation of styrenes by controlling ligands

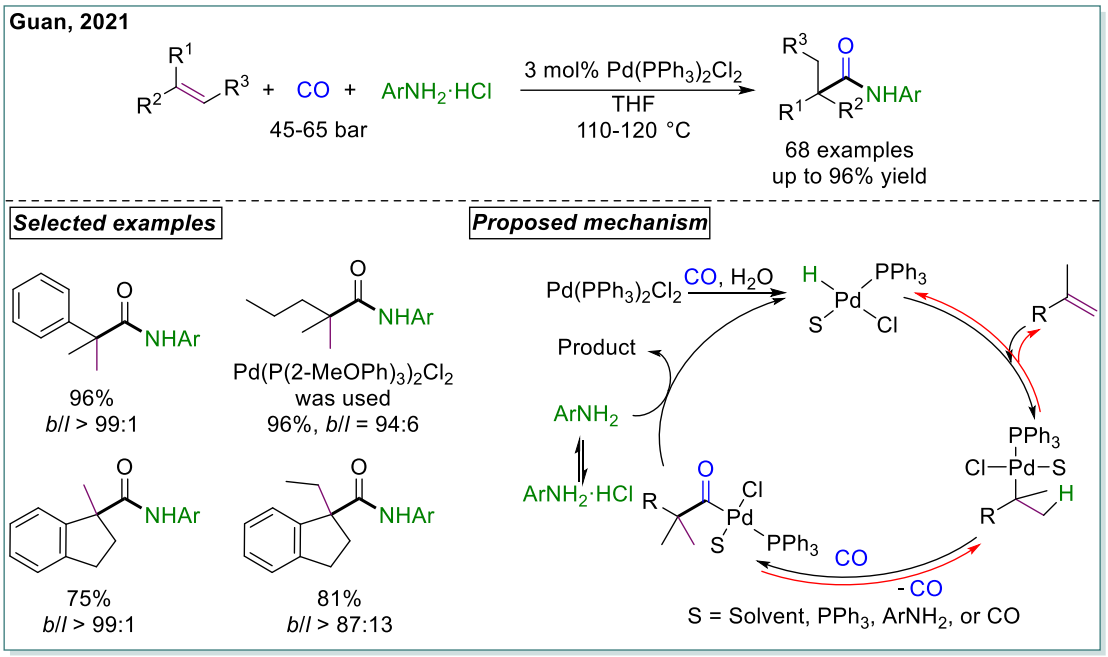
In 2021, Guan and co-workers reported the direct palladium-catalyzed asymmetric Markovnikov hydroaminocarbonylation of alkenes with anilines for highly regio- and enantioselective synthesis of 2-substituted propanamides (Scheme 30).[58] In this case, the phosphoramidite ligand was discovered and exhibited very high reactivity and selectivity in the reaction. However, the formation of amides bearing an *α*-quaternary carbon has not been realized by the hydroaminocarbonylation of 1,1-disubstituted or 1,1,2-trisubstituted alkenes, which is also identified as a challenging field in the organic synthesis.



Scheme 30. Pd-catalyzed asymmetric Markovnikov hydroaminocarbonylation of alkenes in the presence of monodentate phosphoramidite

Later, Guan and co-workers disclosed a novel palladium-catalyzed Markovnikov hydroaminocarbonylation of multisubstituted alkenes (Scheme 31).[59] Using aniline hydrochloride salts, 1,1-disubstituted or 1,1,2-trisubstituted alkenes worked well to offer amides bearing an *α*-quaternary carbon. Mechanistic studies suggested that the reaction undergoes through a palladium hydride pathway. The

palladium hydride and CO insertion processes are reversible, and the aminolysis of acyl palladium intermediate is probably the rate-limiting step.

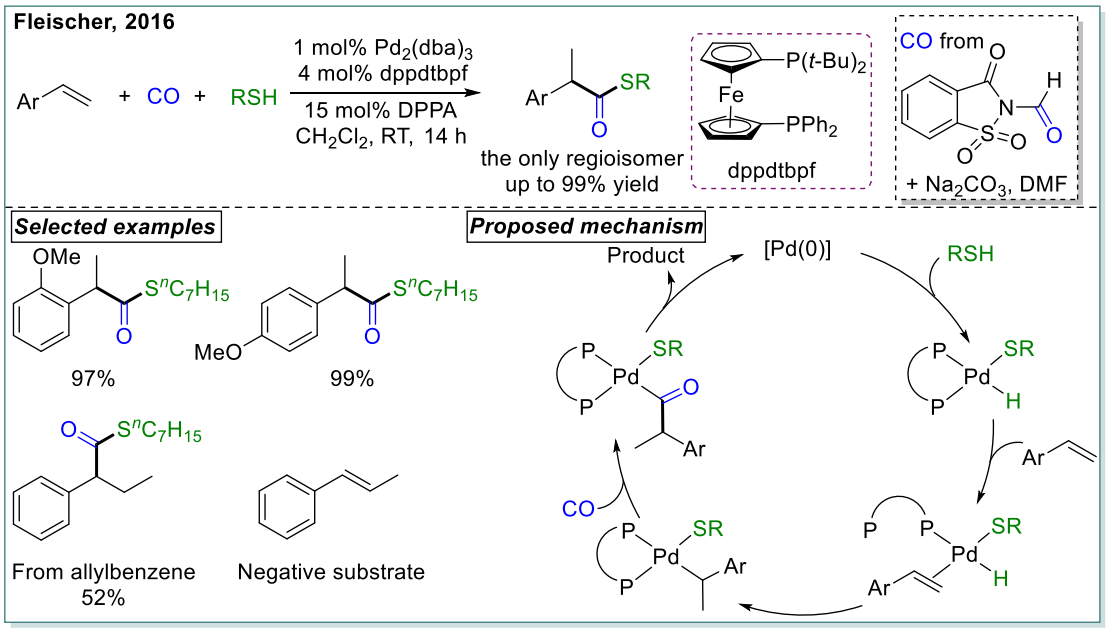


Scheme 31. Pd-catalyzed Markovnikov hydroaminocarbonylation of 1,1-disubstituted and 1,1,2-trisubstituted alkenes with amines

1.3.3 Palladium-catalyzed regioselective carbonylation of alkenes with *S*-nucleophiles.

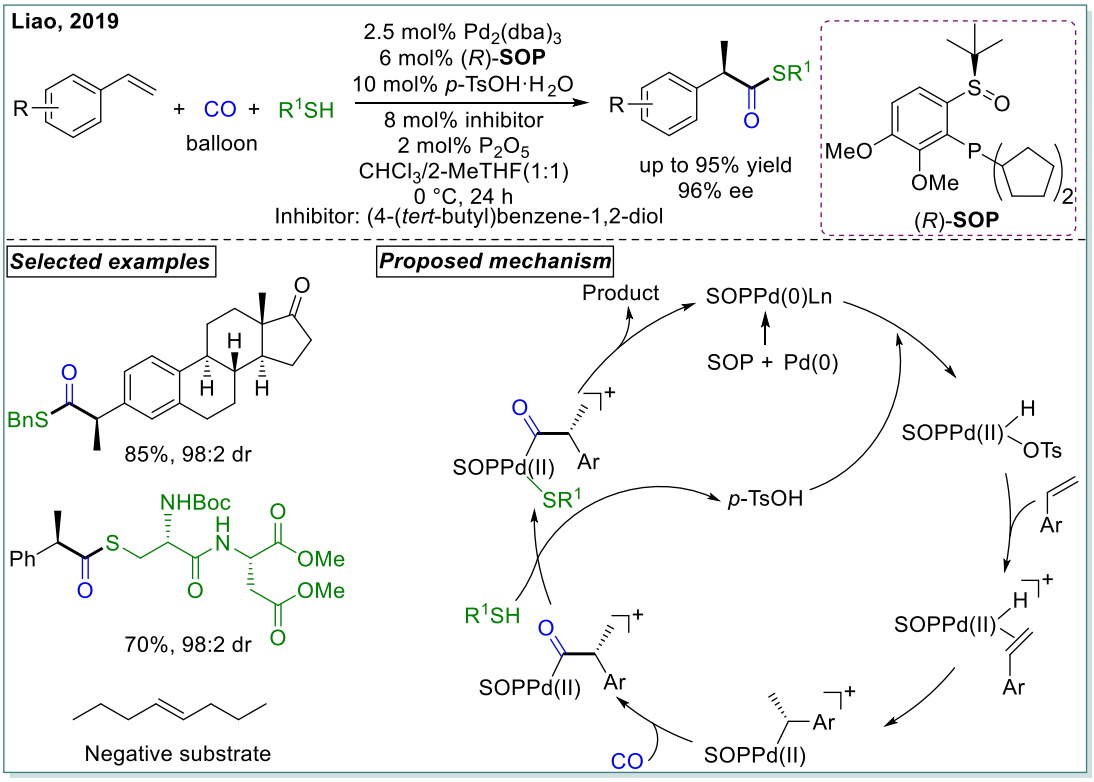
Compared to the well-developed carbonylation reactions *vide supra*, the related thiocarbonylation of alkenes with thiols has been significantly less developed. Previous studies of this transformation, mainly carried out by Alper and co-workers, predominantly focused on the thiocarbonylation of conjugated alkynes dienes, enynes, allenes and other relatively active unsaturated bonds.[60] In this regard, the thiocarbonylation of alkenes, especially with high regioselectivity, needs to be further investigated.

In 2016, Fleischer and co-workers disclosed the palladium-catalyzed thiocarbonylation of styrene derivatives, giving a wide range of exclusively branched thioesters even from *ortho*-substituted styrenes (Scheme 32).[61] The devised catalytic system features high functional group tolerance and mild reaction conditions (room temperature, low pressure or CO surrogate), which make this reaction a versatile strategy for the synthesis of branched thioesters from available feedstocks. In addition, no desired product was observed using internal alkene as substrate, whereas terminal nonconjugated alkenes were converted to branched products in moderate yields. The authors suggested that a direct carbonylation at the benzylic position of the internal alkene is not possible due to its steric hindrance, but an insertion of the terminal nonconjugated alkene, followed by an isomerization, is reasonable. According to the obtained results, the authors proposed a possible mechanism, the palladium hydride species is formed from Pd(0) by oxidative addition of the thiol and a ligand exchange. After styrene coordination to the palladium hydride species, the palladium hydride species with one phosphorus atom coordinated is formed. Markovnikov insertion of styrene into the Pd−H bond furnishes the alkyl palladium species, which undergoes CO coordination and insertion. The resulting acyl palladium complex affords the corresponding product and palladium hydride species via reductive elimination/oxidative addition steps.



Scheme 32. Pd-catalyzed thiocarbonylation of vinyl arenes to branched thioesters

A highly enantioselective thiocarbonylation of styrenes with thiols was realized by Liao group in 2019.[62] Here, applying a novel chiral sulfoxide-(P-dialkyl)-phosphine (SOP) ligand, this reaction reacted well under mild reaction conditions (1 atm CO and 0 °C), providing highly branched enantioenriched thioesters in good yields (Scheme 33). In terms of the internal alkene, it didn't work, neither.

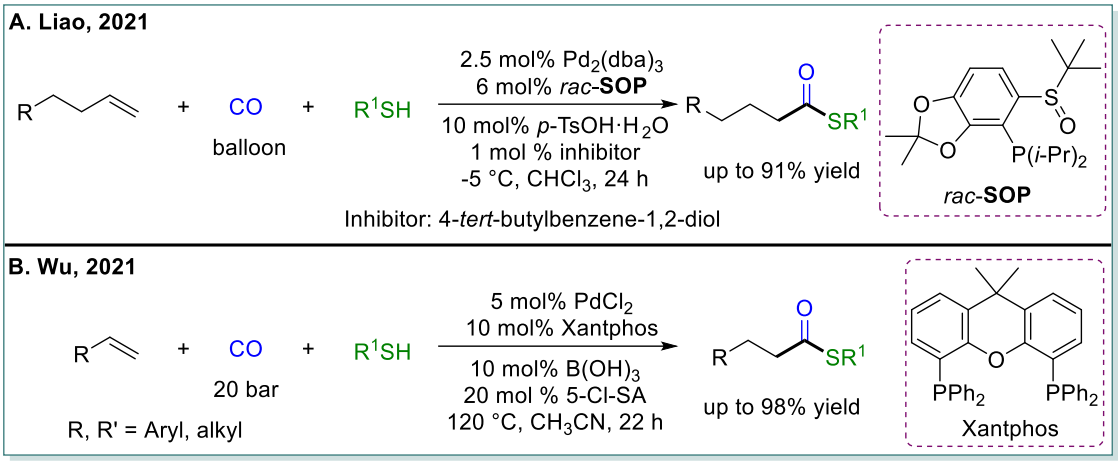


Scheme 33. Pd-catalyzed enantioselective thiocarbonylation of styrenes to branched thioesters

The experiments demonstrate that PTSA, rather than thiol, plays an important role in the formation of palladium hydride species in the presence of electron-rich SOP. Unlike the formation of Pd(II) hydride

species described above that is proposed to be formed by oxidative addition of thiol, the authors proposed Pd(II) hydride species is generated through oxidative addition of Pd(0) species to PTSA. Followed by coordination and Markovnikov insertion of styrene, the alkyl palladium species is formed, which undergoes CO coordination and insertion to furnish the acyl Pd(II) species. The acyl Pd(II) species reacts with thiol to offer the desired product and regenerate the Pd(II) hydride species.

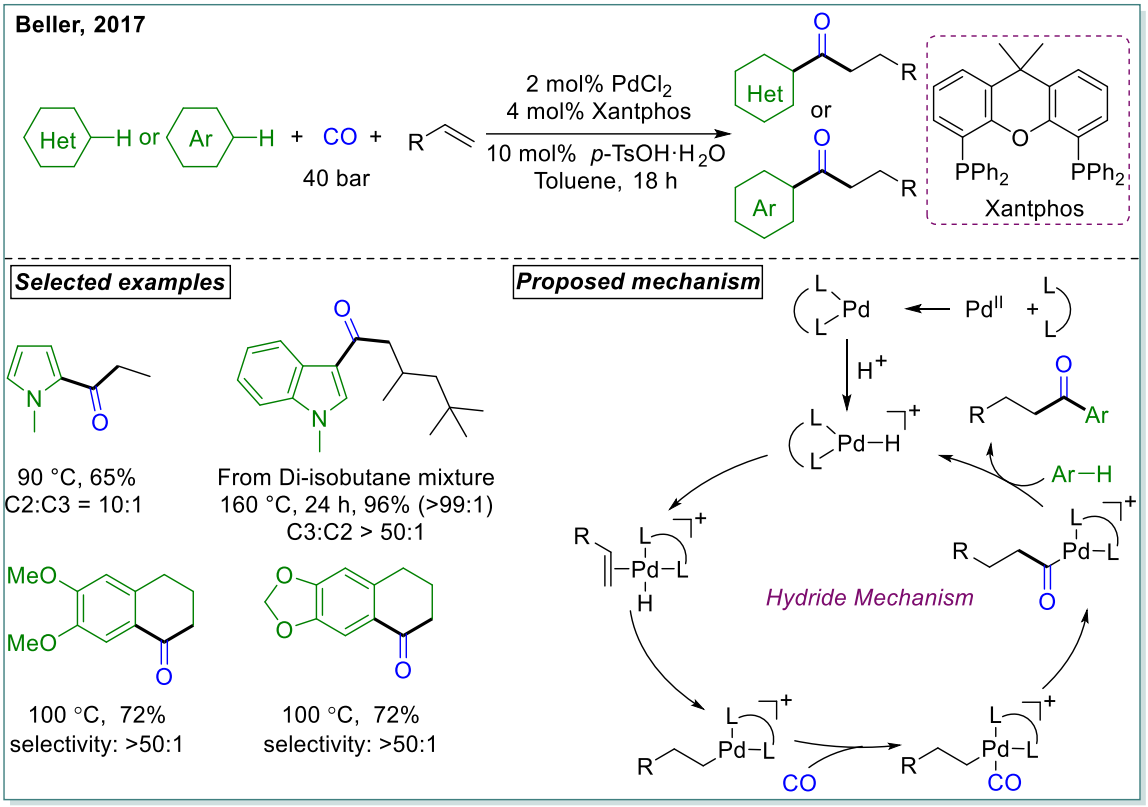
Subsequently, Liao and co-workers presented a mild palladium-catalyzed hydrothiocarbonylation of unactivated terminal alkenes in the presence of SOP ligand, which gave a wide range of aliphatic thioesters in good yields with high linear selectivities (Scheme 34A).[63] In 2021, a general strategy for the synthesis of linear thioesters by palladium-catalyzed thiocarbonylation of alkenes was developed by Wu and co-workers (Scheme 34B).[64] Both aliphatic alkenes and styrenes were readily converted into linear thioesters in the presence of Xantphos.



Scheme 34. Pd-catalyzed thiocarbonylation of alkenes to linear thioesters

1.3.4 Palladium-catalyzed carbonylation of alkenes with other nucleophiles.

Palladium-catalyzed carbonylation of alkynes with heteroarenes towards *α*, *β*-unsaturated ketones has been developed by Alper and our group.[65] Later, our group disclosed the palladium-catalyzed carbonylation of olefins with (hetero)arenes to linear ketones in the presence of Xantphos.[66] Compared to the classical Friedel–Crafts reaction, this novel method is demonstrated to be more economical and environmentally friendly. The synthetic utility of this strategy was demonstrated further in the direct carbonylation of natural products (eugenol and safrole) as well as industrial feedstocks (ethylene and diisobutene). Using nonanoic acid or the corresponding acyl chloride under the standard conditions with or without catalyst, no corresponding product was observed, thus excluding the traditional process of Friedel–Crafts acylation. The carbonylation of ethylene with *N*-methylpyrrole was carried out with Pd(II) or Pd(0) precatalysts (Scheme 35). The induction time of approximately one hour was observed with $PdCl_2$, which indicated that Pd(II) catalyst is not the true active species. On the contrary, almost no induction period was observed in the presence of $Pd_2(dba)_3$, and the substrate started to react immediately. These observations show that the mechanism via C–H activation of the heteroarenes is not possible. Instead, it is most likely that this reaction occurs through the palladium hydride mechanism.



Scheme 35. Pd-catalyzed carbonylation of olefins to ketones

2 Objectives of this work

As mentioned in the introduction, palladium-catalyzed carbonylation of carbon-carbon unsaturated bonds has been a focal point of research in both industry and academia for several decades. These carbonylation reactions allow for the introduction of carbonyl groups into organic compounds, which is important for the synthesis of valuable chemicals. Although a wide range of alkenes, alkynes and nucleophiles have been used in previous carbonylation reactions, there remains a compelling interest in exploring new substances and catalyst systems to increase reaction efficiency and selectivity.

