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an der Universität Rostock

Development of selective and efficient catalysts for carbonylation of alkenes

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Achievements are reached by hard work rather than recreation.

Actions are done after thorough consideration rather than casual decision.

业精于勤，荒于嬉；行成于思，毁于随。-- 唐·韩愈

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How time flies! I am going to finish my PhD study in a twinkling of an eye.

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Abstract

Development of selective and efficient catalysts for carbonylation of alkenes

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The dissertation is mainly concerned with the selective carbonylation of alkenes in the presence of homogeneous catalysts. More specifically, domino hydroaminomethylation reactions, alkoxy- and aminocarbonylations of alkenes and allenes are presented. The resulting aliphatic amines, amides and esters constitute important intermediates for both organic synthesis and chemical industries. Regarding methodology developments, firstly a selective ruthenium-catalyzed water–gas shift/hydroformylation of internal olefins and olefin mixtures to linear amines is presented. Additionally, the development on branched selective aminocarbonylation of alkenes is displayed in the presence of a palladium/*N*-phenylpyrrole phosphine type ligand catalyst system. Furthermore, the palladium-catalyzed regioselective alkoxycarbonylation of allenes with aliphatic alcohols allows to produce synthetically useful α,β- and β,γ-unsaturated esters in good yields, while efficient selectivity control is achieved in the presence of appropriate ligands. In all the above mentioned areas systematic catalyst optimization studies were performed and the scope and limitations of the respective protocol were presented.

Entwicklung von selektiven und effizienten Katalysatoren zur Carbonylierung von Alkenen

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Die Dissertation befasst sich hauptsächlich mit der selektiven Carbonylierung von Alkenen in Gegenwart homogener Katalysatoren. Hauptaugenmerk liegt auf Domino-Hydroaminomethylierungsreaktionen, sowie der Alkoxy- und Aminocarbonylierungen von Alkenen und Allenen. Die dabei entstehenden aliphatischen Amine, Amide und Ester sind wichtige Zwischenprodukte für die organische Synthese sowie der chemische Industrie. Bezüglich methodischer Entwicklungen erfolgt zunächst die Vorstellung einer selektiven rutheniumkatalysierten Wassergas-Shift-Reaktion/Hydroformylierung von internen Olefinen und Olefinmischungen zu linearen Aminen. Zusätzlich wird die Entwicklung einer verzweigten selektiven Aminocarbonylierung von Alkenen in Gegenwart eines Palladium/N-Phenylpyrrol-Phosphin-Liganden-Katalysatorsystems beschrieben. Als abschließendes Beispiel für Carbonylierungsreaktion wird die palladiumkatalysierte regioselektive Alkoxycarbonylierung von Allenen mit aliphatischen Alkoholen behandelt. Diese ermöglicht die Herstellung von synthetisch wertvollen α, β- und β, γ-ungesättigten Estern mit hohen

Ausbeuten sowie eine effiziente Selektivitätskontrolle in Gegenwart geeigneter Liganden. In allen oben genannten Bereichen wurden systematische Katalysatoroptimierungsstudien durchgeführt und der Umfang und die Grenzen des jeweiligen Protokolls dargestellt.

List of abbreviations

acac	Acetylacetone
Ar	Aryl
atm	atmosphere
b	branch
BASF	Badische Anilin- & Soda-Fabrik
^{t}Bu	*tert*-butyl
Bn	Benzyl
cat.	catalyst
CO	carbon monoxide
cod	Cycloocta-1,5-diene
Cy	Cyclohexyl
dba	Dibenzylideneacetone
d^{t}bpx	1,2-bis(di-tert-butyl-phophanylmethyl)benzene
DCM	Dichloromethane
diglyme	Bis(2-methoxyethyl)ether
DME	Dimethoxyethane
DMF	Dimethylformamide
DPEPhos	(Oxydi-2,1-phenylene)bis(diphenylphosphine)
dppb	1,4-Bis(diphenylphosphino)butane
dppf	1,1'-Ferrocenediyl-bis(diphenylphosphine)
dppp	1,3-Bis(diphenylphosphino)propane
dpppen	1,5-Bis(diphenylphosphino)pentane
dr	diastereomeric ratio
E	Entgegen (describing the absolute stereochemistry of double bonds)
ee	Enantiomeric excess
Et$_2$O	Diethylether
EtOH	Ethanol
h	hour
iso or *i*	Sum of branched products
l	linear
L	ligand
MSA	Methanesulfonic acid
MeCN	Acetonitrile
MeOH	Methanol