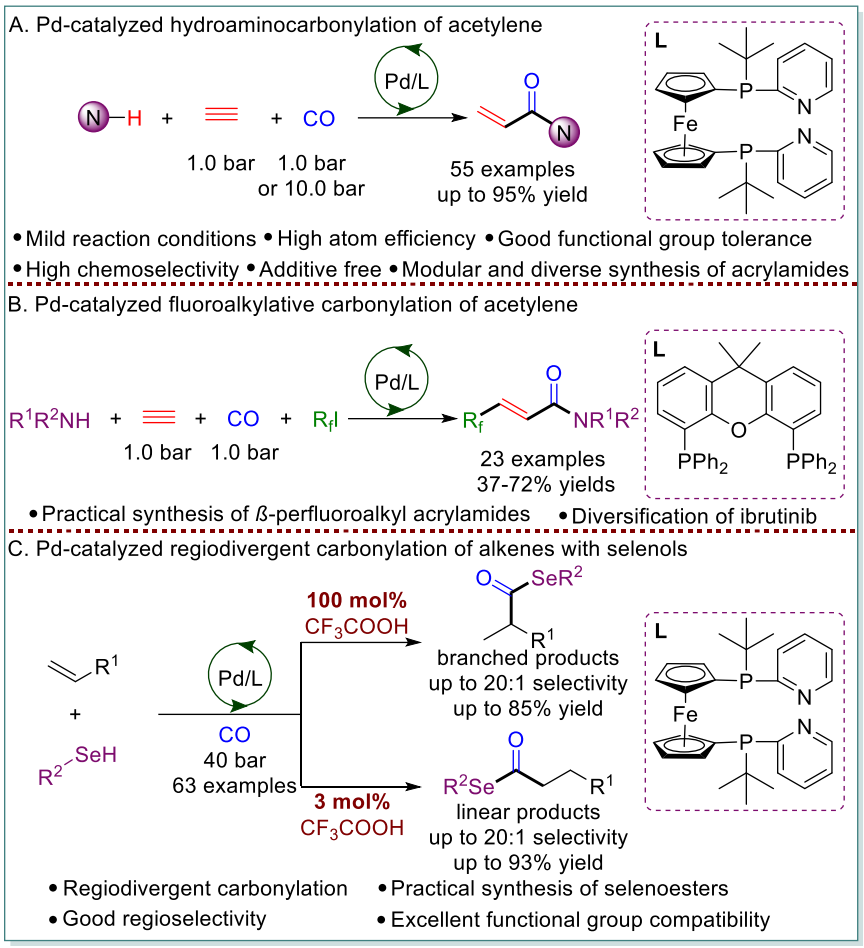
Over the past decade, acrylamides have emerged as one of the most popular warheads in covalent drugs, which has attracted chemists' interest in the straightforward synthesis of such kind of acrylamides. Traditional approaches to acrylamides often suffer from some limitations such as low atom efficiency and environmental concerns, alongside issues related to chemoselectivity. Although Reppe reported Ni-catalyzed hydroaminocarbonylation of acetylene in the last century, the harsh reaction conditions (high acetylene pressure and temperature), the possible formation of extremely toxic $Ni(CO)_4$ and the limited substrate scope have prevented such reactions from being widely applied. As such, there is a growing demand for the efficient synthesis of arylamides. Meanwhile, *β*-perfluoroalkyl acrylamides are of interest for drug discovery as the fluorinated motif could alter their intrinsic properties.

Furthermore, the control of regioselectivity in the palladium-catalyzed carbonylation of alkenes continues to be one of the major challenges. In this regard, complementary catalyst systems have been established for carbonylation of alkenes with different nucleophiles such as water, alcohols, amines, and thiols, which allow the selective formation of both linear and branched products. However, the direct regiodivergent carbonylation of alkenes with selenols to give linear or branched selenoesters has not been achieved yet.

Therefore, the specific objectives of the present thesis are the following:

1. Develop a palladium catalyst system that enables to synthesize acrylamides in a mild and efficient manner.
2. Develop the palladium-catalyzed four-component carbonylation of acetylene with amines towards *β*-perfluoroalkyl acrylamides.
3. Develop an efficient strategy for regiodivergent carbonylation of alkenes with selenols with a novel catalyst system.

3 Summary of publications



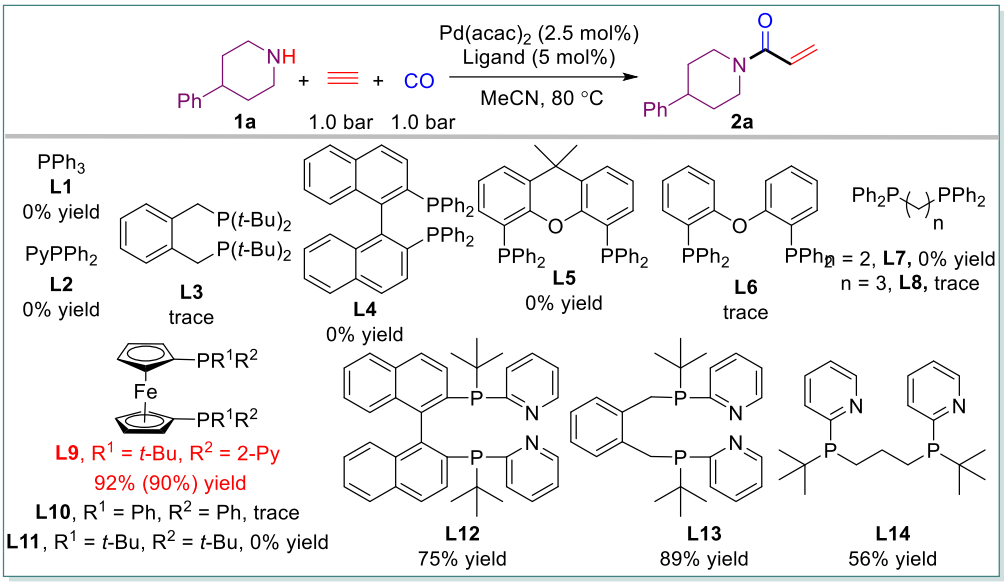
Scheme 36. Research summary

3.1 Modular and diverse synthesis of acrylamides by palladium-catalyzed hydroaminocarbonylation of acetylene.

Acrylamides represent interesting building blocks, which are widely applied in drug molecules as warheads.[6b,c] In general, traditional methods for the synthesis of acrylamides are based on the nucleophilic condensation or nucleophilic addition-elimination of carboxylic acid derivatives with amines.[7] Obviously, such processes have some limitations, such as being less environmentally friendly, less atomic efficient and sometimes encountering chemoselectivity problems.

Despite these problems, we thought that an efficient approach to this valuable class of compounds could be achieved by palladium-catalyzed hydroaminocarbonylation of acetylene. The initial study was performed with 4-phenylpiperidine and acetylene as the model substrates. After intensive investigations, we found that using 1 bar CO and 1 bar acetylene in the presence of $Pd(acac)_2$ (2.5 mol%) and 1,1'-ferrocenediyl-bis(tert-butyl(pyridin-2-yl)phosphine) (5.0 mol%) at 80 °C in MeCN, the desired product could be obtained in 90% isolated yield (Table 1).

Table 1. Pd-catalyzed hydroaminocarbonylation of the acetylene: Variation of ligands, solvents, and palladium catalysts[a]

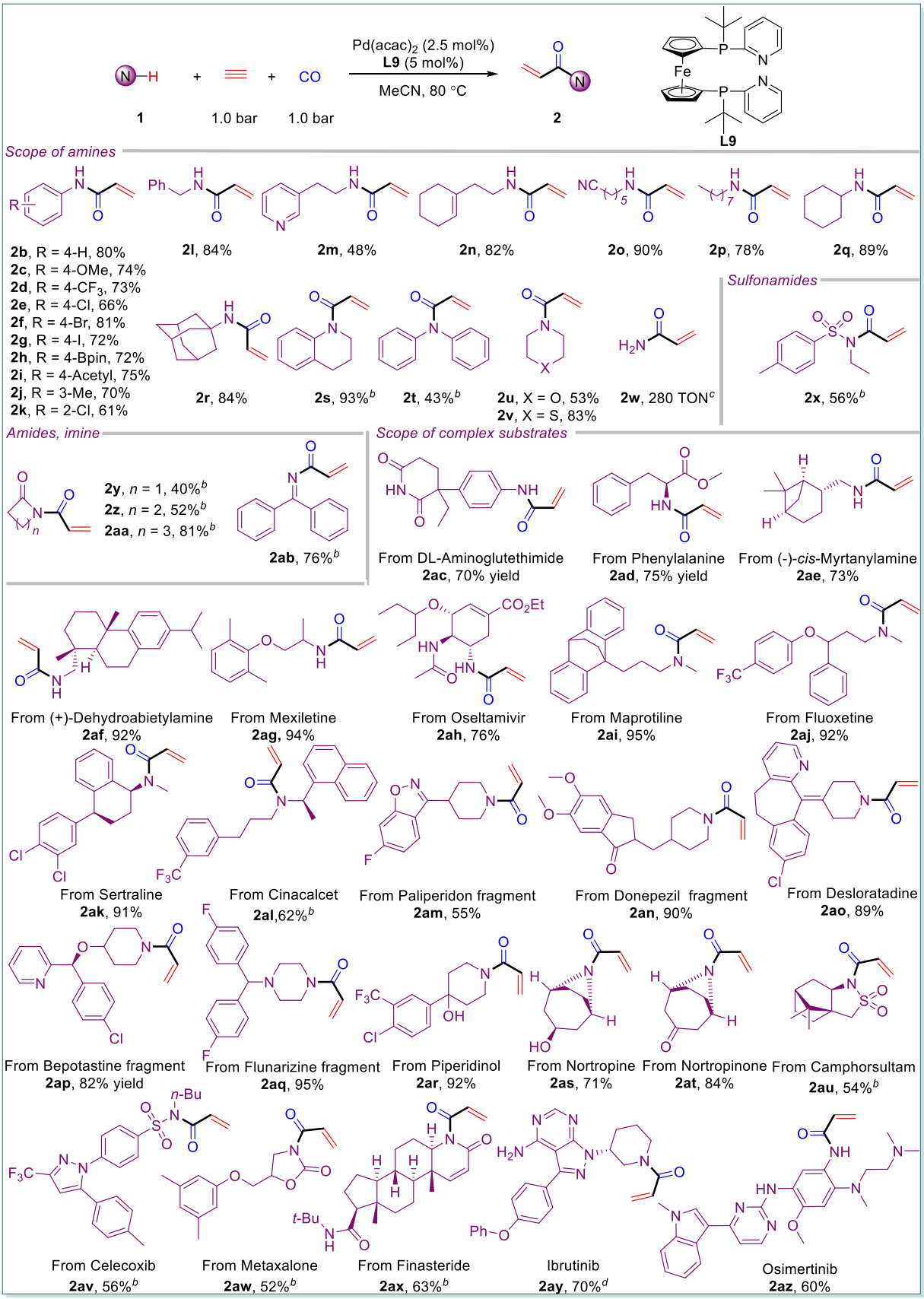


Entry	Solvent[b]	Yield / %	Entry	[Pd][c]	Yield / %
1	THF	Trace	6	$Pd(OAc)_2$	82
2	1,4-Dioxane	0	7	$PdCl_2$	91
3	Toluene	5	8	$Pd(MeCN)_2Cl_2$	90
4	DMF	10	9	$Pd(PPh_3)_4$	0
5	Heptane	Trace	10[d]	$Pd(acac)_2$	0

[a] Pd-catalyzed hydroaminocarbonylation of the acetylene. Yields were determined by ^1H NMR with 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields in parentheses. Reaction conditions: **1a** (0.2 mmol), [Pd] (2.5 mol%), ligand (5 mol%), CO (1.0 bar), acetylene (1.0 bar), solvent (2.0 mL), stirred at 80 °C for 18 h. Influence of phosphine ligands: $Pd(acac)_2$ was used as palladium catalyst and MeCN was used as solvent. 2-Py = 2-pyridinyl. [b] $Pd(acac)_2$ was used as palladium catalyst and **L9** was used as ligand. [c] **L9** was used as ligand and MeCN was used as solvent. [d] Room temperature.

Next, a series of aryl- and alkylamines were evaluated at first, offering corresponding products in moderate to high yields (Scheme 37). In these cases, halo, pinacolboryl, acetyl, cyano, pyridinyl, and vinyl groups are well accommodated with reaction conditions, exhibiting good functional group tolerance. It is worth mentioning that the parent compound ammonia can be successfully applied in this reaction, providing the acrylamide monomer with a TON of 280 without further optimization. Even less nucleophilic *N*-nucleophiles such as sulfonamide, amides and imine were readily converted to desired products in moderate to good yields.

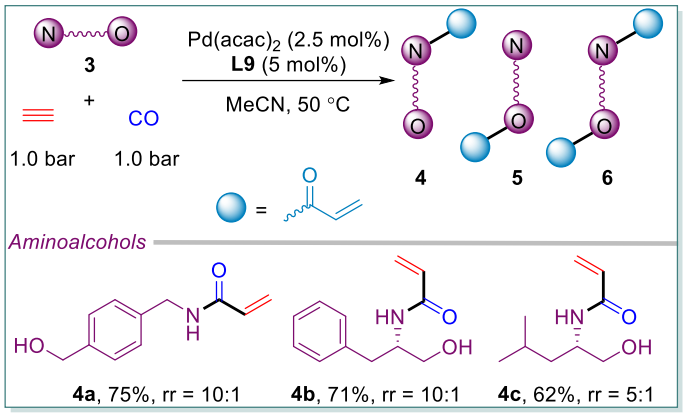
The importance of this efficient approach is demonstrated by the late-stage modification of natural and bioactive products under mild reaction conditions, which could be of interest for many life science applications. Here, a variety of acrylamide-containing products were obtained from corresponding bioactive molecules such as oseltamivir, fluoxetine, metaxalone, finasteride, etc. To our delight, this method was successfully applied to synthesize ibrutinib as well as osimertinib in decent yields.



Scheme 37. Pd-catalyzed hydroaminocarbonylation of acetylene with *N*-nucleophiles

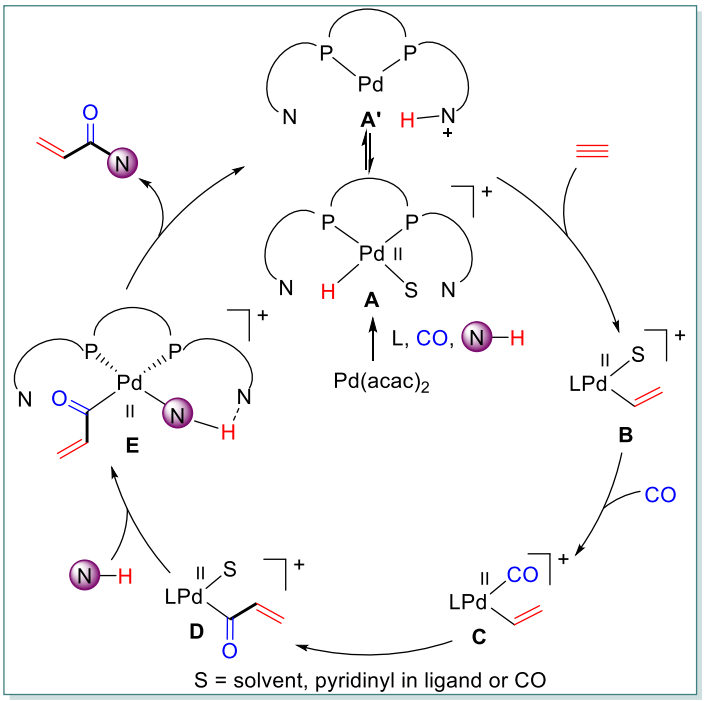
[a] Reaction conditions: Pd(acac)2 (2.5 mol%), **L9** (5 mol%), 1 (0.2 mmol), CO (1.0 bar), acetylene (1.0 bar), MeCN (2.0 mL), stirred at 80 °C for 18 h. Isolated yields. [b] CO (10.0 bar) was used at 120 °C for 14 h. [c] Ammonia gas (1.0 bar) was used at 100 °C. [d] Stirred at 70 °C for 14 h.

According to previous studies about chemoselective carbonylation with aryl aminoalcohols,[57] this methodology was applied to acrylation of alkyl aminoalcohols to investigate the chemoselectivity between *N*- and *O*-nucleophiles (Scheme 38). Here, the corresponding acrylamides were obtained in 62-75% yields and good chemoselectivities (5-10:1).



Scheme 38. Pd-catalyzed chemoselective carbonylation of acetylene with aminoalcohols.
Reaction conditions: $Pd(acac)_2$ (2.5 mol%), **L9** (5 mol%), **3** (0.2 mmol), CO (1.0 bar), acetylene (1.0 bar), MeCN (2.0 mL), stirred at 50 °C for 9 h. Chemoselectivity rr = **4**/(**5**+**6**), determined by ^{1}H NMR.

Based on previous studies,[16,53,58,67] we propose that the so-called palladium hydride took place in the process (Scheme 39). It is likely that the palladium hydride species **A** is in equilibrium with the *N*-protonated pyridinium species **A'**. Acetylene coordinates to species **A** or **A'** and insertion of acetylene furnishes the species **B**, which could be transformed into species **C** through CO coordination. Subsequent insertion of CO gave species **D**. Finally, *N*-assisted aminolysis leads to desired acrylamide and regenerates the active palladium species **A** or **A'**.



Scheme 39. Proposed mechanism for Pd-catalyzed hydroaminocarbonylation of acetylene

3.2 Palladium-catalyzed four-component carbonylation of acetylene: efficient synthesis of *β*-perfluoroalkyl acrylamides

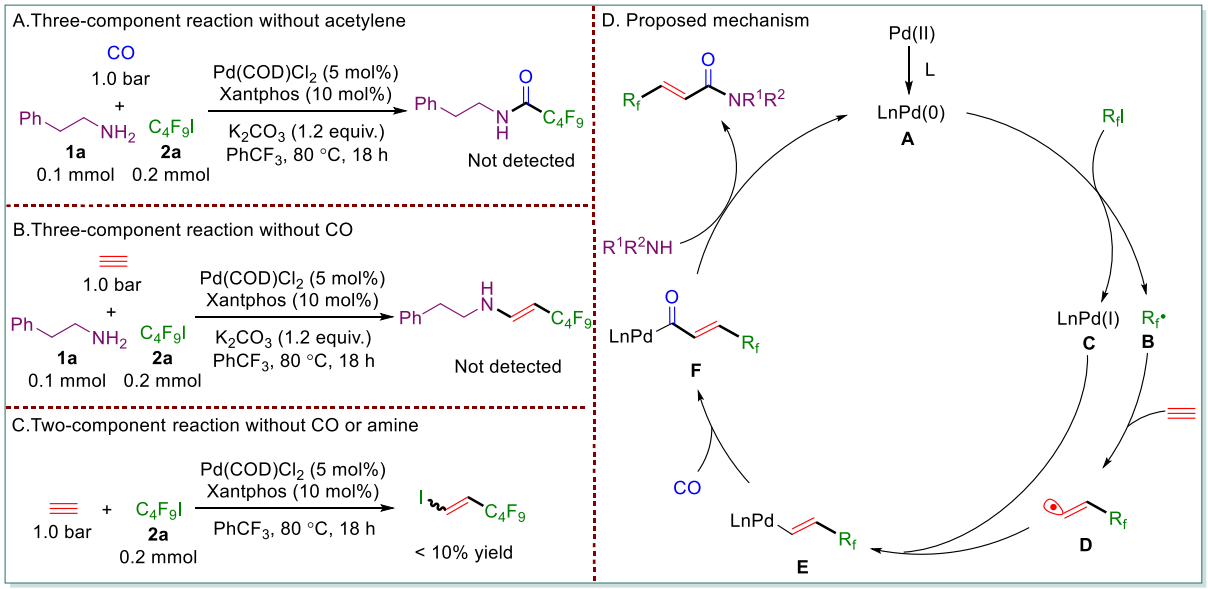
The introduction of fluorine into drugs can significantly change their biological properties such as enhancing lipophilicity and metabolic stability compared to non-fluorinated compounds. Consequently, methods to introduce a fluorinated moiety into bioactive molecules are of great importance.

Following the palladium-catalyzed hydroaminocarbonylation of acetylene, we disclose a straightforward palladium-catalyzed four-component carbonylation of acetylene for the synthesis of *β*-perfluoroalkyl acrylamides.