MMA	Methylmethacrylate
n	Amount of linear product
NMP	*N*-Methylpyrrolidone
NuH	Nucleophile
OAc	Acetate
Ph	Phenyl
p-TsOH	*para*-Toluenesulfonic acid
S	Solvent
TBS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TON	Turnover Number
UCC	Union Carbide Corporation
X	Leaving group, (pseudo)halide
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Z	Zusammen (describing the absolute stereochemistry of double bonds)

Table of Contents

A

1. Introduction

The world chemical turnover was valued at €3,534 billion in 2015, among which the European Union (EU) accounts for 14.7% of the total (Figure 1).[1] The global sales grew by 14.0% from €3,100 billion in 2014 to €3,534 billion in 2015. It is noteworthy that the chemicals sales in China swelled impressively from €1,084 billion in 2014 to €1,409 billion in 2015, almost 30% increase in value terms. Besides the achievement on sales, the efforts on energy consumption reduction and environmental protection also made great improvement. For example, EU fuel and power consumption falls 22% and total greenhouse gas emissions fall nearly 60% since 1990.
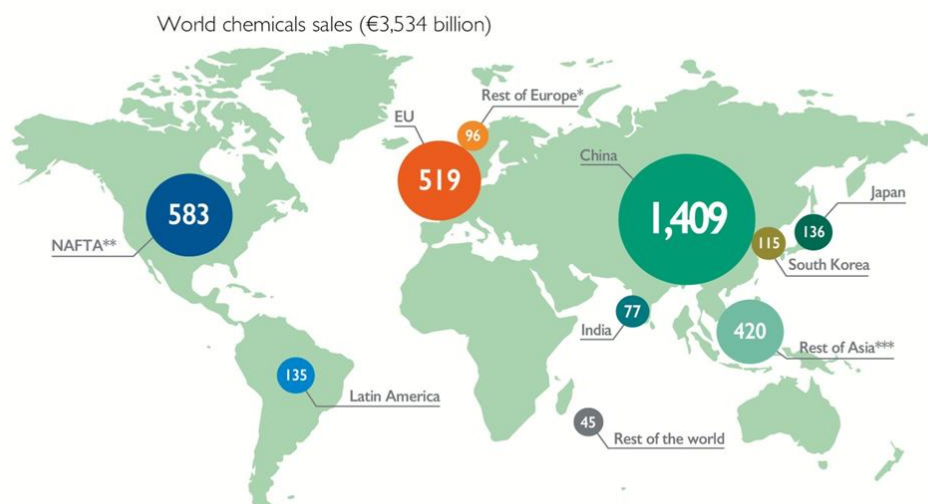

Figure 1: Global chemical sales in 2015

Today 8 out of 10 processes in the chemical industry make use of catalytic reactions.[2] Since the catalytic methods can significant decrease production cost (energy and material) and substantial reduce harmful wastes, it has been widely recognized as an economically and ecologically improved process in chemical industry. Depending on whether a catalyst exists in the same phase, catalyst can be heterogeneous or homogeneous. Well-known heterogeneous catalytic processes such as Haber–Bosch process for ammonia synthesis[3] and Fischer-Tropsch process[4] for liquid hydrocarbon production have greatly contributed to the human society and already demonstrated the power of catalysis.

Meanwhile, homogeneous catalysis also receives a lot of attention in academics as well as in industry. For example, carbonylation reactions are one of the most important homogenous catalytic reactions which have been already widely used in industrial production of fine and bulk chemicals as well as organic synthesis.[5] Within this class of reactions, hydroformylation[6] and Reppe carbonylation[7] represent a straightforward method for the conversion of widely available unsaturated compounds,

CO into the corresponding aldehydes and carboxylic acid derivatives. The present dissertation highlights recent achievements in hydroformylation reactions and Reppe carbonylation reactions. It is also presented as a cumulative collection of publications which have been already released in international journals.

1.1 Hydroformylation reactions

Hydroformylation, also called "oxo process", was first discovered in 1930s by Otto Roelen.[8] After 80 years development, this transformation has become one of the largest homogenous catalytic reactions in industry. The products of hydroformylation-aldehydes, are valuable final products and intermediates in the synthesis of bulk chemicals like alcohols, acids, esters, amides and amines (Scheme 1).[6]
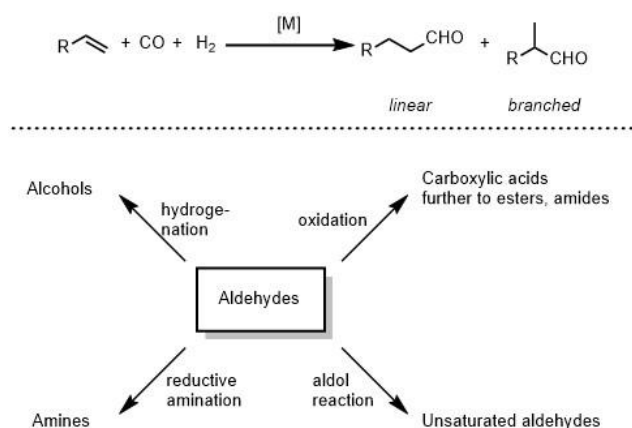
Scheme 1: Hydroformylation reactions and versatile products derived from aldehydes