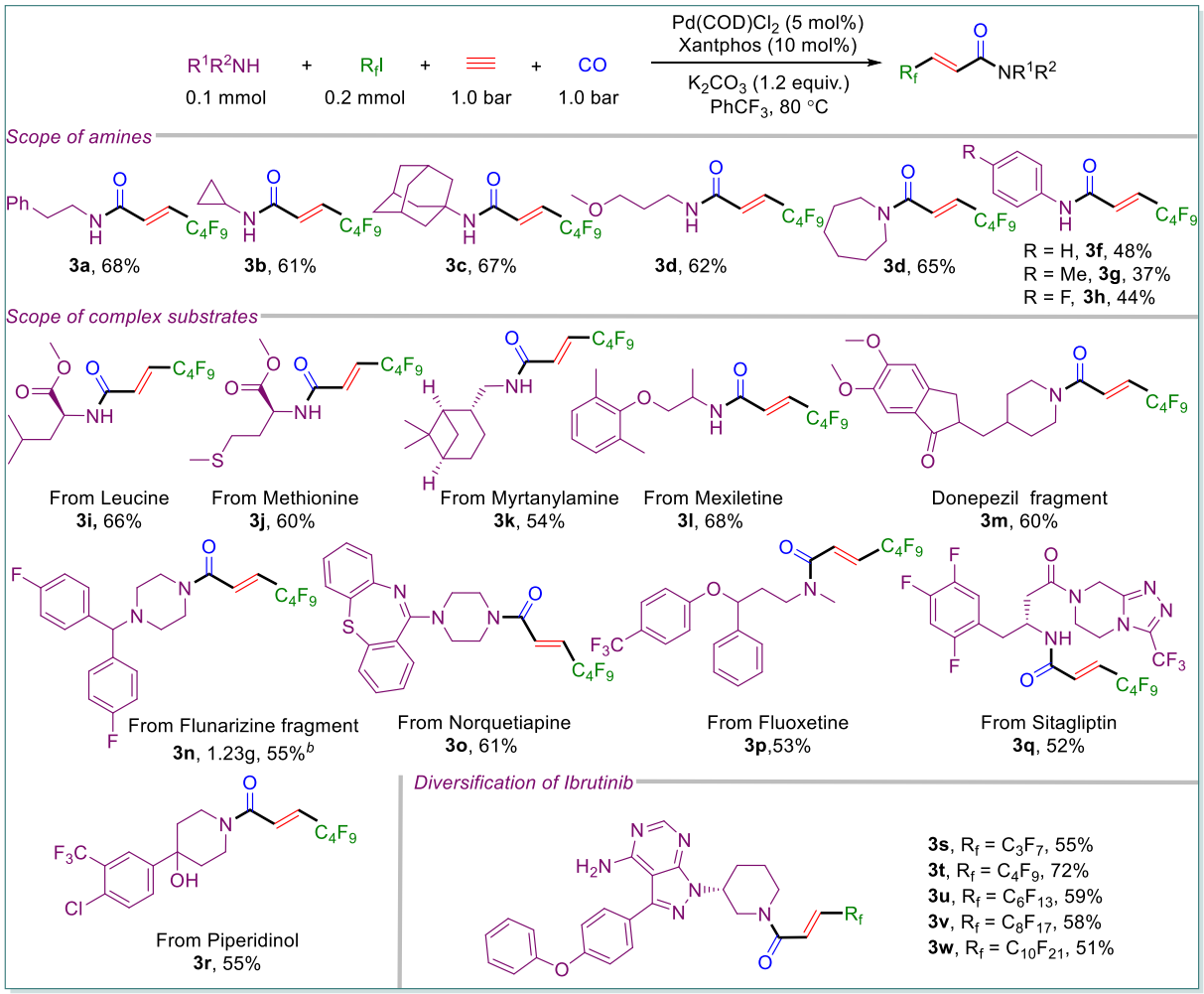
At the beginning of this work, the commercially available phenethylamine, *n*-perfluorobutyl iodide (C_4F_9I) were selected as coupling partners for the carbonylation of acetylene. We found that the combination of $Pd(COD)Cl_2$ (5 mol %) with Xantphos ligand (10 mol%) in the presence of K_2CO_3 in benzotrifluoride at 80 °C gave the desired fluorinated product in 68% isolated yield.

Some control experiments were carried out for preliminary mechanism studies. The direct product of the three-component reaction without acetylene was not observed due to the polarity mismatch between the perfluoroalkyl radical and CO (Scheme 40A). Similarly, the corresponding product of three-component reaction without CO was not detected, indicating that reductive elimination could not occur without CO (Scheme 40B). The palladium-catalyzed iodoperfluoroalkylation of acetylene provided *β*-perfluoroalkyl vinyl iodide in very low yield (Scheme 40C), demonstrating that *β*-perfluoroalkyl acrylamides were not possible from *β*-perfluoroalkyl vinyl iodide. Based on control experiments and previous studies,[25-28] we proposed a possible mechanism for this reaction (Scheme 40D). Initially, the Pd(II) precursor is reduced to Pd(0) phosphine complex **A** in the presence of an excess amount of ligand. The species **A** then reduces the perfluoroalkyl iodide via a single electron transfer (SET) reaction, providing fluoroalkyl radical **B** and Pd(I) species **C**. After a radical addition of the fluoroalkyl radical **B** to acetylene, the vinyl radical **D** is formed. Subsequently, the vinyl radical **D** is captured by species **C** to generate the intermediate **E**, which undergoes coordination and insertion of CO to afford the acyl species **F**. Finally, the acyl species **F** reacts with amine to offer the desired *β*-perfluoroalkyl acrylamide and regenerate the Pd(0) species **A**.

With optimized conditions in hand, we then explored the reaction of acetylene with a variety of amines and perfluorobutyl iodide under 1 bar CO. As shown in Scheme 41, alkyl- and arylamines are easily transformed into corresponding products in 37-68% yields. To showcase the importance of this straightforward methodology, we applied this method for the diversification of bioactive molecules, offering a variety of *β*-perfluoroalkyl acrylamides in decent yields. Furthermore, this novel protocol was successfully used to late-stage functionalization of ibrutinib, affording diverse perfluoroalkyl-containing ibrutinib derivatives in 51-72% yields in the presence of different perfluoroalkyl iodide, which demonstrates great potential for drug discovery.



Scheme 40. Mechanism studies for Pd-catalyzed four-component carbonylation of acetylene



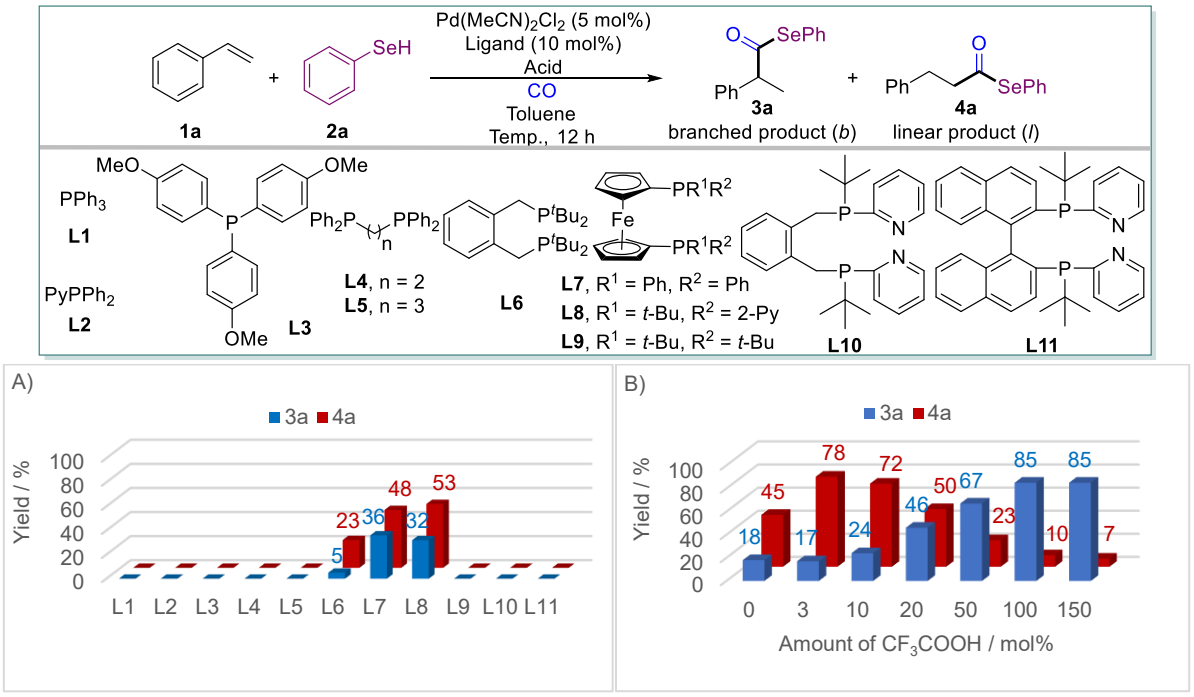
Scheme 41. Pd-catalyzed four-component carbonylation of acetylene

Scope of the palladium-catalyzed four-component carbonylation reaction. a. Reaction conditions: $Pd(COD)Cl_2$ (5 mol%), Xantphos (10 mol%), **1** (0.1 mmol), **2** (0.2 mmol), K_2CO_3 (1.2 equiv.), CO (1.0 bar), acetylene (1.0 bar), $PhCF_3$ (1.5 mL), stirred at 80 °C for 18 h. Isolated yields. b. 4 mmol **1n** was used.

3.3 Regiodivergent carbonylation of alkenes: selective palladium-catalyzed synthesis of linear and branched selenoesters

To the best of our knowledge, the direct regiodivergent carbonylation of alkenes using the same metal catalyst and ligand to offer linear or branched carboxylic acid derivatives has not been realized yet. From both a scientific and a fundamental point of view, such a protocol would make it possible to switch the selectivity of the reaction and to achieve any desired regioselectivity with the same catalyst system. On the other hand, selenoesters are important building blocks in organic synthesis, commonly applied as mild acyl-transfer agents to synthesize natural products.[68] Furthermore, selenoesters have gained more attention following the development of diselenide selenoester ligation (DSL) for protein synthesis, as their properties are more reactive than thioesters.[69] In addition, small molecules containing selenoesters also have potential pharmacological activity.[70]

Initially, styrene and phenylselenol were chosen as benchmark substrates to develop an optimal catalyst system. To our delight, using $Pd(MeCN)_2Cl_2$ (5 mol%) as metal precursor and 1,1'-ferrocenediyl-bis(tert-butyl(pyridin-2-yl)phosphine) (10 mol%) as ligand, the linear product was obtained in 78% yield with 4.5:1 *l*/*b* selectivity in the presence of 3 mol% trifluoroacetic acid (TFA) at 75 °C. While 100 mol% TFA leaded to branched product in 83% yield with 8.1:1 *b*/*l* selectivity (Scheme 42).

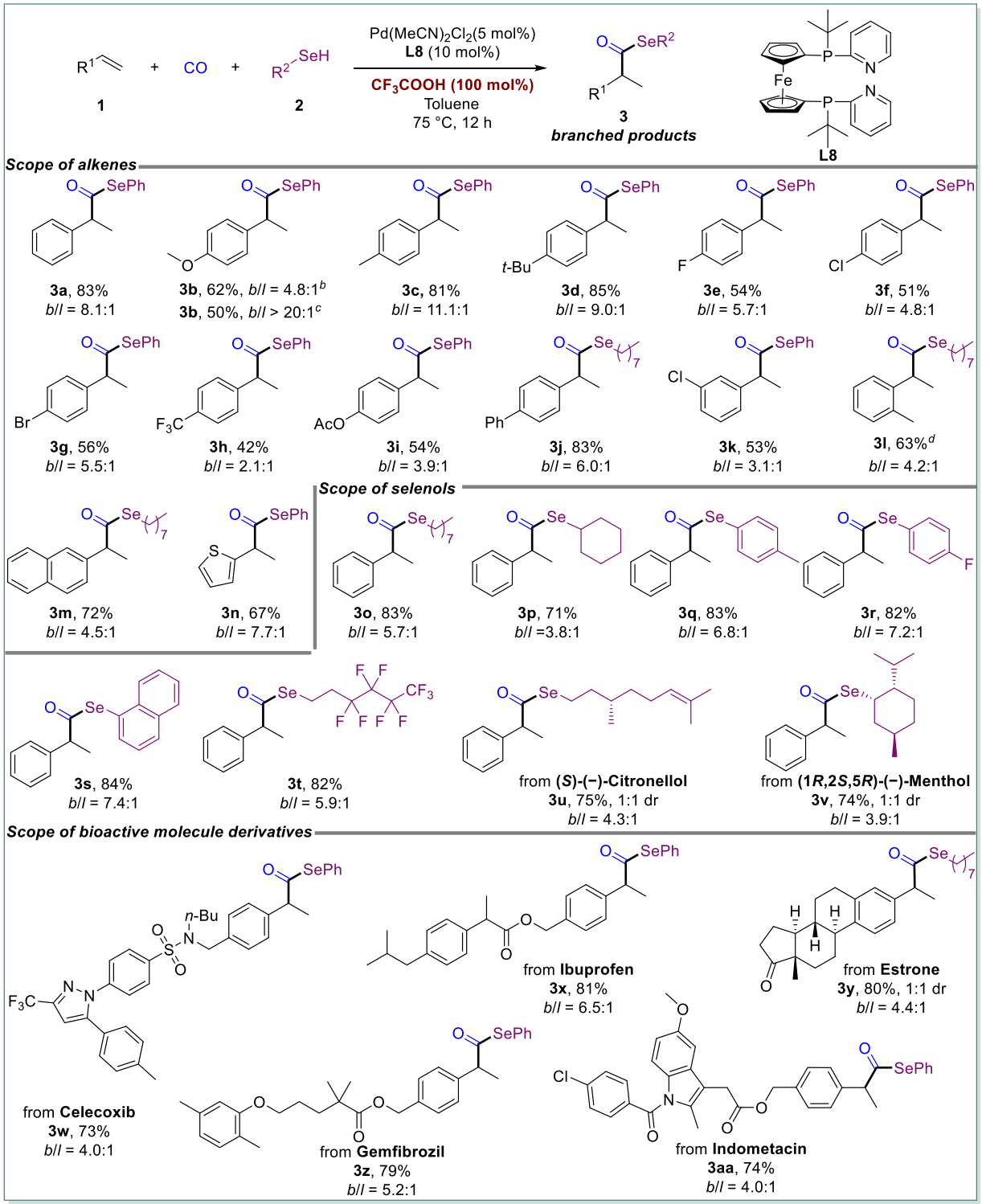


Scheme 42. Pd-catalyzed selenocarbonylation of alkenes: Variation of ligands, amounts of acid[a]

A) Influence of ligands. Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Pd(MeCN)_2Cl_2$ (5 mol%), ligand (10 mol%), $PTSA{\cdot}H_2O$ (10 mol%), CO (40 bar), toluene (1.5 mL), stirred at 100 °C for 12 h. $PyPPh_2$, Py = 2-pyridinyl. B) Influence of different amount of TFA (trifluoroacetic acid). Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Pd(MeCN)_2Cl_2$ (5 mol%), **L8** (10 mol%), TFA (x mol%), CO (40 bar), toluene (1.5 mL), stirred at 75 °C for 12 h. Yields and regioselectivities were determined by ^1H NMR and GC.

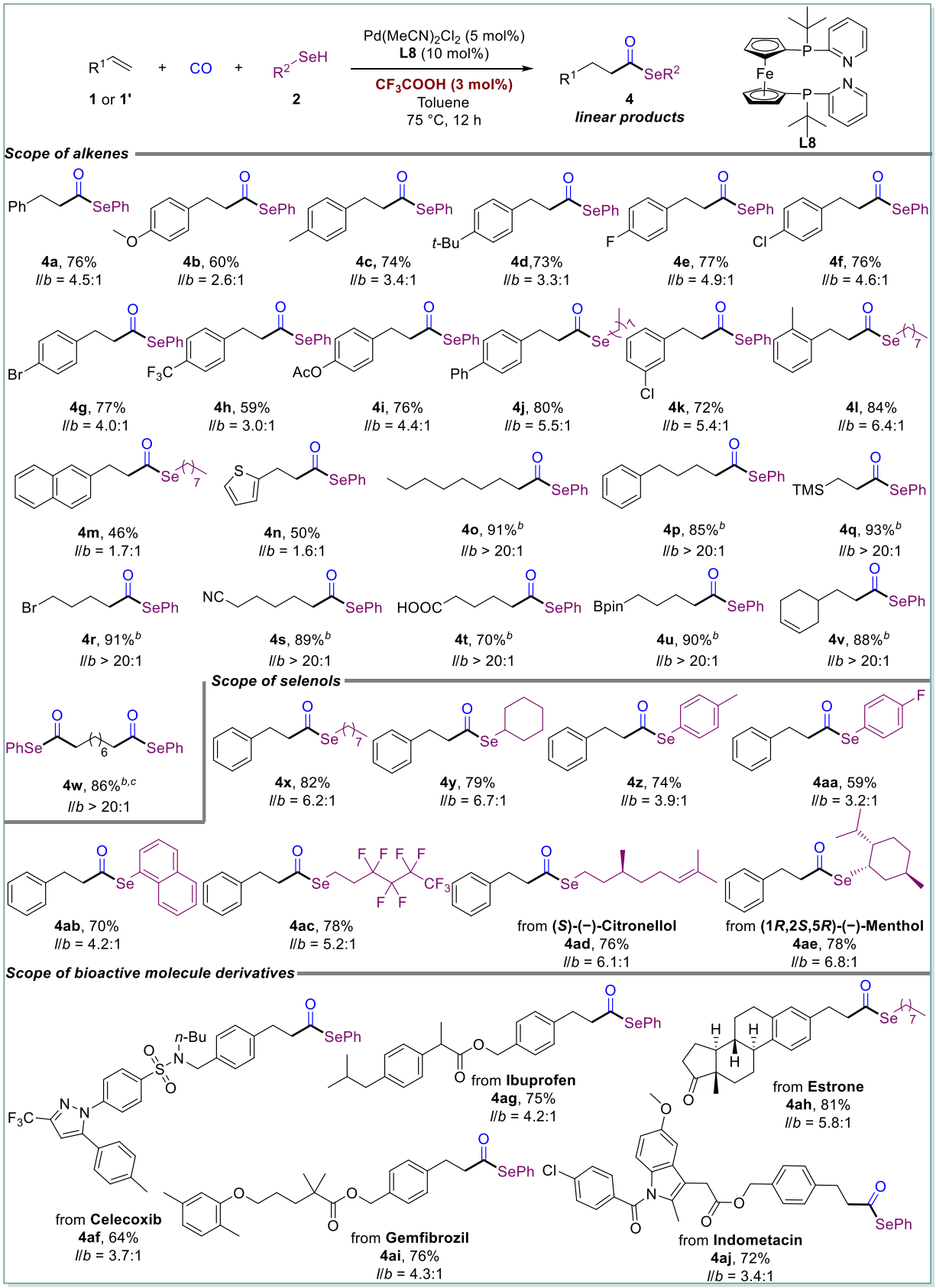
Next, with optimized reaction conditions for the synthesis of branched selenoesters, we explored its applicability for selenocarbonylation of alkenes (Scheme 43). An array of alkenes including styrenes with different substituents were evaluated, providing branched selenoesters in 42-85% yields with 2.1-

9.0:1 *b*/*l* selectivities. In addition, a wide range of selenols were successfully converted to corresponding products in 71-84% yields with 3.8-7.4:1 *b*/*l* selectivities. Notably, bioactive substrates (derivatized from drugs and natural products) are well compatible under the benchmark reaction conditions and products were afforded in 73%-81% yields with 4.0-6.5:1 *b*/*l* selectivities.