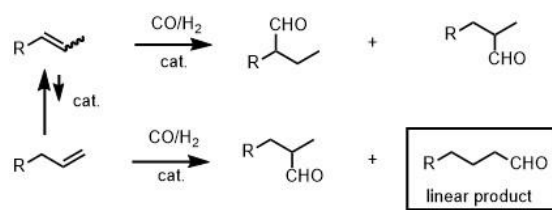### 1.1.1 Co- and Rh-based hydroformylation reactions

The first generation of hydroformylation process used cobalt carbonyl [$Co_2(CO)_8$] as the pre-catalyst since it was the first metal catalyst found to present sufficient activity in the 1930s.[8] Although these metal catalysts are easily accessible to obtain and therefore have a relative low price, however, the severe reaction conditions (high pressure of 200-350 bar CO was needed to prevent decomposition of catalyst and high temperature 150-180 ^{o}C to retain an acceptable activity), unavoidable byproducts alkanes and limited substrates scope impeded further applications of these processes. In the 1950s, Shell introduced a phosphine (PPh_3) modified catalyst system for the synthesis of alcohols, which is still in use today.[9] The generally accepted mechanism proposed by Heck and Breslow[10] is depicted in Scheme 2.
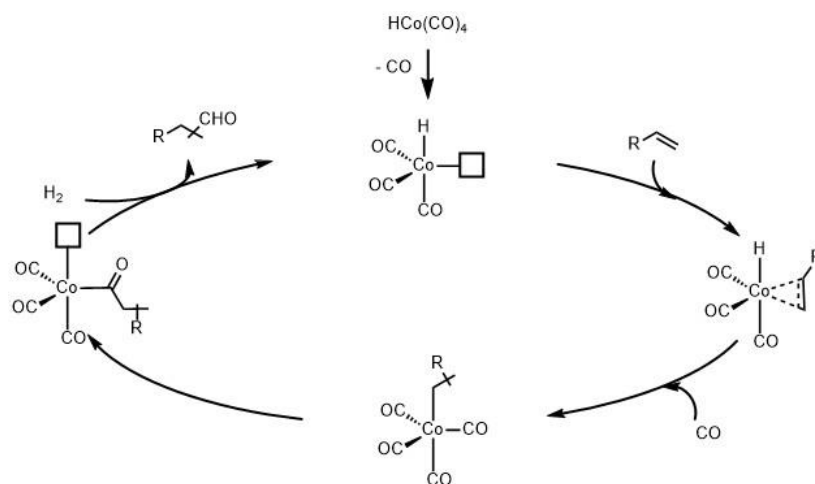
Scheme 2: Mechanism of Co catalyzed hydroformylation

Unfortunately, the cobalt-based processes suffer from low chemo- and regioselectivity. With the tremendous increasing chemical market after Second World War, the research on this field was much intensified. Since 1970s, rhodium based catalysts gradually replace cobalt to apply in hydroformylation process.[11] Comparing with Co, Rh catalyst demonstrates a more active manner, requires much lower pressure and allows for higher selectivity. At the same time, the phosphine ligands have been extensive synthesized and applied in this process.

In bulk chemical industry, a key point for large scale application is the price of starting materials.[6] For example, mixtures of internal olefins such as butenes, hexenes and octenes are more cost-efficient than the corresponding terminal olefins. However, the synthesis of linear products like aldehydes, alcohols and amines from internal olefins are more challenging than terminal olefins due to their lower reactivity and selectivity. A general scheme of the isomerization-hydroformylation sequence is shown in Scheme 3.[12] To selectively produce linear aldehyde from the corresponding internal olefins, isomerization of internal olefins must occur faster than the hydroformylation reaction. Additionally, the hydroformylation of the terminal olefin must occur much faster and with high regioselectivity compared with the reaction of the internal olefin.

Scheme 3: Isomerization-hydroformylation sequence

Generally, the cobalt-based catalyst systems normally show almost the same hydroformylation

reactivity for terminal and internal olefins. However, for the rhodium catalyst system, especially in the presence of different ligands, the reactivity and selectivity of hydroformylation of internal olefins are much improved. Such active rhodium catalysts are formed in the presence of sterically demanding phosphites or phosphines. The *n*-regiodirecting properties of the catalyst can be enhanced by incorporation of sterically demanding substituents, chelating effects, electronic nature in the organic backbone (Scheme 4). Our group started working on this topic in the late 1990s. Since then, several groups including us reported excellent regioselectivities for the rhodium-catalyzed hydroformylation of internal olefins with chelating bulky phosphites or phospines as ligands.[13]
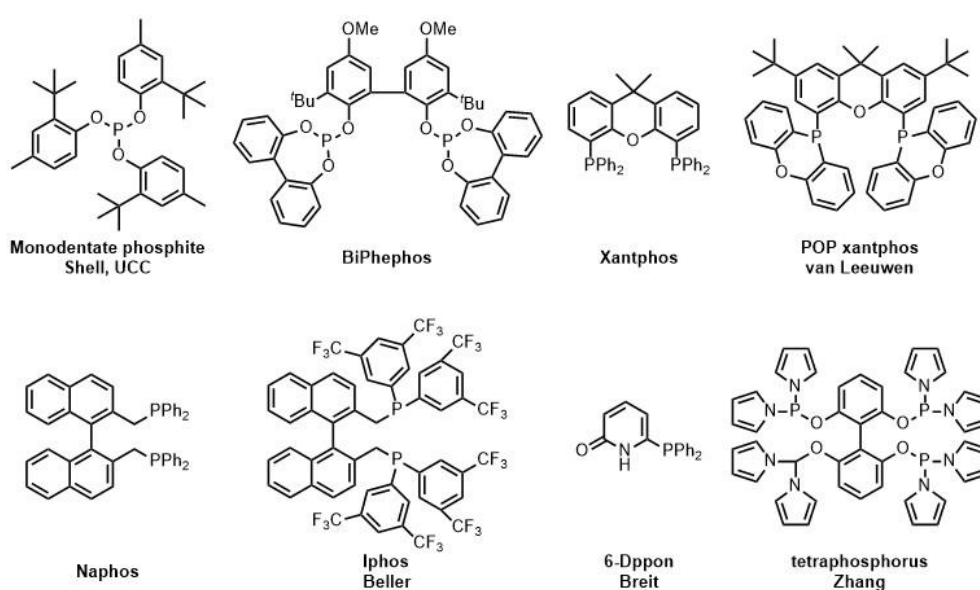
Scheme 4: Selected phosphite and phosphine ligands in Rh-catalyzed hydroformylation

### 1.1.2   Alternative metals in hydroformylation reactions

Interestingly, most of the known hydroformylation reactions of olefins require relatively expensive rhodium/ligand catalyst systems to ensure high activity and selectivity in the carbonylation step. Hence, it is highly desirable to apply less costly alternative metals to realize this process. However, other metals have been scarcely applied in hydroformylations so far. The main reasons are the low reactivity of the corresponding metal carbonyl complexes as well as the tendency to undergo increased side reactions such as hydrogenations and alkene isomerizations (Scheme 5).[14]

$$Rh \gg Co > Ir, Ru > Os > Pt > Pd > Fe > Ni$$

**Scheme 5:** Hydroformylation activity of different metal carbonyls

The first example for the application of ruthenium catalysts in homogenous hydroformylation was initially reported by Wilkinson and co-workers in 1965 (Scheme 6).[15] The well-defined complex

[Ru(CO)$_3$(PPh$_3$)$_2$] was able to hydroformylate with 1-pentene to give C6-aldehydes in the presence of 100 bar of syngas in benzene solution.
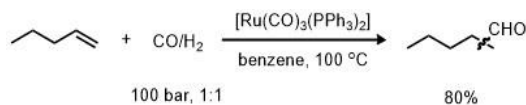