Scheme 43. Pd-catalyzed selenocarbonylation of alkenes to branched selenoesters

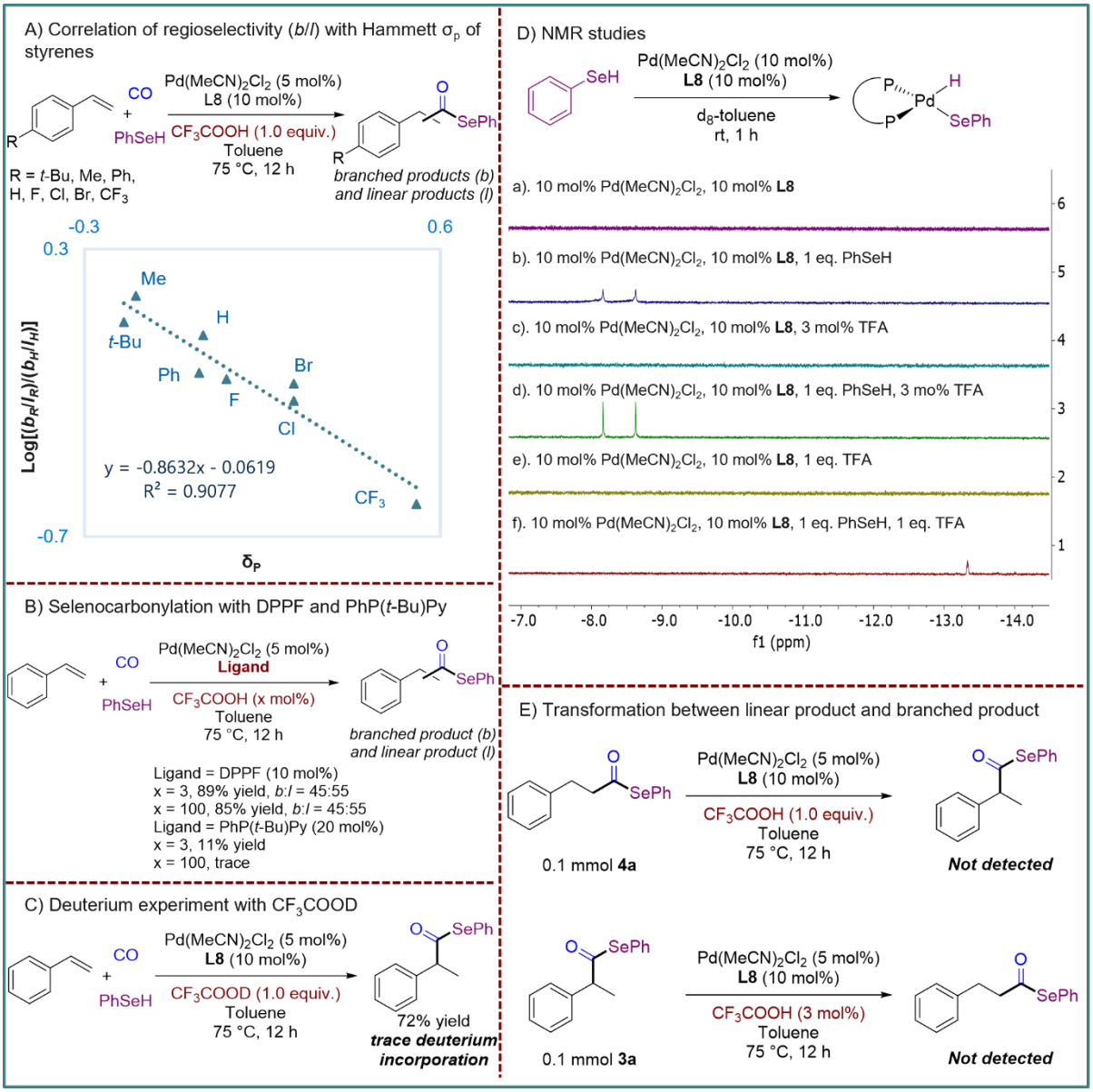
[a] Reaction conditions: alkenes **1** (0.2 mmol), selenols **2** (0.3 mmol), $Pd(MeCN)_2Cl_2$ (5 mol%), **L8** (10 mol%), CF_3COOH (100 mol%), CO (40 bar), toluene (1.5 mL), stirred at 75 °C for 12 h. Regioselectivities were determined by ^1H NMR and GC of crude reaction mixtures. Isolated yields of branched products without isomers. [b] 33 mol% TFA was used. [c] 55 mol% TFA was used. [d] 150 mol% TFA was used.



Scheme 44. Pd-catalyzed selenocarbonylation of alkenes to linear selenoesters

[a] Reaction conditions: alkenes **1** or **1'** (0.2 mmol), selenols **2** (0.3 mmol), $Pd(MeCN)_2Cl_2$ (5 mol%), **L8** (10 mol%), CF_3COOH (3 mol%), CO (40 bar), toluene (1.5 mL), stirred at 75 °C for 12 h. Regioselectivities were determined by ^1H NMR and GC of crude reaction mixtures. Isolated yields of linear products without isomers. [b] Stirred at 100 °C. [c] $Pd(MeCN)_2Cl_2$ (7.5 mol%), **L8** (15 mol%), **2a** (3.0 equiv.) were used.

After demonstrating that it is possible to achieve a variety of branched selenoesters, we turned our attention to the synthesis of linear products. As illustrated in Scheme 44, all the alkenes tested above were also readily converted to corresponding linear products in 46-84% yields with 1.6-6.8:1 *l*/*b* selectivities. Meanwhile, aliphatic alkenes containing various functional groups, e.g. trimethylsilyl, bromide, cyano, carboxyl, pinacolboryl and internal vinyl group, gave the desired linear products in good yields (70%-93%) with high regioselectivities (>20:1).

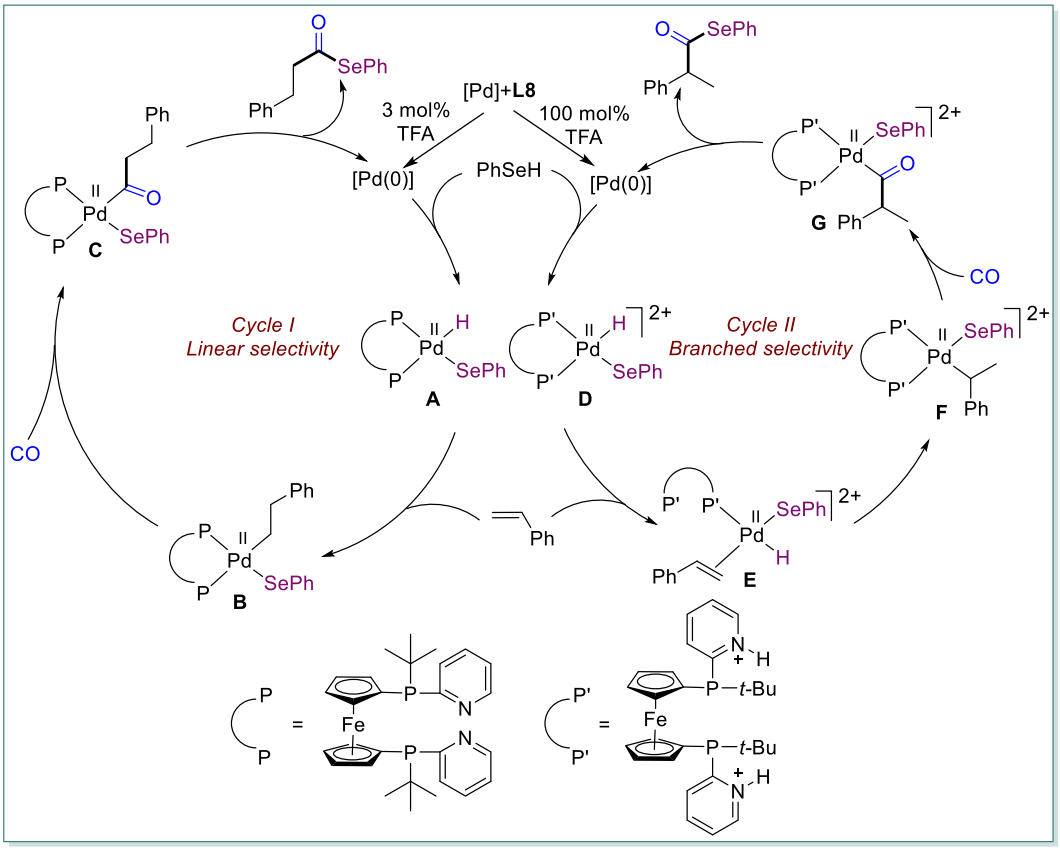


Scheme 45. Mechanism studies for Pd-catalyzed selenocarbonylation of alkenes

To gain mechanistic insight into this Markovnikov selenocarbonylation with 100 mol% TFA, controlled experiments were performed. Initially, the negative slope of the plot in Hammett analysis demenstrated that the more electron-rich alkenes favored bonding with the electron-deficient palladium species to form a transient branched-type palladium(II) intermediate (Scheme 45A). Then, DPPF ligand was used in the benchmark reaction, in which case the *b*/*l* ratio did not change in the presence of different amounts of TFA, indicating that the protonation of pyridinyl substituent on the ligand might be crucial for reversing the regioselectivity in this reaction. And the monophosphine 2-PyP(*t*-Bu)Ph showed low reactivity,

implying that a bidentate ligand is also vital in this process (Scheme 45B). When trifluoroacetic acid-D (99.5% D) was used in this reaction, only trace amount of deuterium incorporation was detected in the branched product (Scheme 45C). Palladium hydride signals were detected at -8.44 ppm in the ^{1}H NMR spectrum after mixing $Pd(MeCN)_2Cl_2$ (10 mol%), L8 (10 mol%) and benzeneselenol with or without 3 mol% TFA (Scheme 45D, b, d). All these experiments suggest that high amount of TFA changes the properties of the ligand via protonation. Additionally, we performed reactions by applying linear product and branched product under corresponding standard reaction conditions, respectively. In both cases no transferred products were observed (Scheme 45E), precluding the possibility of mutual transformation between linear and branched products.

Based on obtained results and previous mechanistic studies,[16,61] the following reaction mechanism is proposed (Scheme 46). Initially, Pd(II) salt is in situ reduced to Pd(0) species in the presence of an excess amount of phosphine ligand. After oxidative addition of selenol, the active complex **A** is formed. Subsequently, styrene coordination of resulting species **A** and insertion of styrene into Pd−H bond produces the species **B**, which could be converted to acyl species **C** by CO coordination and insertion. Finally, the species **C** is transformed to linear product and species **A** by reductive elimination/oxidative addition. However, in the presence of high amount of TFA, pyridinyl groups on the ligand are protonated, resulting in complex **E** being coordinated to one phosphorus atom after styrene coordination of complex **D**. Thus, Markovnikov insertion of styrene occurs to provide the branched product.



Scheme 46. Proposed mechanism for Pd-catalyzed selenocarbonylation of alkenes

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5 Publications

5.1 Modular and Diverse Synthesis of Acrylamides by Palladium-Catalyzed Hydroaminocarbonylation of Acetylene

Zhusong Cao, Qiang Wang, Helfried Neumann, and Matthias Beller

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Author contributions:

In this paper, I performed all the experiments, and wrote an original draft of the manuscript. My contribution as the first author of this paper is approximately 80%.

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Carbonylation Hot Paper

Modular and Diverse Synthesis of Acrylamides by Palladium-Catalyzed Hydroaminocarbonylation of Acetylene

Zhusong Cao, Qiang Wang, Helfried Neumann, and Matthias Beller**

Abstract: The development of all kinds of covalent drugs had a major impact on the improvement of the human health system. Covalent binding to target proteins is achieved by so-called electrophilic warheads, which are incorporated in the respective drug molecule. In the last decade, specifically acrylamides emerged as attractive warheads in covalent drug design. Herein, a straightforward palladium-catalyzed hydroaminocarbonylation of acetylene has been developed, allowing a modular and diverse synthesis of bio-active acrylamides. This general protocol features high atom efficiency, wide functional group compatibility, high chemoselectivity and proceeds additive free under mild reaction conditions. The synthetic utility of this protocol is showcased in the synthesis of ibrutinib, osimertinib, and other bio-active compound derivatives.

Covalent drugs have been widely applied as successful therapies for numerous medical indications in the past century.[1] The structure of a covalent drug is typically made of two parts: the non-covalent binding guidance system and the reactive group or so-called warhead. Generally, warheads target nucleophilic amino acid residues in certain proteins. Hence, electrophilic groups such as epoxides, aziridines, halomethyl ketones, Michael acceptors, and so on are used for this purpose.[2] In particular, acrylamides have emerged as bio-orthogonal Michael acceptors and occur in various covalent drugs (Figure 1). For example blockbuster drugs such as ibrutinib and osimertinib were approved as Bruton's tyrosine kinase (BTK) inhibitor and as EGFR inhibitor, respectively.[3] Notably, in the past five years several other covalent drugs containing acrylamide units were successfully launched including zanubrutinib, sotorasib, mobocertinib, futibatinib, ritlecitinib, and so on.[4] Apart from these medicinal applications, polymerized acrylamides have a plethora of applications such as soil conditioning,[5] oil recovery,[6] and fillers in surgery.[7]

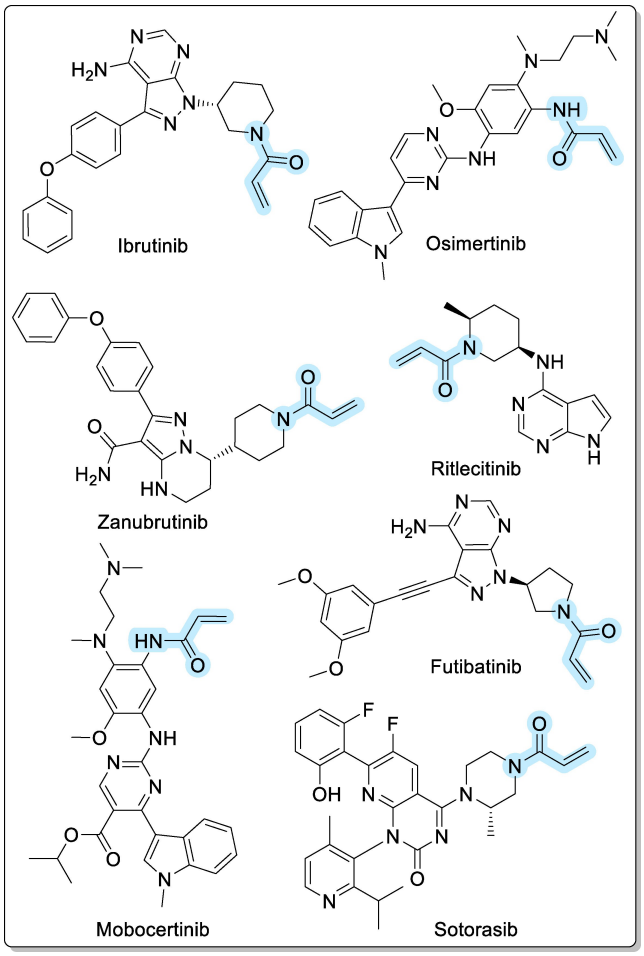

Figure 1. Selected FDA-approved covalent drugs containing acrylamide warheads.

Traditionally, covalent drugs bearing acrylamides are prepared by nucleophilic condensation or substitution of carboxylic acid derivatives with amines in the presence of stoichiometric amounts of base or condensation reagents (Scheme 1A).[8] Obviously, such methods are not environmental-friendly, atom-efficient and face sometimes chemoselectivity problems, too. The direct hydroaminocarbonylation of acetylene with bio-active amines could be a straightforward tool for the synthesis of warhead acrylamides to overcome these limitations. Based on our general interest in the development of novel and improved carbon-

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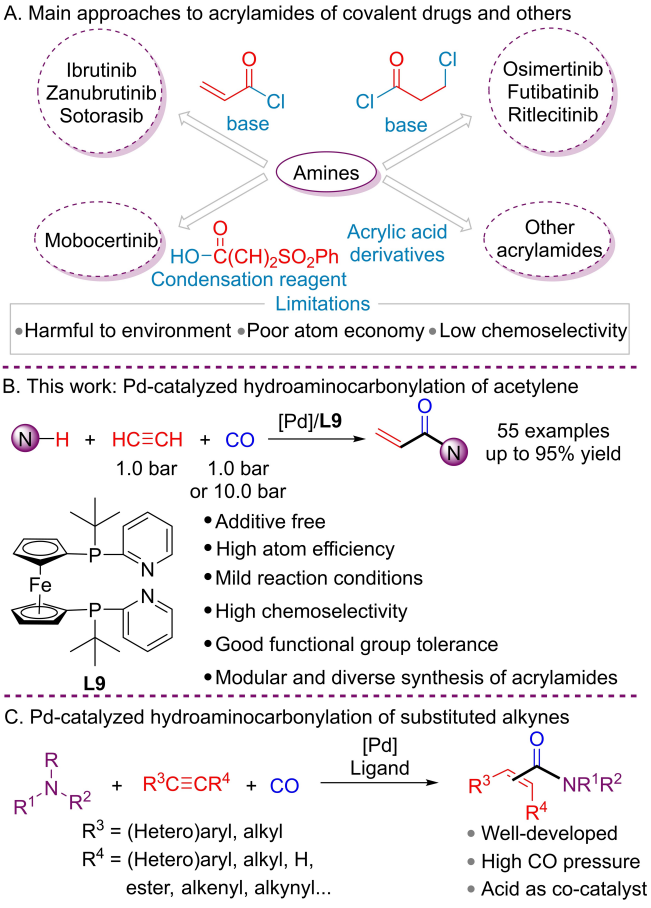


Scheme 1. Synthesis of drug-relevant acrylamides and palladium-catalyzed hydroaminocarbonylation of alkynes.

ylation processes,[9] we describe the mild palladium-catalyzed hydroaminocarbonylation of acetylene gas toward various acrylamides (Scheme 1B).

Transition metal-catalyzed carbonylation reactions represent the largest scale homogeneous catalytic reactions in industry,[10] and have been widely used in organic synthesis.[11] A plethora of value-added compounds, from commodity chemicals to pharmaceuticals, are accessible via transition metal-catalyzed hydroaminocarbonylation of alkenes,[12] alkynes,[13] and so on.[14] In particular, Pd-catalyzed hydroaminocarbonylation of substituted alkynes is well-developed, usually with high CO pressure and acid as co-catalyst (Scheme 1C).[13a–g, 14a, b] Despite all these works, related carbonylations of thesimplest and parent alkyne, acetylene, with *N*-nucleophiles have been scarce and to the best of our knowledge, only Reppe and co-workers reported the catalytic hydroaminocarbonylation of acetylene leading to acrylamides.[15] Unfortunately, this original discovery has serious limitations: acetylene was used at high pressure (> 12 atm acetylene) and high temperature (up to 180 °C), which can lead to explosive decomposition of acetylene. And the possible formed catalyst species ($Ni(CO)_4$) is extremely toxic. Furthermore, only five examples of different substrates were reported in the catalytic work.

Because of its availability and production on million ton-scale as well as its high reactivity, the functionalization of acetylene has raised significant interest in recent years, especially the production of vinyl-containing monomers as polymeric materials.[16] Besides, acetylene has also received attention in various fields of organic synthesis such as radical 1,2-difunctionalization reactions,[17] cyclizations,[18] and selective di-/tri-/polymerizations,[19] etc.[20]

At the beginning of this research project, the hydroaminocarbonylation of acetylene with 4-phenylpiperidine **1a** was chosen as a model system to develop a suitable catalyst and optimal reaction conditions. As the ligand is crucial in many carbonylation reactions, a variety of ligands were tested under conditions typical for alkyne carbonylations with amines (Table 1).[12] Initially, we used $Pd(acac)_2$ as metal precursor at 1 bar CO and 1 bar acetylene at varying temperatures.