Scheme 6: First example of Ru-catalyzed hydroformylation

In this reaction, the complex [Ru(H)$_2$(CO)$_2$(PPh$_3$)$_2$] was proposed as the key active catalytic species, which formed from the oxidative addition of hydrogen to the metal center with dissociation of one carbonyl ligand. Next dissociation of the PPh$_3$ allows for the coordination of the alkene to Ru center. Subsequently the CO insertion to Ru-alkyl bond to give the corresponding acyl species and finally transfer of a second hydrogen molecule results in the formation of aldehyde and regeneration of the active species (Scheme 7).
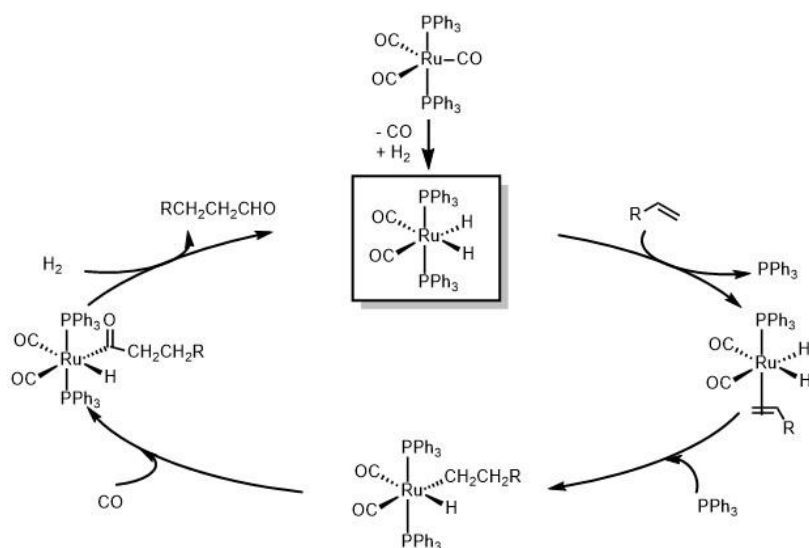
Scheme 7: Proposed catalytic cycle for [Ru(CO)$_3$(PPh$_3$)$_2$]-catalyzed hydroformylation

In 2012 Nozaki group has reported a ruthenium-catalyzed hydroformylation of aliphatic alkenes to aldehydes with high linear selectivity (Scheme 8).[16] Similar to the conventional rhodium catalyzed hydroformylation a monohydridorhodium(I) species acts as the key intermediate, the authors successfully synthesized a corresponding monohydrridoruthenium complex, which was proved to be the real catalytic species in this transformation.
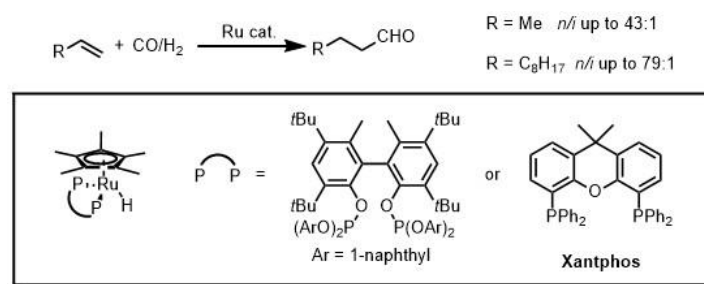
Scheme 8: Ru/bisphosphino- or bisphophite-based catalysts for *n*-selective hydroformylation

It is well known that iridium exhibits similar chemical properties and coordination environment to rhodium. Therefore, iridium may result in comparable hydroformylation activity to rhodium. This has led to the development of alternative iridium based catalysts for hydroformylation of alkenes. In 2011, our research group developed a broadly applicable Ir/PPh$_3$-based hydroformylation catalyst (Scheme 9).[17] This catalyst was able to convert a variety of terminal alkenes with an average regioselectivity of 3:1 in favor of the linear aldehyde. The dinuclear [Ir$_2$(CO)$_6$(PPh$_3$)$_2$] was obtained from the precipitation after cooling the reaction mixture, and it still demonstrated moderate hydroformylation activity (46%), with almost no change in the *l/b* ratio (74:26).
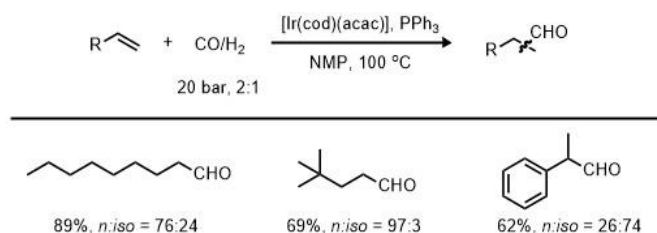
Scheme 9: Ir catalysts for the hydroformylation of alkene

Apart from oxidation reactions, osmium catalysts received much less attention in hydroformylation reactions compared to other transition-metals. In 2015, our research group reported a highly regioselective and general osmium-catalyzed hydroformylation of olefins to aldehydes (Scheme 10).[18] In this reaction, imidazoyl-substituted phosphine ligands played an important role to lead high *n*-selectivities and yields. However, it should be note that the osmium catalysts are always toxic and should be careful to handle them.
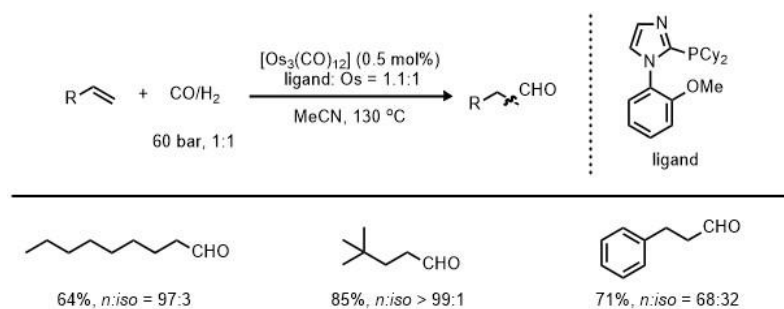
Scheme 10: Os-catalyzed hydroformylation

It is interesting to note that palladium catalysts have found widespread applications in hydrocarboxylation and hydroesterification processes (Reppe carbonylation) in recent years. However, far fewer studies have been conducted on palladium-catalyzed hydroformylation reactions. In 2009, our group investigated a palladium catalyzed hydroformylation using a catalytic system comprising [Pd(acac)$_2$] (acac=acetylacetonato), a bidentate pyrrole type ligand, and *p*-TsOH as the additive at 60 bar syngas pressure (Scheme 11).[19] In this reaction, the isomerization to internal alkenes was found to be the major side product.
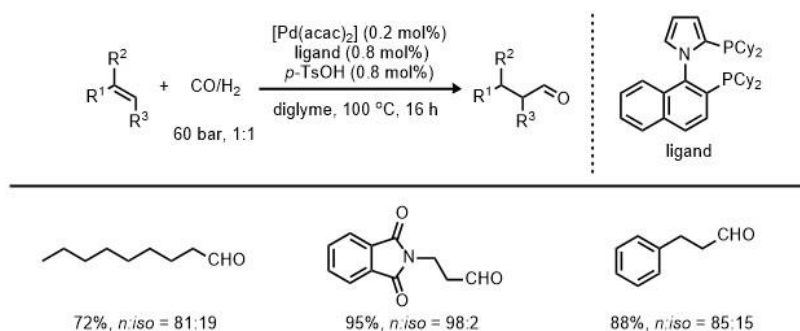

Scheme 11: Pd-catalyzed hydroformylation of alkenes

1.1.3   Domino hydroformylation reactions

Domino reaction, also known as cascade reaction or tandem reaction, is a chemical process involved two or more bond-forming reactions.[20] The main benefit of domino reaction include high atom economy, reduction of waste generated by the several reaction processes, as well as of the time and work required to carry them out. Therefore, domino reactions find broad application in efficient synthesis of natural products and pharmaceuticals, also in the chemical industry, etc.

Hydroformylation allows for the straightforward conversion of inexpensive alkenes into broadly applicable aldehydes. Due to the versatile further functionalization of -CHO group, the resulting aldehydes can be easily converted to alcohols, amines, carboxylic acid derivatives, aldol condensation

products (Scheme 12).[8] However, the additional reagents, products or variations of reaction conditions optimized for the subsequent functionalization step, may suppress even inhibit the initial hydroformylation step. Therefore, key to the success for such reaction is the development of a suitable catalytic system compatible with all the steps in the domino hydroformylation. Here, several elegant examples on domino hydroformylation reactions are summarized in this part.
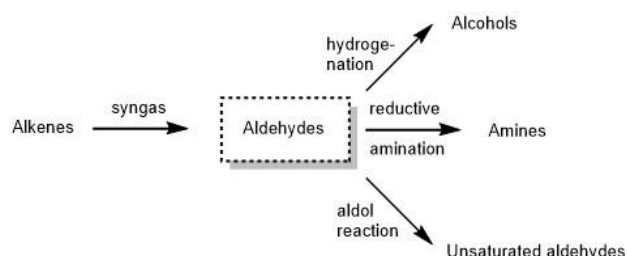

Scheme 12: Versatile products from domino hydroformylation reactions

In 2012, Nozaki group developed a Rh/Ru dual catalyst system for tandem hydroformylation/hydrogenation of terminal alkenes to the corresponding normal alcohols (Scheme 13).[21] The reaction mechanism investigated by in situ IR and NMR study proved a mutual interaction of Rh-catalyzed hydroformylation and Ru-catalyzed hydrogenation. Moreover, they found that the sole ruthenium catalyst was also capable for hydroformylation and hydrogenation with high reactivity and selectivity.
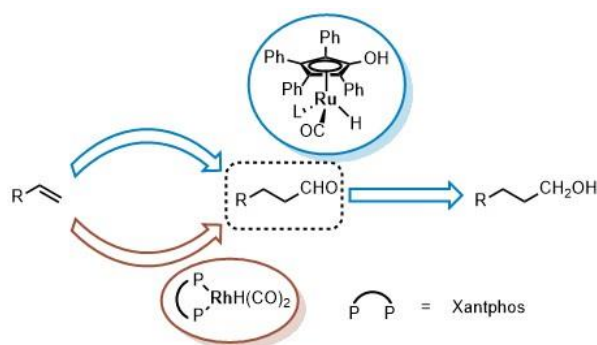
Scheme 13: Rh/Ru dual for catalyst for domino hydroformylation/hydrogenation