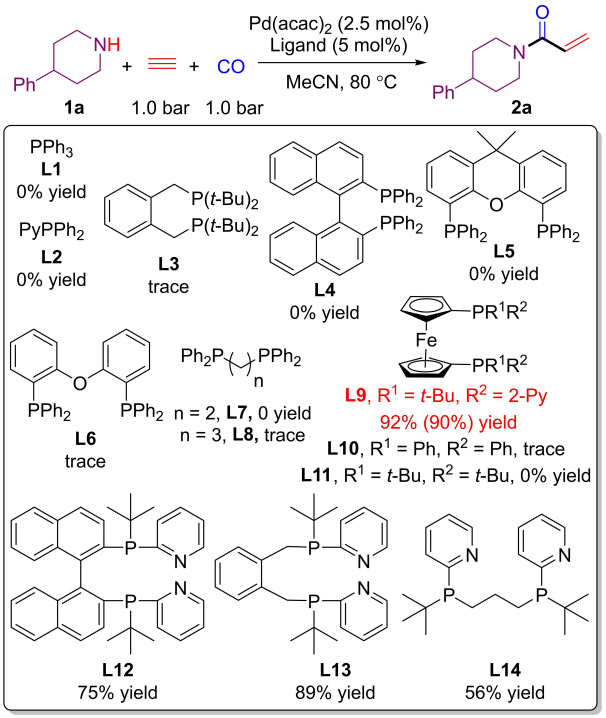
Importantly, acetylene gas poses an additional hazard to other flammable gases due to its reactivity. Hence, no pressurized acetylene was used throughout our studies. We recommend the reader to follow the general safety instructions for handling of acetylene.[21]

As shown in Table 1, both monodentate (**L1** and **L2**) and bidentate phosphine ligands (**L3** to **L8**), which have been shown to be active in several carbonylation reactions, didn't allow the reaction to proceed at 80 °C. In the past years, we have shown that incorporation of basic pyridine sites into phosphine ligands increased the reactivity of palladium-catalyzed alkoxy- and hydroxycarbonylations of olefins and dienes.[9b–e] Following this concept,[22] the desired product **2a** was obtained in high yield at 80 °C utilizing ferrocenylphosphine **L9** with a pyridinyl substituent on the phosphorus atom. The importance of the basic sites in the ligand scaffold is demonstrated by the performance of ligands **L10** and **L11**, which exhibited no activity. Using ligands **L12**, **L13** and **L14** with pyridinyl substituents on the P atom in different ligand backbones, also provided the desired product, albeit in somewhat lower yields (56 %–89 %). Apparently, the internal basic site as well as a suitable bite angle of ligand are crucial for the optimal activity in this reaction.

Next, the performance of the catalyst system $Pd(acac)_2$/**L9** was tested in other solvents such as THF, 1,4-dioxane, toluene, DMF, and heptane. In all cases, only traces or low yields of product **2a** were observed. In contrast, apart from $Pd(acac)_2$ several palladium precursors can be used in the model reaction and only $Pd(PPh_3)_4$ was detrimental to the reaction with **L9**. It didn't work at room temperature either.

With optimized conditions established for the model reaction in hand, we explored the general applicability of this hydroaminocarbonylation of acetylene gas. As shown in Figure 2, a variety of arylamines were examined at first. The electronic nature of the arylamine showed a subtle effect on the reactivity. Here, anilines with either electron-donating or electron-withdrawing substituents gave the corresponding products **2b**–**2d** in good yields (73 %–80 %). From a synthetic point of view, it is important that many reactive functional groups, such as halo **1e**–**1g**, pinacolboryl **1h**, and acetyl **1i**, were compatible with the mild reaction conditions

Table 1: Pd-catalyzed hydroaminocarbonylation of the acetylene: Variation of ligands, solvents, and palladium catalysts.[a]



Entry	Solvent[b]	Yield/%	Entry	[Pd][c]	Yield/%
1	THF	Trace	6	$Pd(OAc)_2$	82
2	1,4-Dioxane	0	7	$PdCl_2$	91
3	Toluene	5	8	$Pd(MeCN)_2Cl_2$	90
4	DMF	10	9	$Pd(PPh_3)_4$	0
5	Heptane	Trace	10[d]	$Pd(acac)_2$	0

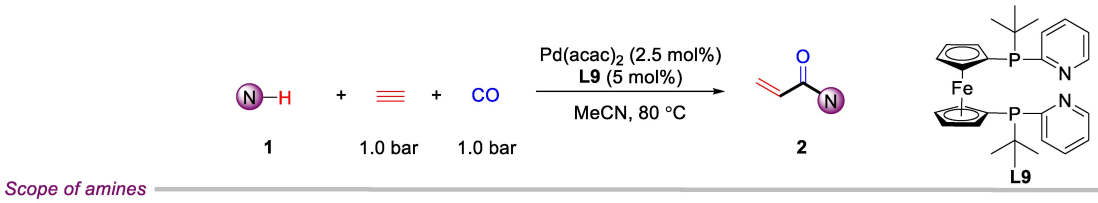
[a] Pd-catalyzed hydroaminocarbonylation of the acetylene. Yields were determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields in parentheses. Reaction conditions: **1a** (0.2 mmol), [Pd] (2.5 mol%), ligand (5 mol%), CO (1.0 bar), acetylene (1.0 bar), solvent (2.0 mL), stirred at 80 °C for 18 h. Influence of phosphine ligands: $Pd(acac)_2$ was used as palladium catalyst and MeCN was used as solvent. 2-Py = 2-pyridinyl. [b] $Pd(acac)_2$ was used as palladium catalyst and **L9** was used as ligand. [c] **L9** was used as ligand and MeCN was used as solvent. [d] Room temperature.

and generated the corresponding products (**2e**-**2i**) in 66 %–81 % yields. The reactions of aniline with substituents (**1j** and **1k**) in *ortho*- and *meta*-position proceeded smoothly, too. Next, a series of amines including primary alkylamines **1l**–**1r** and secondary ones **1s**-**1v** were tested and afforded **2l**–**2v** in up to 93 % yield. Noteworthy, cyano, pyridinyl, and vinyl groups are tolerated well in these substrates. In addition, the parent compound ammonia can be applied in this reaction, offering the acrylamide monomer **2w** with a TON of 280 without further optimization. To our surprise, the present methodology worked also well with less nucleophilic nitrogen species. Hence, amidocarbonylations and sulfonamidocarbonylation were effective to give products **2x**–**2aa** in moderate to good yields. Even the imine **1ab**, which is unstable under acidic conditions, also worked well and provided **2ab** in 76 % yield.

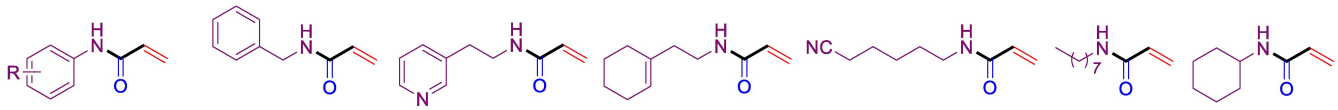
To showcase the importance of this straightforward methodology, late-stage modifications of natural and bioactive products were performed under very mild conditions, which can be of interest for many life science applications. Under standard reaction conditions, aminoglutethimide **1ac** containing glutarimide was smoothly transformed to the desired product **2ac** in 70 % yield. In addition, primary amine **1ad** as well as monoterpene amine **1ae** and diterpene amine **1af** delivered the corresponding products **2ad**-**2af** in 73 %–92 % yields. Mexiletine **1ag** and oseltamivir **1ah** are also readily converted into the corresponding products **2ag** and **2ah** in 94 % and 76 % yields, respectively. An array of bio-active acyclic secondary amines with increased steric bulk such as maprotiline **1ai**, fluoxetine **1aj**, sertraline **1ak** and cinacalcet **1al** also reacted effectively, enabling efficient access to acrylamides **2ai**-**2al** in 62 % to 95 % yields. Cyclic secondary amines bearing isoxazole **1am**, acetyl **1an**, pyridinyl **1ao** and **1ap**, piperazyl **1aq**, and hydroxyl **1ar** were tolerated well with our reaction conditions, giving products **2am**-**2ar** in moderated to excellent yields. Similarly, bridged bicyclic amines **1as** and **1at** provided products **2as** and **2at** in good yields (71 % and 84 %, respectively). Meanwhile, sulfonamide derivatives **1au** and **1av** gave the corresponding products. Furthermore, amides such metazalone **1aw** and finasteride **1ax** provided products **2aw** and **2ax** without problems. Finally, this method was successfully applied to synthesize ibrutinib **2ay** as well as osimertinib **2az**.

Because of the relatively mild reaction conditions and the broad synthetic applicability mentioned above, we thought that our reaction protocol might allow chemoselective acylation of molecules with multiple nucleophilic centers. Based on previous studies about chemoselective carbonylation of aryl aminoalcohols,[12f,i] we tested the selective "acrylation" of aminoalcohols (Figure 3). Obviously, such substrates can react both at the *N*-nucleophile and *O*-nucleophile. Gratifyingly, acrylamide **4a** is obtained in 75 % yield and good chemoselectivity (10 : 1). Similarly, L-phenylalaninol **3b** and L-leucinol **3c** worked well providing **4b** and **4c** in acceptable yields and good chemoselectivity (10 : 1 and 5 : 1).

According to our previous work[9e,14b] as well as the mechanism studies of Drent, Cole-Hamilton, Sparkes, Dyson and Guan,[12f, 22, 23] it is most likely that this reaction goes through the so-called palladium hydride mechanism shown in Scheme 2A. To investigate competing pathways the palladium-catalyzed hydroamination of acetylene was performed separately (Scheme 2B). In this case, no conversion is observed which indicates that apart from the ligand also CO may play a vital role in the formation of palladium hydride complex **A**. And this reaction can work well under strictly anhydrous conditions. Base on previous studies,[13b,24] palladium hydride complex **A** may be formed in the presence of the *N*-nucleophile (see SI). It is likely that palladium hydride complex **A** is in equilibrium with the *N*-protonated pyridinium complex **A′**.[9e,14b] Acetylene coordinates to complex **A** or **A′** and insertion of acetylene furnishes intermediate **B**, which could be converted into complex **C** through the CO coordination. Followed by

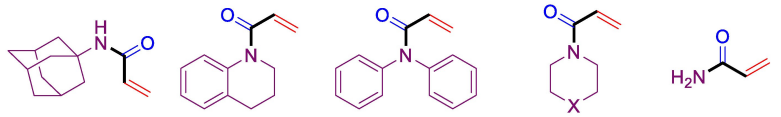


Scope of amines



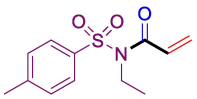
2b, R = 4-H, 80%
2c, R = 4-OMe, 74%
2d, R = 4-CF_3, 73%
2e, R = 4-Cl, 66%
2f, R = 4-Br, 81%
2g, R = 4-I, 72%
2h, R = 4-Bpin, 72%
2i, R = 4-Acetyl, 75%
2j, R = 3-Me, 70%
2k, R = 2-Cl, 61%

2l, 84% **2m**, 48% **2n**, 82% **2o**, 90% **2p**, 78% **2q**, 89%



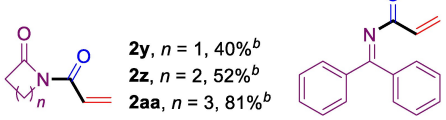
2r, 84% **2s**, 93%[b] **2t**, 43%[b] **2u**, X = O, 53% **2v**, X = S, 83% **2w**, 280 TON[c]

Sulfonamides



2x, 56%[b]

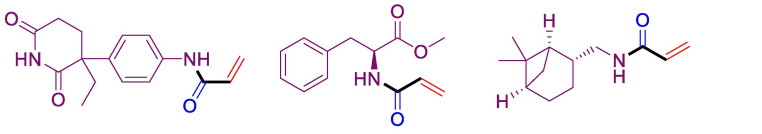
Amides, imine



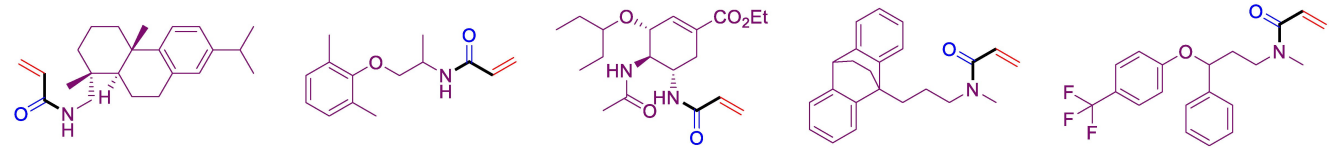
2y, *n* = 1, 40%[b]
2z, *n* = 2, 52%[b]
2aa, *n* = 3, 81%[b]

2ab, 76%[b]

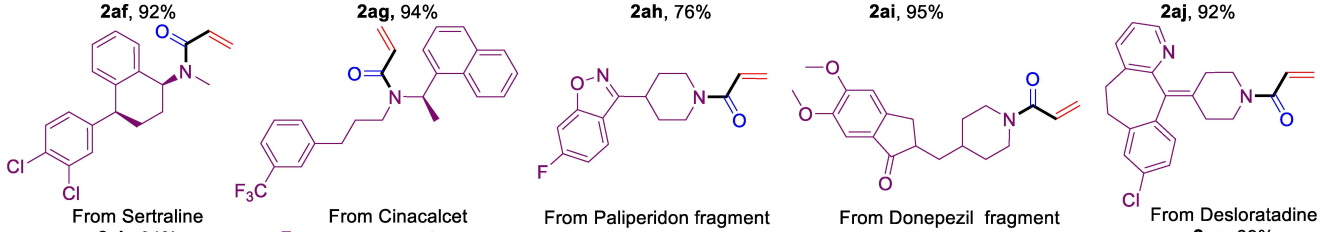
Scope of complex substrates



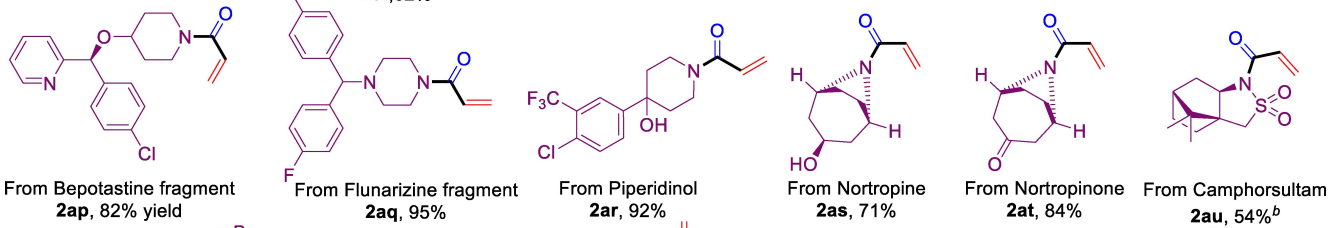
From DL-Aminoglutethimide **2ac**, 70% yield
From Phenylalanine **2ad**, 75% yield
From (-)-*cis*-Myrtanylamine **2ae**, 73%



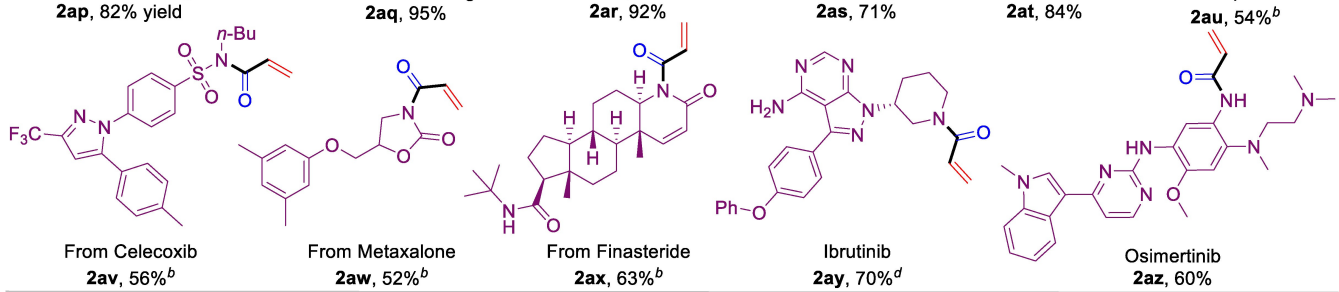
From (+)-Dehydroabietylamine **2af**, 92%
From Mexiletine **2ag**, 94%
From Oseltamivir **2ah**, 76%
From Maprotiline **2ai**, 95%
From Fluoxetine **2aj**, 92%



From Sertraline **2ak**, 91%
From Cinacalcet **2al**,62%[b]
From Paliperidon fragment **2am**, 55%
From Donepezil fragment **2an**, 90%
From Desloratadine **2ao**, 89%



From Bepotastine fragment **2ap**, 82% yield
From Flunarizine fragment **2aq**, 95%
From Piperidinol **2ar**, 92%
From Nortropine **2as**, 71%
From Nortropinone **2at**, 84%
From Camphorsultam **2au**, 54%[b]



From Celecoxib **2av**, 56%[b]
From Metaxalone **2aw**, 52%[b]
From Finasteride **2ax**, 63%[b]
Ibrutinib **2ay**, 70%[d]
Osimertinib **2az**, 60%

Figure 2. [a] Reaction conditions: $Pd(acac)_2$ (2.5 mol%), **L9** (5 mol%), **1** (0.2 mmol), CO (1.0 bar), acetylene (1.0 bar), MeCN (2.0 mL), stirred at 80 °C for 18 h. Isolated yields. [b] CO (10.0 bar) was used at 120 °C for 14 h. [c] Ammonia gas (1.0 bar) was used at 100 °C. [d] stirred at 70 °C for 14 h.

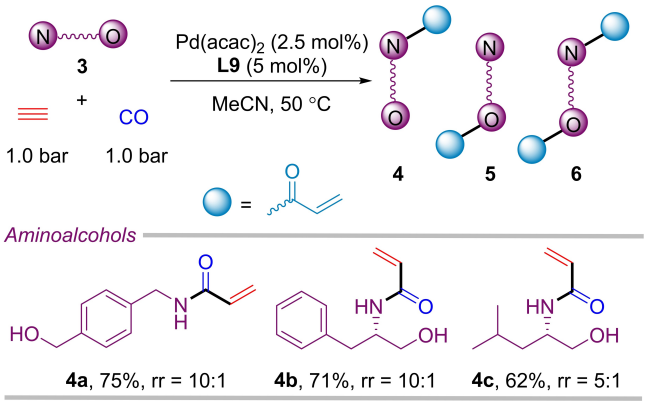
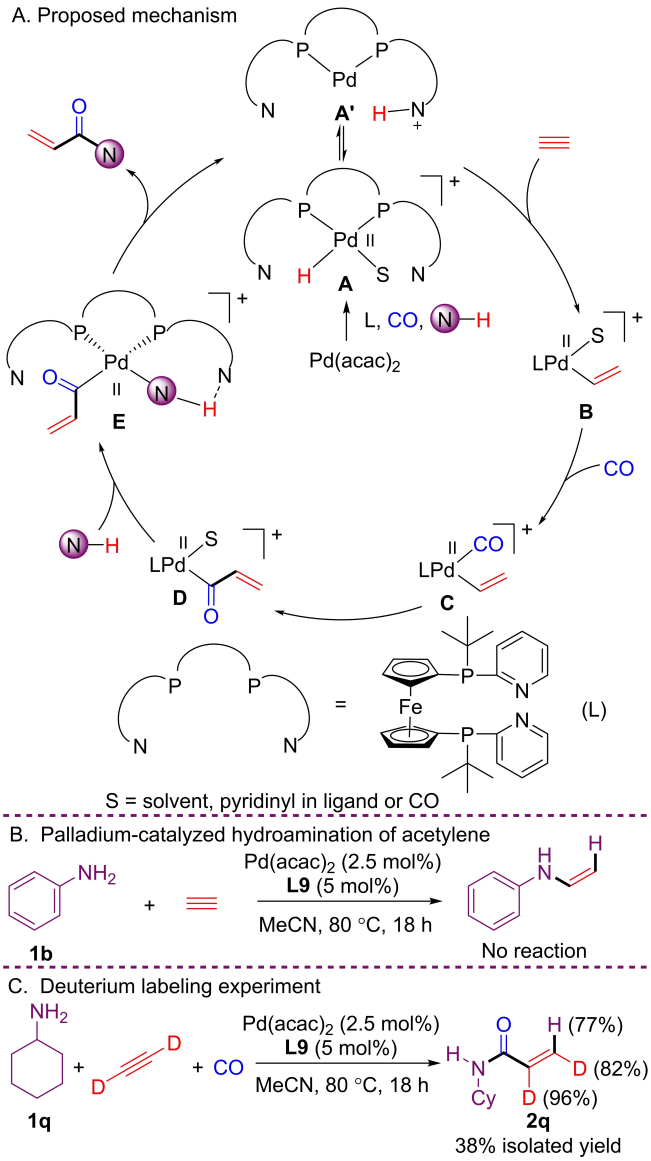


Figure 3. Chemoselective carbonylation of selected aminoalcohols. Reaction conditions: $Pd(acac)_2$ (2.5 mol%), **L9** (5 mol%), **3** (0.2 mmol), CO (1.0 bar), acetylene (1.0 bar), MeCN (2.0 mL), stirred at 50 °C for 9 h. Chemoselectivity rr = **4**/(**5** + **6**), determined by ^1H NMR.

insertion of CO, complex **D** could be obtained. Finally, *N*-assisted aminolysis results in the desired acrylamide and regenerates the active palladium hydride complex **A′**. Besides, there is another possible mechanism in which Pd–H does not play a key role (see SI). A deuterium labeling experiment showed *syn*-addition of acetylene with the palladium hydride species (Scheme 2C), thereby precluding a direct nucleophilic addition reaction of possible existing Pd(II)-acetylene complexes.

In conclusion, we have developed the first palladium-catalyzed hydroaminocarbonylation of acetylene towards acrylamides. The presented methodology does not need any specific additives and proceeds at mild reaction conditions. It exhibits high functional group tolerance, good chemoselectivity, and high atom efficiency. The straightforward synthesis of important drugs including ibrutinib, osimertinib, and other various biologically active molecules demonstrates the synthetic utility of this method. This protocol provides other valuable acrylamide-containing building blocks for modern organic synthesis and complements the currently known carbonylative methodologies.



Scheme 2. A. Proposed mechanism B. Palladium-catalyzed hydroamination of acetylene. C. Deuterium labeling experiment.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Carbonylation · Acetylene · Acrylamides · Palladium · Chemoselectivity

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5.2 Palladium-Catalyzed Four-Component Carbonylation of Acetylene: Efficient Synthesis of *β*-Perfluoroalkyl Acrylamides

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Author contributions:

In this paper, I performed all the experiments, and wrote an original draft of the manuscript. My contribution as the first author of this paper is approximately 80%.

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Palladium-Catalyzed Four-Component Carbonylation Reactions of Acetylene: Synthesis of β-Perfluoroalkyl Acrylamides

Zhusong Cao,[a] Qiang Wang,[a] Helfried Neumann,*[a] and Matthias Beller*[a]

The simplest alkyne, acetylene, is a suitable C2 linker synthon that enables the connection of organic molecules with different functional groups. However, reactions of acetylene with advanced organic building blocks are much less explored compared to substituted alkynes. In this article, we present a straightforward palladium-catalyzed four-component carbonylation reaction with acetylene, CO, amines, and perfluoroalkyl halides that enables the preparation of various β-perfluoroalkyl acrylamides in one step. This protocol also provides a new strategy for the late-stage modification of bioactive molecules, as demonstrated by the construction of β-perfluoroalkyl ibrutinib derivatives.

Introduction

Covalent drugs have been used successfully for more than a century to treat a wide range of diseases. They are essentially made up of two main parts: the binding guidance system and the reactive group or so-called warhead.[1] As one of the popular warheads of covalent drugs, acrylamides have been widely applied in many drugs such as ibrutinib, osimertinib, afatinib, and adagrasib (Figure 1).[1] A general advantage of covalent inhibitors is their enhanced potency, which means that drugs can be delivered in lower and less frequent doses. Thus, the development of covalent drugs is still a growing area of drug discovery. Consequently, modification of the acrylamide unit in covalent drugs has the potential to identify improved bio-active compounds. In this respect, introducing a fluorinated motif into the acrylamide part of bio-active molecules can be interesting due to their unique physical and chemical properties. It is well-known that the exchange of C–H bonds by C–F bonds has significant influence on biological properties including altered reactivity, lipophilicity, and metabolic stability.[2] Hence, organofluorine compounds play an important role in many pharmaceuticals, agrochemicals, and special materials.[3]

Since the original work in the 1950s, the iodoperfluoroalkylation of alkynes has been generally developed by several research groups.[4] As a result, nowadays various β-perfluoroalkyl vinyl iodides are accessible by this method, which can be subsequently functionalized by cross-coupling reactions.[5] Interestingly, few related three-component coupling reactions are known to construct perfluoroalkylated trisubstituted alkenes in one step. For example, palladium-catalyzed carboperfluoroalkylations of alkynes with perfluoroalkyl iodides (or iododifluoroacetate) and arylboronic acids, were reported by the groups of Nevado, Liang, and Chaładaj.[6]

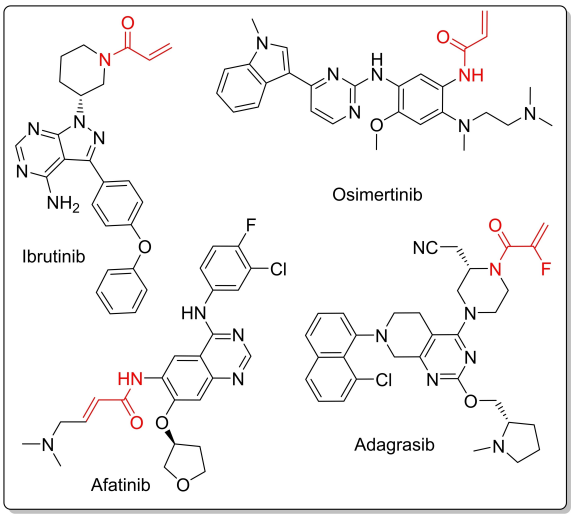

Figure 1. A selection of acrylamide-containing covalent drugs.

Complementary to transition metal-catalyzed coupling reactions, related carbonylations permit the synthesis of various carboxylic acid derivatives.[7] Among them, transition metal-catalyzed carbonylative reactions of alkenes[8] and alkynes[9] have emerged as a straightforward tool for the synthesis of perfluoroalkyl-containing compounds. Notable developments include palladium-catalyzed domino perfluoroalkylation/carbonylation reactions of alkynes with various nucleophiles such as alcohols, amines, arylboronic acids, and alkynes (Figure 2A).[9] Despite all these works, to the best of our knowledge the

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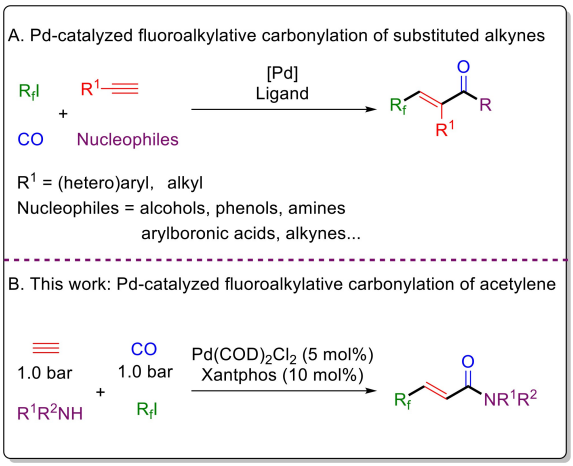


Figure 2. Pd-catalyzed perfluoroalkylative carbonylation of substituted alkynes and acetylene.

carbonylative coupling reactions of the simplest alkyne, acetylene, have not been reportedyet.

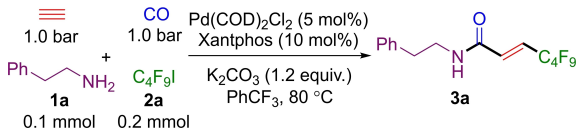
Unlike most (di)substituted alkynes, acetylene is an abundant chemical feedstock with annual production exceeding one million tons.[10] Acetylene is used extensively in the production of vinyl-containing monomers for polymeric materials, but has also recently attracted attention in organic synthesis, particularly in cyclizations,[11] 1,2-difunctionalization reactions,[12] and selective di-/tri-/polymerizations,[13] etc.[14]

Based on our long-standing interest in carbonylation catalysis, we recently disclosed an efficient palladium-catalyzed hydroaminocarbonylation of acetylene, offering a wide range of bio-active compounds containing the acrylamide motif.[15] Here, we report the follow-up project of this work: straightforward palladium-catalyzed four-component carbonylation of acetylene to provide β-perfluoroalkyl acrylamides in moderate to good yields (Figure 2B).

Results and Discussion

We started our studies by selecting commercially available phenethylamine **1a**, *n*-perfluorobutyl iodide **2a** (C_4F_9I) as the coupling partners for the carbonylation of acetylene. As shown in Table 1, the combination of palladium precursor $Pd(COD)Cl_2$ (5 mol%) with Xantphos ligand (10 mol%) in the presence of base (K_2CO_3) in benzotrifluoride at 80 °C afforded the desired fluorinated acrylamide **3a** in 68% isolated yield (entry 1). When using mono-phosphine PPh_3, the product yield dropped dramatically (entry 2). Similarly, the use of bidentate ligands such as BINAP, DPPP and DPPF instead of Xantphos significantly reduced the yield of product **3a** (entries 3–5). Among the different palladium precursors tested, other complexes such as $Pd(OAc)_2$, $PdCl_2$, $Pd(PPh_3)_4$ and $Pd(dba_3)_2$ were slightly less effective than $Pd(COD)Cl_2$ (entries 6–9). Changing K_2CO_3 to Na_2CO_3, Cs_2CO_3, K_3PO_4 resulted in lower yields, too (entry 10). Interestingly, the solvent plays a decisive role in the model

Table 1. Four-component model reaction: Optimization of reaction conditions[a].



Entry	Variations from standard conditions	Yield/%[b]
1	None	71 (68)
2	PPh_3 instead of Xantphos	25
3	BINAP instead of Xantphos	16
4	DPPP instead of Xantphos	5
5	DPPF instead of Xantphos	43
6	$Pd(OAc)_2$ instead of $Pd(COD)Cl_2$	70
7	$PdCl_2$ instead of $Pd(COD)Cl_2$	66
8	$Pd(PPh_3)_4$ instead of $Pd(COD)Cl_2$	58
9	$Pd_2(dba)_3$ instead of $Pd(COD)Cl_2$	59
10	Na_2CO_3, Cs_2CO_3, K_3PO_4 instead of K_2CO_3	57–67
11	MeCN, 1,4-Dioxane, DMF instead of $PhCF_3$	0–53

[a] Standard reaction conditions: $Pd(COD)Cl_2$ (5 mol%), Xantphos (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphane) (10 mol%), **1a** (0.1 mmol), **2a** (0.2 mmol), K_2CO_3 (1.2 equiv.), CO (1.0 bar), acetylene (1.0 bar), $PhCF_3$ (1.5 mL), stirred at 80 °C for 18 h. [b] Yield was determined by ^1H NMR with 1,1,2,2-tetrachloroethane as internal standard. Isolated yield in parentheses. BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; DPPE: 1,2-bis(diphenylphosphino)ethane; DPPP: 1,3-bis(diphenylphosphino)propane. DPPF: 1,1′-ferrocenediyl-bis(diphenylphosphine).

reaction, and all other evaluated solvents such as MeCN, 1,4-dioxane, or DMF, gave inferior product yields (entry 11).

Next, some control experiments were carried out to demonstrate that all components are necessary to achieve activity, and to understand the order of the different reaction steps. Without acetylene, no formation of the corresponding amide is observed, which is explained by the polarity mismatch between the perfluoroalkyl radical and CO (Figure 3A). Similarly, no reaction took place between acetylene, **1a**, and **2a** without CO, indicating that reductive elimination cannot occur without CO (Figure 3B). In both cases, the only product detected was formed via the addition of perfluoroalkyl radical across benzotrifluoride. Applying the optimal conditions for the direct iodoperfluoroalkylation of acetylene, the corresponding β-perfluoroalkyl vinyl iodide was obtained in very low yield (Figure 3C). This latter experiment demonstrates that β-perfluoroalkyl acrylamides are likely not formed from β-perfluoroalkyl vinyl iodide. Based on the control experiments and previous studies,[8,9] we propose the following mechanism shown in Figure 3D for this reaction: Initially, a Pd(0) phosphine complex **A** is formed from the Pd(II) precursor in the presence of an excess amount of ligand. Then, species **A** activates the perfluoroalkyl iodide via a single electron transfer (SET) reduction, resulting in formation of fluoroalkyl radical **B** and Pd(I) complex **C**. After radical addition of the perfluoroalkyl radical **B** to acetylene, the vinyl radical **D** is afforded. Subsequently, this vinyl radical **D** is trapped by the palladium

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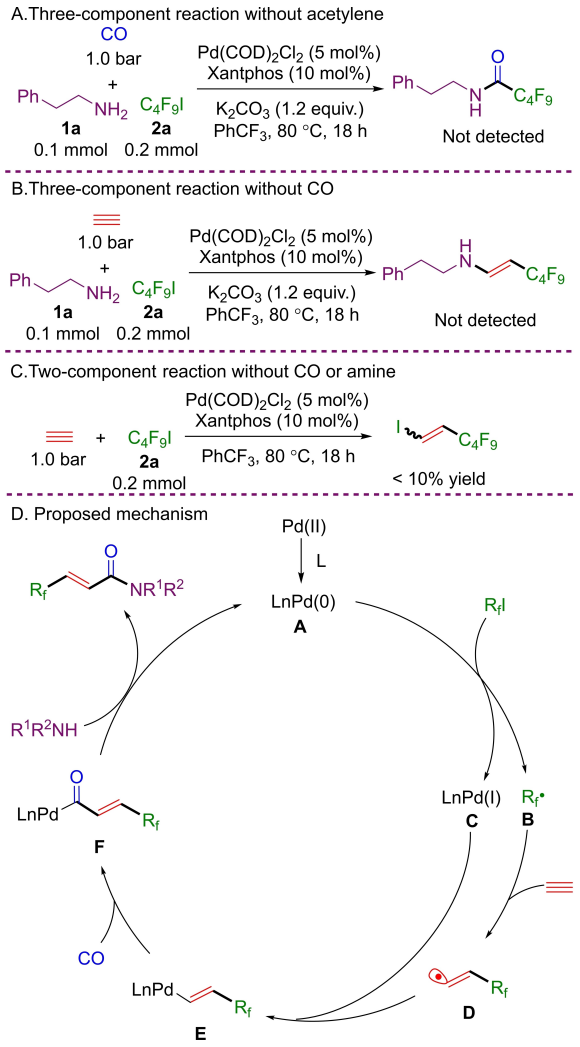

Figure 3. Four-component model reaction: Control experiments and proposed mechanism.

complex **C** to afford intermediate **E**, which undergoes coordination and insertion of carbon monoxide to provide the acyl complex **F**. Finally, the acyl complex **F** reacts with the amine to form the desired β-perfluoroalkyl acrylamide product and regenerates Pd(0) complex **A**.

With optimized conditions for this four-component aminocarbonylation in hand, we then explored the reaction of acetylene with a variety of amines **1** and perfluorobutyl iodide **2a** under 1 bar of CO. As shown in Figure 4, alkylamines (**1a**–**1c**) with the gradually increasing steric bulk, are easily converted into the corresponding products **3a**–**3c** in decent yields (61%–68%). Primary amine **1d** and secondary amine **1e** also reacted smoothly, providing the corresponding products **3d** and **3e** in moderate yields (62% and 65%, respectively). Aniline **1f** as well as 4-methylaniline **1g** and 4-fluoroaniline **1h** were also tested and gave the desired products **3f**–**3h**. To demonstrate the synthetic utility of this protocol, we applied this protocol for the diversification of bio-active molecules. Initially, amino acid derivatives **1i** and **1j** afforded products **3i** and **3j** in 66% and 60% yields, respectively. The terpene-based

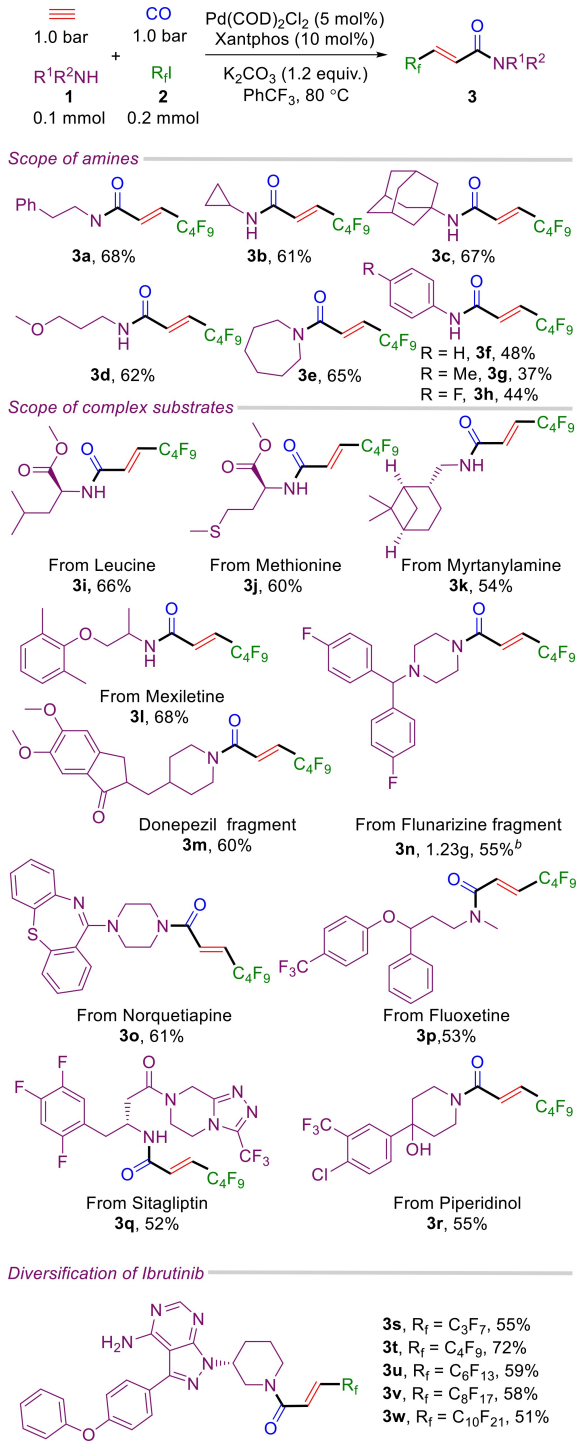

Figure 4. Scope of the palladium-catalyzed four-component carbonylation reaction. a. Reaction conditions: $Pd(COD)Cl_2$ (5 mol%), Xantphos (10 mol%), **1** (0.1 mmol), **2** (0.2 mmol), K_2CO_3 (1.2 equiv.), CO (1.0 bar), acetylene (1.0 bar), $PhCF_3$ (1.5 mL), stirred at 80 °C for 18 h. Isolated yields. b. 4 mmol **1n** was used.

amine **1k** and mexiletine **1l** were readily converted into corresponding products **3k** and **3l** in moderate yields. The donepezil fragment **1m** bearing a keto group was compatible with the reaction conditions, giving product **3m** in 60% yield. To our delight, the reaction proceeded at a 40-fold scale-up and

provided **3n** in 55% yield. When using the piperazinyl-containing norquetiapine **1o** as substrate, the corresponding product **3o** was obtained in decent yield, indicating that the imine group is also tolerated under our reaction conditions. The secondary amine fluoxetine **1p** also performed well. Notably, the presented methodology also tolerated triazole and hydroxyl groups, and the corresponding products **3q** and **3r** were obtained from sitagliptin **1q** and piperidinol **1r**. Finally, this novel methodology was successfully applied to late-stage modification of ibrutinib, providing diverse perfluoroalkyl-containing ibrutinib derivatives **3s**–**3w** in 51%–72% yields. This highlights the potential utility of this method in organic synthesis.