Our research group disclosed a novel ruthenium imidazoyl phosphine catalyst system in domino hydroformylation/reduction of alkenes to alcohols in 2013 (Scheme 14).[22] This catalyst was able to convert a variety of terminal alkenes with high reactivities and regioselectivities in favor of the linear aldehydes. The two proposed reaction intermediates **A** and **B** was obtained and characterized by NMR, and the hydroformylation reaction catalyzed by **B** was slower than the standard system, also contrary to the performance of **A**, which demonstrated similar result to the in situ catalyst.[23]
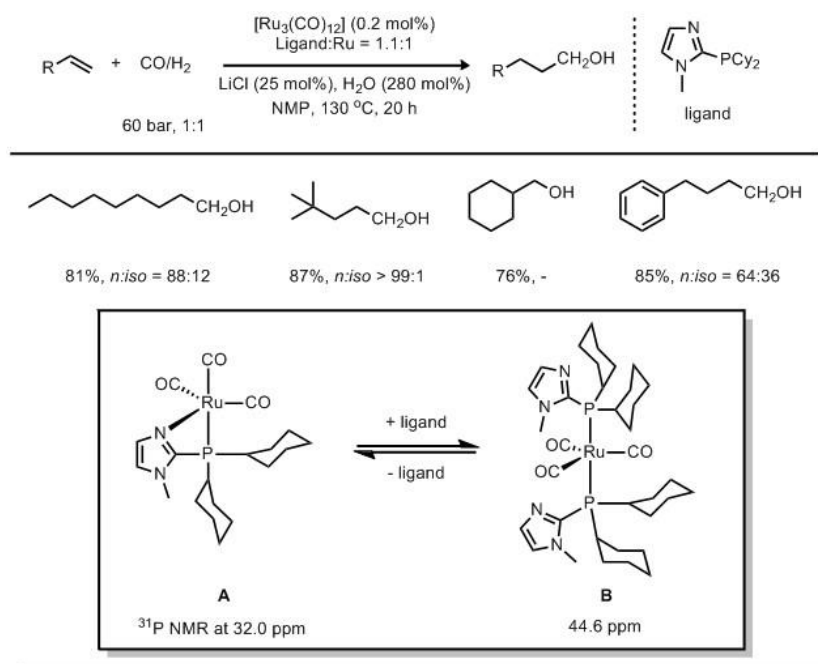
Scheme 14: Ruthenium imidazoyl phosphine catalyst in domino hydroformylation/reduction

Later on, our group continued in this ruthenium catalyzed domino hydroformylation/reduction sequence, and we extended the substrates scope to internal alkenes with high reactivity and linear selectivity (Scheme 15).[24] In comparison to previous work, advantageously a convenient additive-free catalytic system with the modified imidazoyl phosphine ligand allows extending the scope to internal alkenes.
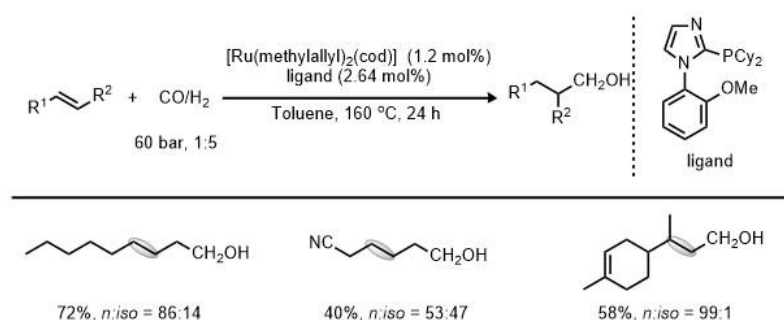
Scheme 15: Domino hydroformylation/reduction of internal alkenes

With the same ligand, our group presented an efficient and regioselective ruthenium-catalyzed hydroaminomethlyation of alkenes to linear amines (Scheme 16).[25] Both industrially important alkenes react with primary and secondary amines to give the corresponding secondary and tertiary amines generally in high yields (up to 96%) and excellent regioselectivities (*n/iso* up to 99:1). This domino sequence includes hydroformylation of olefins to aldehydes, followed by condensation with amine to imines or enamines and final hydrogenation gives the desired alkylated amines (Scheme 16,