Conclusions

In conclusion, we have developed a novel palladium-catalyzed four-component carbonylation reaction of acetylene. The presented protocol allows the synthesis of different β-perfluoroalkyl acrylamides under mild reaction conditions. The methodology tolerates various functional groups and the synthetic utility of this one-pot transformation was showcased in the late-stage functionalization of bio-active molecules such as ibrutinib.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Carbonylation · Palladium · Acetylene · Acrylamide · Perfluoroalkylation

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5.3 Regiodivergent Carbonylation of Alkenes: Selective Palladium-Catalyzed Synthesis of Linear and Branched Selenoesters

Zhusong Cao, Qiang Wang, Helfried Neumann, and Matthias Beller

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Author contributions:

In this paper, I finished the optimization of reaction conditions, investigation of substrate scope and writing the manuscript. My contribution as the co-first author of this paper is approximately 45%.

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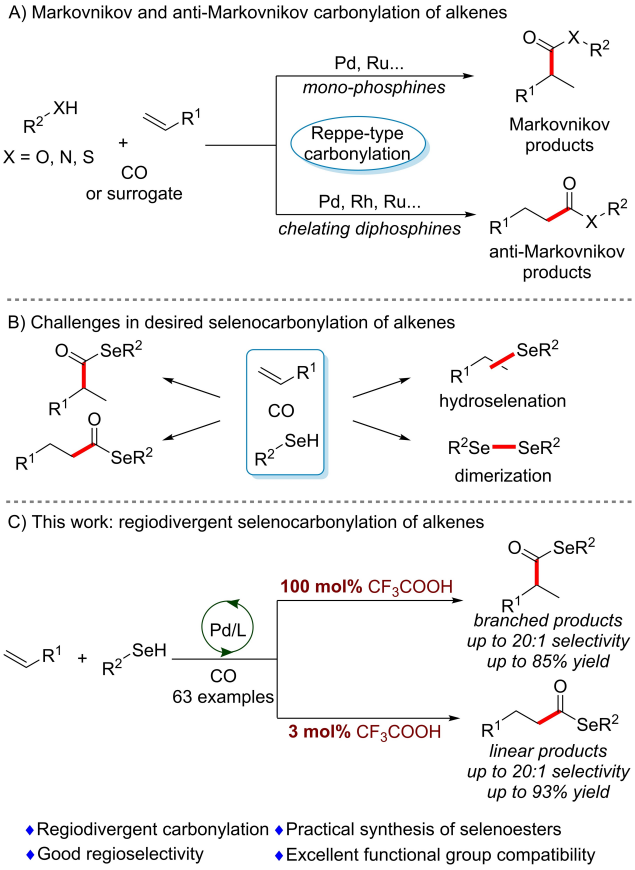
Carbonylation

Regiodivergent Carbonylation of Alkenes: Selective Palladium-Catalyzed Synthesis of Linear and Branched Selenoesters

Zhusong Cao[+], Qiang Wang[+], Helfried Neumann, and Matthias Beller**

Abstract: An unprecedented regiodivergent palladium-catalyzed carbonylation of aromatic alkenes has been developed. Utilizing commercially available Pd-$(CH_3CN)_2Cl_2$ in the presence of 1,1′-ferrocenediyl-bis(*tert*-butyl(pyridin-2-yl)phosphine) ligand **L8** diverse selenoesters are obtained in a straightforward manner. Key to success for the control of the regioselectivity of the carbonylation step is the concentration of the acidic co-catalyst. This general protocol features wide functional group compatibility and good regioselectivity. Mechanistic studies suggest that the presence of stoichiometric amounts of acid changes the properties and coordination mode of the ligand leading to reversed regioselectivity.



Scheme 1. Transition-metal-catalyzed regioselective carbonylation of alkenes: background and development.

Introduction

Transition metal-catalyzed carbonylation reactions represent the largest scale processes in the chemical industry utilizing molecularly defined organometallic complexes. They offer a powerful toolbox of reactions for the synthesis of numerous value-added bulk and fine chemicals.[1,2] Among these reactions, palladium-catalyzed carbonylation of alkenes with various nucleophiles such as H_2O[3] and alcohols (O-nucleophiles),[4] amines[5] and amides (N-nucleophiles)[6] and thiols (S-nucleophiles)[7] have been extensively investigated and allow a direct synthesis of valuable carboxylic acid derivatives.

As shown in Scheme 1A, such carbonylation of alkenes can lead to two regioisomeric linear (*l*) and branched (*b*) isomers, which are of interest for different applications. Hence, significant efforts have been devoted to control the *l*:*b* ratio by development of specific catalysts/ligands. Indeed, the complementary catalyst systems have been established for hydroformylation,[8] hydrocarboxylation,[3a,d,e] alkoxycarbonylation,[4d–f] aminocarbonylation[5b–i] and thiocarbonylation[7b,c,e] of aromatic olefins, which allow the selective formation of both regiodivergent products. In general, in these processes, the regioselectivity is mainly controlled by changing the type of ligands (mono-phosphine: branched products, bidentate chelating phosphines: linear products).

To the best of our best knowledge, the direct regiodivergent carbonylation of alkenes with the same metal catalyst and ligand to give linear or branched carboxylic acid derivatives has not been achieved yet. Apart from being scientifically interesting from a fundamental point of view, such methodology would allow to switch the selectivity of the respective reaction on demand, which offers the

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possibility to achieve any desired regioselectivity with the same catalyst system.

Based on our general interest in the development of novel and improved carbonylation processes,[9a–d] recently we became interested in studying alkene carbonylations with selenols as nucleophiles. Compared to the more common thiocarbonylation of alkenes, selenocarbonylation are much less explored and challenging, since selenols have much smaller bond dissociation energy than thiols ($C_6H_5Se–H$ and $C_6H_5S–H$ are 67–74 kcal/mol and 79 kcal/mol, respectively).[10] Thus, selenols tend to dimerize and direct hydroselenation of alkenes also occurs easily (Scheme 1B).[11]

On the other hand, selenoesters are underexplored building blocks in synthetic organic chemistry, which can be applied as designed acyl-transfer agents for the synthesis of complex natural products, such as ent-(−)-Roseophilin,[12a] (+)-Geissoschizine,[12b] (−)-Pseudolaric Acid B,[12c] Crinipellin A[12d] and so on. Due to their more reactive properties than thioesters, selenoesters have gained attention for the development of chemoselective and efficient diselenide selenoester ligation (DSL) for the synthesis of proteins.[12] In addition, small molecules containing selenoesters also showed potential pharmacological activity.[14] In addition to carbonylation of aryl/alkenyl iodides for synthesis of selenoesters,[15a–c] the most common methodologies for the preparation of selenoesters are based on the nucleophilic acyl substitution of acyl (pseudo) halides with appropriate selenium sources.[15d] Obviously, such transformations encounter drawbacks, such as harmful preparation of (pseudo) halides and low atom economy. In contrast, we wondered whether the direct selenocarbonylation of alkenes could provide a more straightforward tool for synthesis of this class of compounds.

Herein, we describe the first catalytic selenocarbonylation of alkenes with selenols utilizing an advanced palladium catalyst with built-in base. Based on the concentration of the acidic co-catalyst, the formation of branched and linear selenoesters can be easily controlled, thereby achieving a regiodivergent synthesis with the same catalyst system (Scheme 1C).

Results and Discussion

At the beginning of our studies, styrene **1a** and phenylselenol **2a** were chosen as model substrates to develop an optimal catalyst system and suitable reaction conditions. As the ligand is crucial for controlling the selectivity and activity in many carbonylation reactions, a variety of ligands were evaluated under conditions typical for olefin carbonylations with other nucleophiles. Specifically, we used $Pd(MeCN)_2Cl_2$ as metal precursor and PTSA·H_2O (*p*-toluenesulfonic acid monohydrate) as acidic co-catalyst at 40 bar CO and 100 °C. As shown in Figure 1A, neither monodentate phosphine ligands (**L1**, **L2** and **L3**) nor bidentate ligands (**L4** and **L5**), which are known to be active in other carbonylations, allowed the reaction to proceed. In all these cases, only the unwanted hydroselenation product or diselenide were

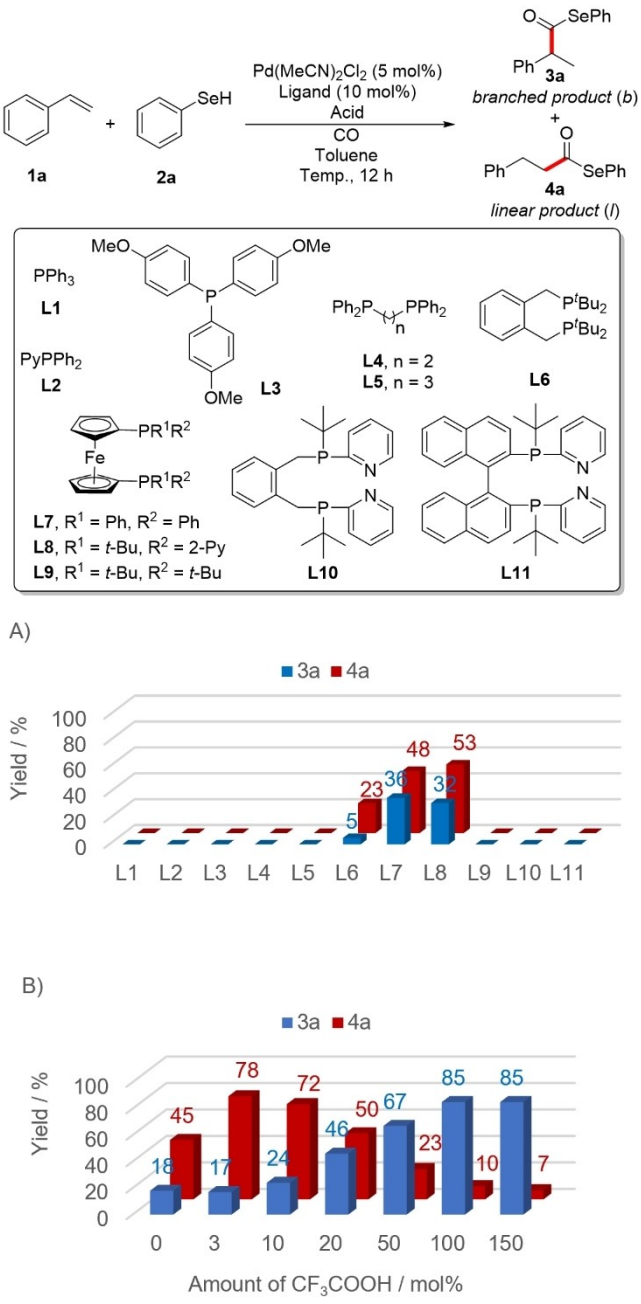


Figure 1. Palladium-catalyzed selenocarbonylation of alkene **1a** with selenol **2a**. A) Influence of ligands. Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Pd(MeCN)_2Cl_2$ (5 mol%), ligand (10 mol%), PTSA·H_2O (10 mol%), CO (40 bar), toluene (1.5 mL), stirred at 100 °C for 12 h. $PyPPh_2$, Py = 2-pyridyl. B) Influence of different amount of TFA (trifluoroacetic acid). Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Pd(MeCN)_2Cl_2$ (5 mol%), **L8** (10 mol%), TFA (x mol%), CO (40 bar), toluene (1.5 mL), stirred at 75 °C for 12 h. Yields and regioselectivities were determined by ^1H NMR and GC.

observed as major products. Interestingly, the bidentate phosphine ligand **L6** showed some activity, albeit the isomeric selenoesters are obtained in poor yields. To our delight, DPPF **L7** was found to generate a highly active catalyst system for this reaction giving 84% yield of selenoesters. Unfortunately, both isomers were achieved in

poor regioselectivity (b:l = 1:1.3). Notably, following built-in-base concept,[9] the yield and regioselectivity of the reaction increased when ferrocenylphosphine **L8** with a pyridyl substituent on the phosphorus atom was used. The related ferrocenylphosphine **L9** with bis-*tert*-butyl substitutents on the phosphine exhibited no activity. Similarly, using ligands **L10** and **L11** with modified backbone, the desired product was not obtained. This clearly indicates that both a suitable bite angle of the diphosphine ligand as well as an internal basic site are crucial for activity and selectivity in this reaction. Next, applying **L8** as the optimal ligand, different acidic co-catalysts were tested. This study revealed that the yield of the linear product **4a** is increased to 78 % with 3 mol % TFA at 75 °C (see SI).

Interestingly, we found that the regioselectivity of the reaction can be switched by changing the acid concentration. More specifically, the yield and regioselectivity of the branched product **3a** were improved with increasing amount of TFA. For example, when one equivalent of TFA was employed, the yield of branched product **3a** is improved to 85 % and high branched regioselectivity (b:l = 8.1:1) was observed. Adding more acid did not improve the yield of branched product **3a** anymore, but the regioselectivity was increased further on (Figure 1B).

With an optimal catalyst system and optimized reaction conditions for both branched products and linear products in hand, we explored the generality of this surprising regiodivergent effect. As shown in Table 1, a variety of styrenes with different substituents on the aromatic rings showed a similar behavior. Using a high concentration of the acidic co-catalyst, the corresponding branched selenoesters were obtained preferentially.

Styrenes containing electron-donating substituents were efficiently converted into products **3a**–**3d** with good regioselectivities and yields (62 %–85 %). In case of **3b**, the regioselectivity is improved up to >20:1 with 55 mol % of TFA. For styrenes with electron-withdrawing substituents (F, Cl, Br, CF_3), the branched products were generated in moderate yields and regioselectivities. Using substrates **1i** and **1j**, the branched selenoesters are achieved in moderate to good yields (54 % and 83 % yield, respectively) and good regioselectivities (b/l = 3.9:1, 6.0:1, respectively). The reactions of styrenes with substituents in *ortho*- and *meta*-positions proceeded smoothly, too, affording the corresponding products (**3k** and **3l**) in moderate yields and good regioselectivities. Furthermore, 2-vinylnaphthalene and 2-vinylthiophene gave the desired products (**3m** and **3n**) without problems.

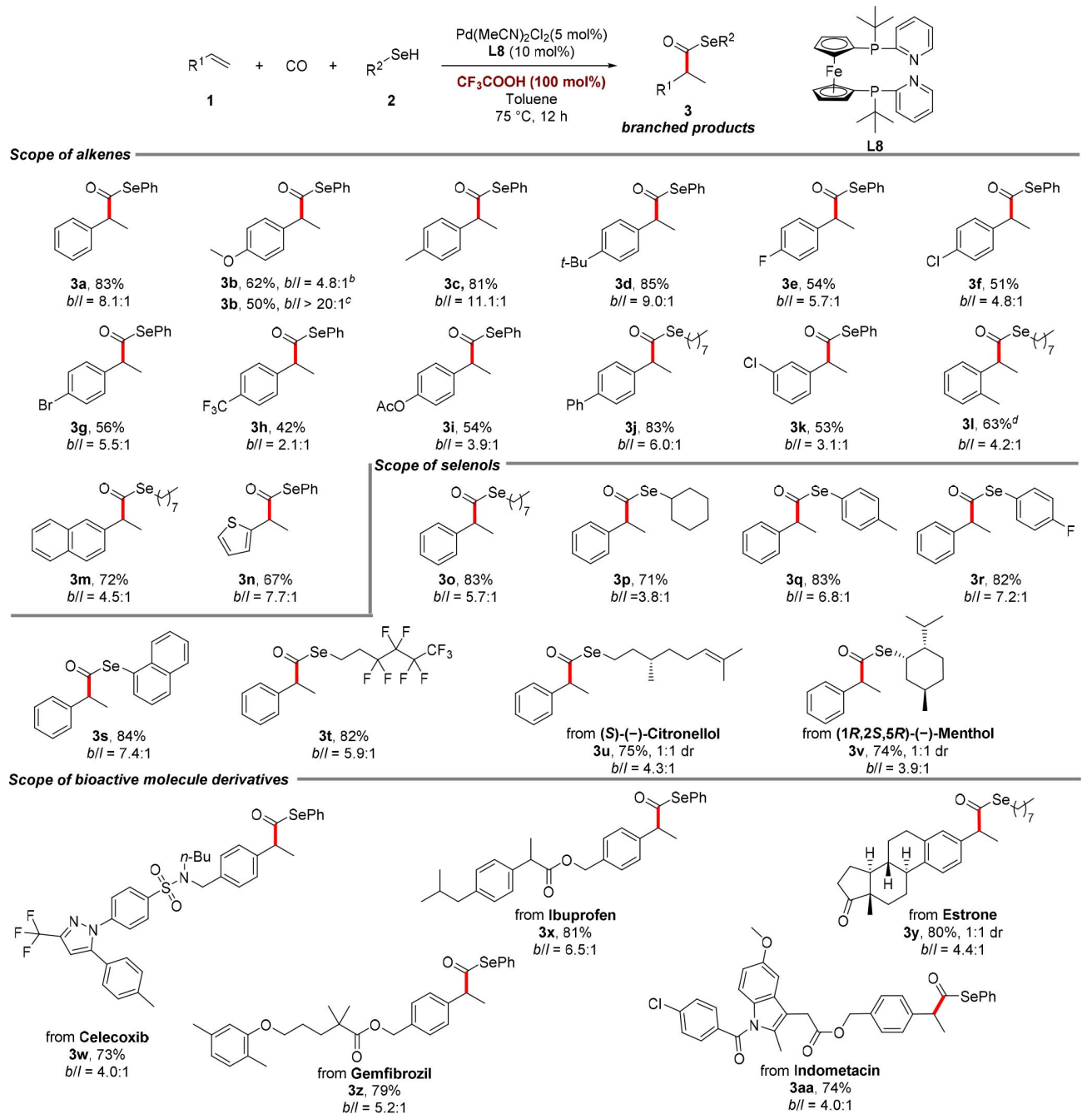
In addition, a wide range of selenols were successfully applied in these transformations, besides primary (**2o**) and secondary alkylselenols (**2p**), arylselenols (**2q**–**2s**) were readily converted into the corresponding selenoesters (**3o**–**3s**) in good yields (71 %–84 %) and regioselectivities (up to 7.4:1). The selenol containing a fluoroalkyl group (**3t**) also performed well. In addition, selenol derivatives from citronellol and menthol afforded the desired products (**3u** and **3v**) with good yields and regioselectivities. Notably, structurally complex substrates (derivatized from drugs and natural products) were well accommodated under the benchmark reaction conditions, with products **3w**–**3aa** being afforded in good yields (73 %–81 %) and regioselectivities (4.0:1–6.5:1).

After demonstrating that it is possible to achieve a variety of branched selenoesters, we studied the scope for the synthesis of the corresponding linear products. As illustrated in Table 2, both electron-donating and electron-withdrawing substituents on the phenyl rings gave the corresponding linear products **4a**–**4h** in moderate to good yields and regioselectivities. Styrenes with *para*-acetyl and -phenyl substituents provided the linear products **4i** and **4j** in good yields and regioselectivities as well as styrenes with other substituents in *ortho*- and *meta*-positions (**4k** and **4l**). Furthermore, 2-vinylnaphthalene and 2-vinylthiophene also worked and afforded **4m** and **4n**. Meanwhile, aliphatic alkenes including many reactive functional groups, e.g. trimethylsilyl, bromide, cyano, carboxyl, Bpin and internal vinyl group, gave the desired linear products **4o**–**4w** with high regioselectivities (up to >20:1) and yields (70 %–93 %). It is worth mentioning that this methodology can be applied to perform highly selective diselenocarbonylation of 1,7-octadiene to provide 1,8-diselenoester **4w** in 86 % yield.

Various alkyl and aryl selenols, including fluorinated ones, were successfully applied to the reaction and the corresponding selenoesters **4x**–**4ac** are provided in moderate to good yields (59 %–82 %) and good regioselectivities (3.2:1–6.7:1). Furthermore, two selenol derivatives from citronellol and menthol were transformed into the corresponding linear products **4ad**–**4ae** with good yields (76 % and 78 % yield) and regioselectivities (6.1:1 and 6.8:1), respectively. Finally, these selective linear transformations were applied to the functionalization of more advanced bioactive styrene derivatives such as celecobix, ibuprofen, estron, gemfibrozil and indometacin, and delivered the target products (**4af**–**4aj**) with 64 % to 81 % yield and 3.4:1 to 5.8:1 l/b ratio.

To understand this regiodivergent carbonylation process, control experiments with the model system utilizing **L8** were performed in the presence of 100 mol % TFA. So far, this ligand has been reported in alkoxycarbonylations to give selectively the respective linear products.[9d] In contrast, we mainly obtained the other regioisomers. Thus, we conducted a Hammett analysis (Figure 2A) for several *para*-substituted styrenes. The plot of log(b/l) values versus Hammett σ_p values showed a linear correlation between regioselectivity and the electronic effect of the *para*-substituent on the styrene. The negative slope of the plot indicated that the more electron-rich olefines favored bonding with the electron-deficient palladium complex to form a transient branched palladium(II) intermediate. Then, we carried out the benchmark reaction in the presence of DPPF instead of **L8**. Interestingly, in this case the b/l ratio did not change with different amounts of TFA. Therefore, we conclude that the protonation of pyridyl substituent on the ligand might be crucial for switching the regioselectivity in this reaction (Figure 2B). Notably, performing the model reaction in the presence of ligand PhP(*t*-Bu)Py, the yields of the desired products were low, which shows that the use of a bidentate ligand is also pivotal in this transformation (Figure 2B).

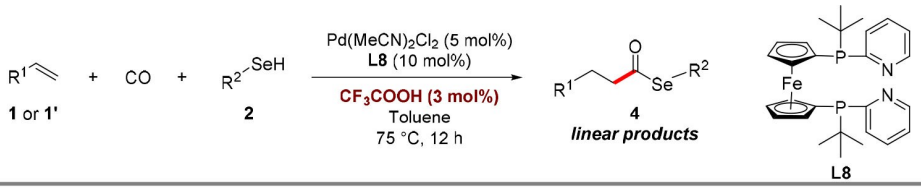
Table 1: Pd-catalyzed selenocarbonylation of olefins: scope of branched products.[a]



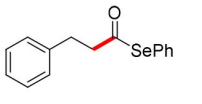
[a] Reaction conditions: alkenes **1** (0.2 mmol), selenols **2** (0.3 mmol), $Pd(MeCN)_2Cl_2$ (5 mol%), **L8** (10 mol%), CF_3COOH (100 mol%), CO (40 bar), toluene (1.5 mL), stirred at 75 °C for 12 h. Regioselectivities were determined by ^1H NMR and GC of crude reaction mixture. Isolated yields of branched products without isomers. [b] 33 mol% TFA was used. [c] 55 mol% TFA was used. [d] 150 mol% TFA was used.

When trifluoroacetic acid-D (99.5 % D) was subjected to the reaction, only trace amounts of deuterium incorporation were found in the branched product (Figure 2C). To prove the formation of an active palladium hydride complex, $Pd(MeCN)_2Cl_2$ (10 mol%), **L8** (10 mol%), and phenylselenol (with or without 3 mol% TFA) were mixed in toluene-d_8 for 1 hour at room temperature. The ^1H NMR spectrum of this mixture showed a palladium-hydride signal with a resonance at −8.44 ppm (d, $J = 184.8$ Hz) (Figure 2D, b, d). When mixing $Pd(MeCN)_2Cl_2$ (10 mol%), **L8** (10 mol%), phenylselenol and TFA (100 mol%) under the same conditions, another palladium-hydride signal appeared at −13.38 ppm (Figure 2D, f). In addition, the proton signals of the pyridyl substituent were significantly shifted in the presence of 100 mol% TFA (see SI). All these experiments imply that TFA changes the properties of the ligand by protonation. To rule out reversible carbonylation reactions, we applied the linear and branched products under standard

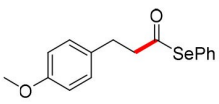
Table 2: Pd-catalyzed selenocarbonylation of olefins: scope of linear products.[a]



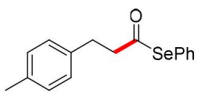
Scope of alkenes



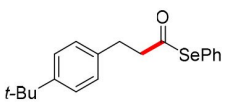
4a, 76%
l/*b* = 4.5:1



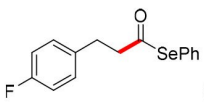
4b, 60%
l/*b* = 2.6:1



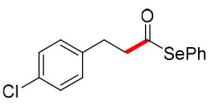
4c, 74%
l/*b* = 3.4:1



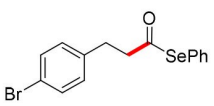
4d,73%
l/*b* = 3.3:1



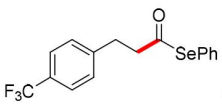
4e, 77%
l/*b* = 4.9:1



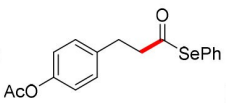
4f, 76%
l/*b* = 4.6:1



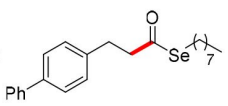
4g, 77%
l/*b* = 4.0:1



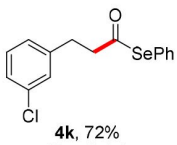
4h, 59%
l/*b* = 3.0:1



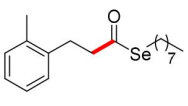
4i, 76%
l/*b* = 4.4:1



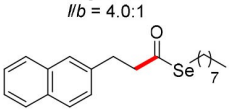
4j, 80%
l/*b* = 5.5:1



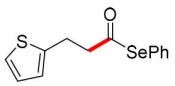
4k, 72%
l/*b* = 5.4:1



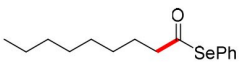
4l, 84%
l/*b* = 6.4:1



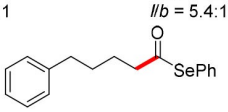
4m, 46%
l/*b* = 1.7:1



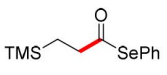
4n, 50%
l/*b* = 1.6:1



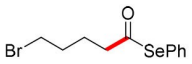
4o, 91%[b]
l/*b* > 20:1



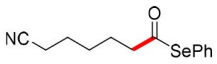
4p, 85%[b]
l/*b* > 20:1



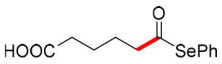
4q, 93%[b]
l/*b* > 20:1



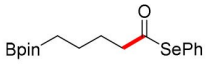
4r, 91%[b]
l/*b* > 20:1



4s, 89%[b]
l/*b* > 20:1



4t, 70%[b]
l/*b* > 20:1



4u, 90%[b]
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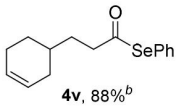

4v, 88%[b]
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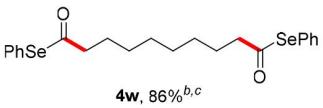
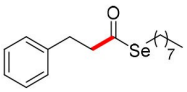
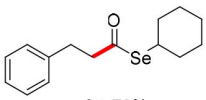


4w, 86%[b,c]
l/*b* > 20:1

Scope of selenols



4x, 82%
l/*b* = 6.2:1



4y, 79%
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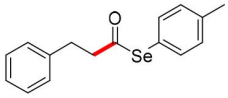

4z, 74%
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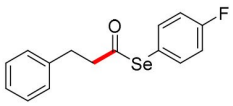

4aa, 59%
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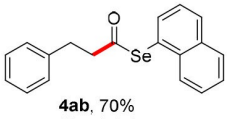

4ab, 70%
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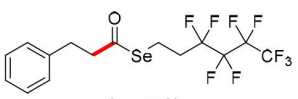
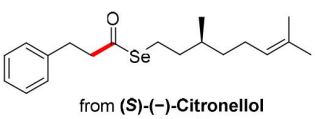
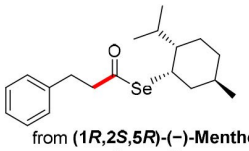


4ac, 78%
l/*b* = 5.2:1

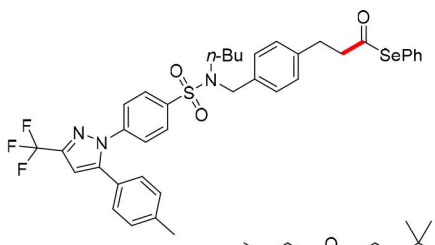


from **(*S*)-(−)-Citronellol**
4ad, 76%
l/*b* = 6.1:1

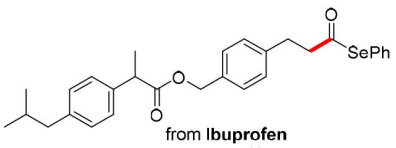


from **(1*R*,2*S*,5*R*)-(−)-Menthol**
4ae, 78%
l/*b* = 6.8:1

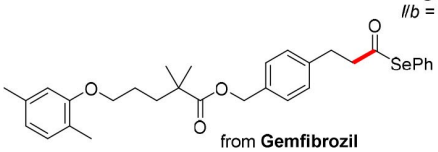
Scope of bioactive molecule derivatives



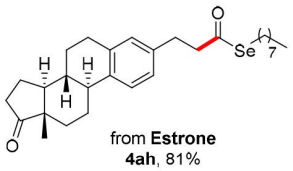
from **Celecoxib**
4af, 64%
l/*b* = 3.7:1



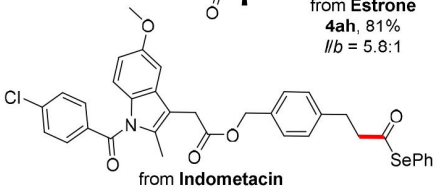
from **Ibuprofen**
4ag, 75%
l/*b* = 4.2:1



from **Gemfibrozil**
4ai, 76%
l/*b* = 4.3:1



from **Estrone**
4ah, 81%
l/*b* = 5.8:1



from **Indometacin**
4aj, 72%
l/*b* = 3.4:1

[a] Reaction conditions: alkenes **1** or **1′** (0.2 mmol), selenols **2** (0.3 mmol), $Pd(MeCN)_2Cl_2$ (5 mol%), **L8** (10 mol%), CF_3COOH (3 mol%), CO (40 bar), toluene (1.5 mL), stirred at 75 °C for 12 h. Regioselectivities were determined by ^1H NMR and GC of crude reaction mixture. Isolated yields of linear products without isomers. [b] stirred at 100 °C. [c] $Pd(MeCN)_2Cl_2$ (7.5 mol%), **L8** (15 mol%), **2a** (3.0 equiv.) were used.

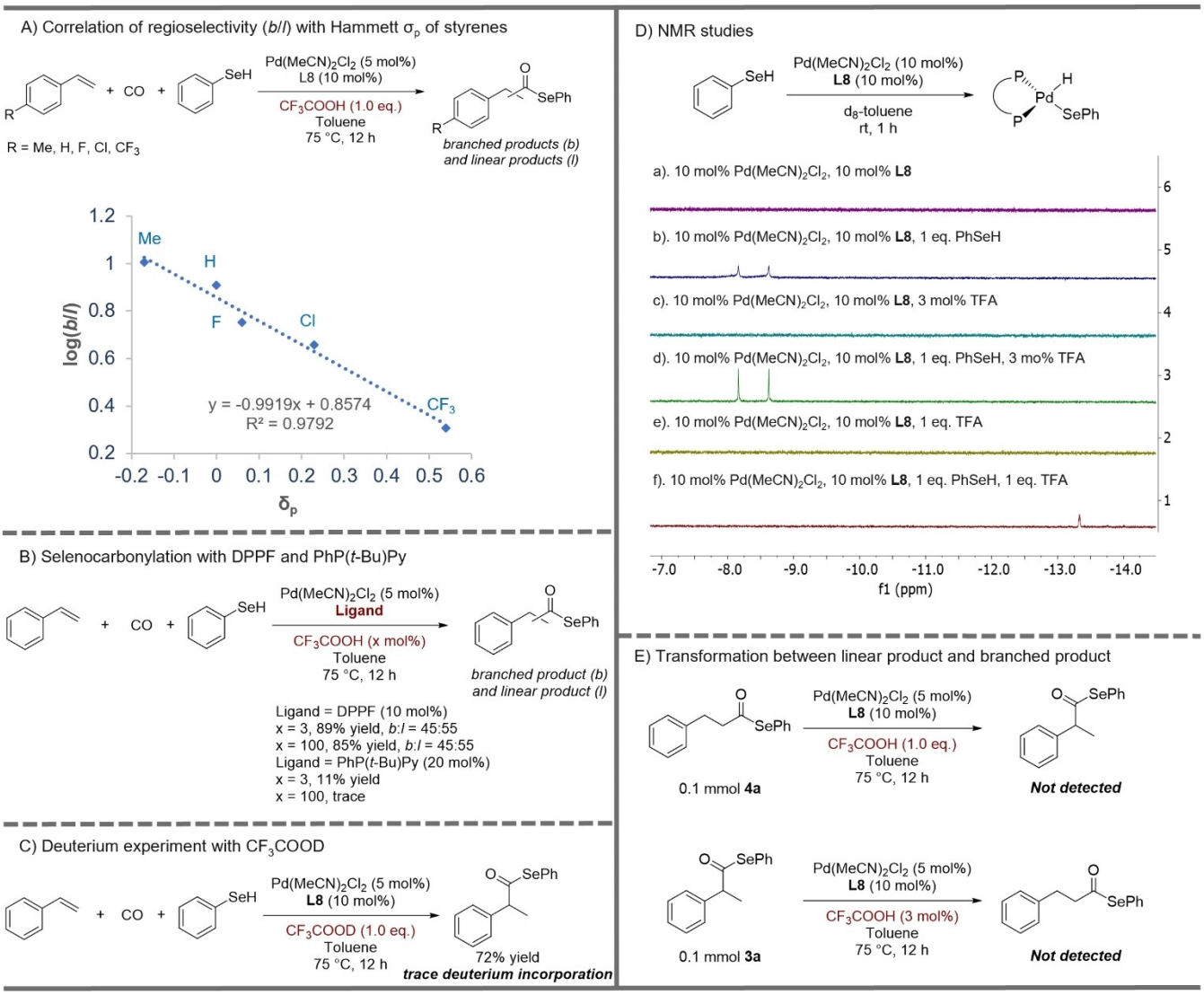


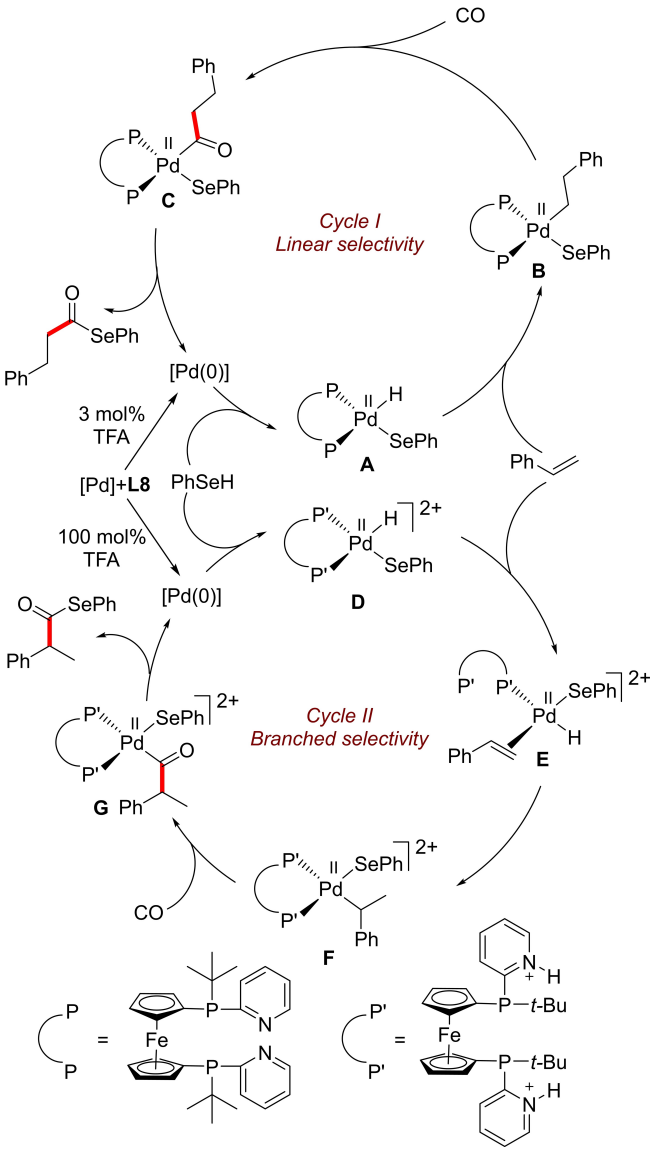
Figure 2. Mechanistic studies: A) Hammett plot, B) control experiments, C) deuterium labeling, D) NMR studies, E) mutual transformation.

conditions, respectively. In both experiments no transfer of the selenoester group was observed (Figure 2E), excluding the possibility of mutual transformation between linear and branched products.

Based on these findings and previous mechanistic studies of other carbonylation reactions,[7b,e,9c] the following reaction mechanism is proposed (Scheme 2). Initially, the Pd(II) precursor is in situ reduced to give Pd(0) phosphine complex in the presence of an excess amount of ligand. After oxidative addition of the selenol, the active complex **A** is afforded. Next styrene coordination to complex **A** and insertion of the styrene into the Pd–H bond furnishes intermediate **B**, which could be transformed into acyl complex **C** through the coordination and insertion of CO. Intermediate **C** is converted to the linear product and complex **A** is regenerated by reductive elimination/oxidative addition.

In the presence of 100 mol % TFA (cycle II), protonated Pd(0) phosphine complexes will be generated in situ before formation of complex **D**. After styrene coordination to complex **D**, complex **E** with one phosphorus atom coordinated is obtained. Markovnikov insertion of the styrene into the Pd–H bond provides complex **F**, which undergoes CO coordination and insertion. The resulting acyl complex **G** affords the branched product via reductive elimination, followed by oxidative addition of the selenol and regenerates complex **D**.

The unique character of the presented selenocarbonylation becomes also clear, when performing related thiocarbonylation of styrene with the developed catalyst system. Noteworthy, there are no products observed at 75 °C, the optimal reaction temperature for selenocarbonylation, which proves that thiols are less reactive than selenols under these reaction conditions. By increasing the reaction temperature, carbonylation product yields increased, but regioselectivities decreased (Table 3).

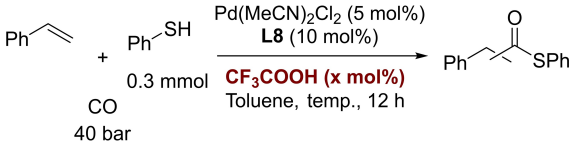


Scheme 2. Proposed mechanism.

Conclusion

In conclusion, we describe the first selenocarbonylation of olefins. Key to success is the combination of a specific "built-in-base" ligand **L8** with trifluoroacetic acid in the presence of suitable palladium precursors. This novel protocol exhibits a high functional group tolerance and offers straightforward access to linear and branched selenoesters in moderate to good yields. This methodology development also provides the basis for the discovery of the first palladium-catalyzed regiodivergent carbonylation of alkenes simply controlled by the amount of acid. Mechanistic investigations suggest that the change of regioselectivity is a result of the decoordination of one phosphorus atom in the presence of equimolar amounts of acid.

Table 3: Thiocarbonylation of styrene at different temperature.[a]



Temperature / °C	X	Yield/%	b:l
75	3	0	–
	100	0	–
100	3	68	28:72
	100	43	77:23
110	3	81	32:68
	100	64	67:33
120	3	82	38:62
	100	85	65:35

[a] Reaction conditions: styrene (0.2 mmol), thiophenol (0.3 mmol), $Pd(MeCN)_2Cl_2$ (5 mol%), **L8** (10 mol%), TFA (x mol%), CO (40 bar), toluene (1.5 mL), 12 h. Yields and regioselectivities were determined by ^1H NMR and GC.

Supporting Information

The authors have cited additional references within the Supporting Information.[16–19]

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Carbonylation · P Ligands · Palladium · Regioselectivity · Selenoesters

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Ich habe eine Dissertation zum Thema

Palladium-Catalyzed Amino- and Selenocarbonylation of Unsaturated Carbon-Carbon Bonds

an der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock angefertigt. Dabei wurde ich von Frau/Herrn

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