Eq (1) to (3)).
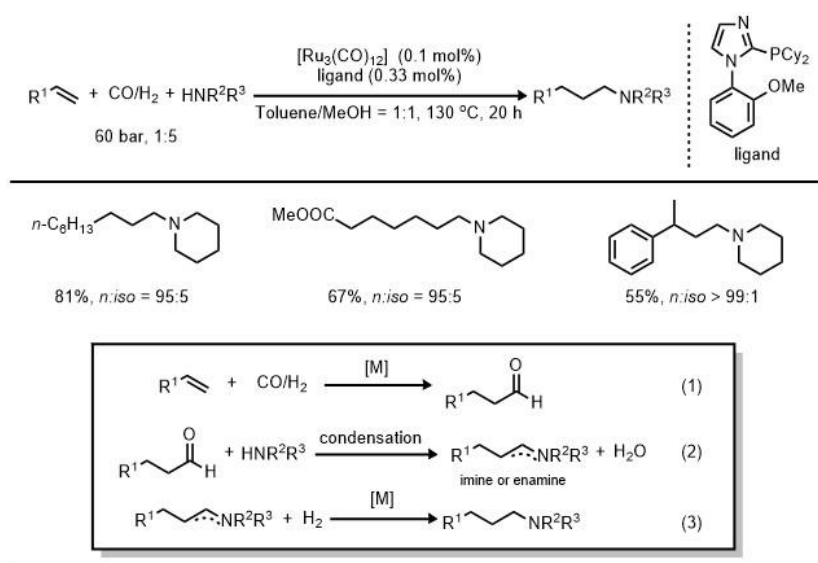
Scheme 16: Ruthenium-catalyzed hydroaminomethlyation of alkenes

It is well known that water-gas shift reaction is an important reaction in both homogenous and heterogenous catalysis.[26] In 2014, our group reported an example of amines synthesis from the combination of water-gas shift reaction, hydroformylation of alkenes, with subsequent imine or enamine formation and final reduction (Scheme 17).[27] Bulk industrial as well as functionalized olefins react with various amines to give the corresponding tertiary amines generally in high yields (up to 92%), excellent regioselectivities (*n/iso*>99:1), and full chemoselectivity in favor of terminal olefins. However, in this transformation, the internal alkenes showed low reactivity.
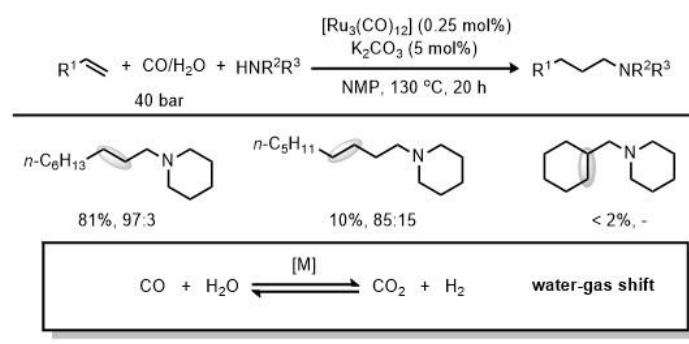
Scheme 17: Ru-catalyzed domino water-gas shift/hydroaminomethylation sequence

Apart from amine, sulphonamide is also a potential substrate for the domino hydroformylation reactions. In 2015, our group disclosed an efficient and highly selective rhodium-catalyzed domino hydroformylation-reductive sulphonamidation reaction (Scheme 18).[28] Various alkenes and sulphonamides are converted into the desired products in good yields and selectivities in the presence

10

of a rhodium/Naphos catalyst.
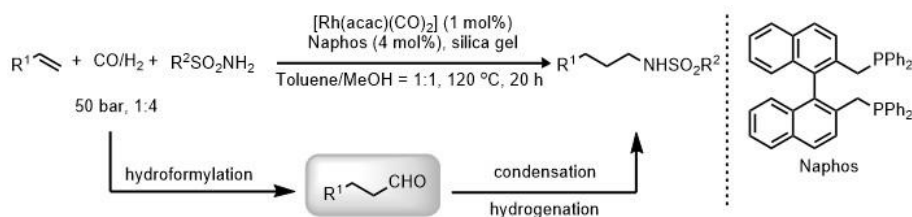
Scheme 18: Rh-catalyzed domino hydroformylation-reductive sulphonamidation

In 2007, Breit and co-workers reported a novel domino hydroformylation/enantioselective cross-aldol reaction sequence (Scheme 19).[29] Key to success is the low concentration of the aldehyde formed in the hydroformylation step, thus avoid the formation of the homo-aldol product. Starting from simple alkenes enantiomerically pure aldol addition products which represent valuable building blocks for polypropionate construction can be obtained in a one pot operation.
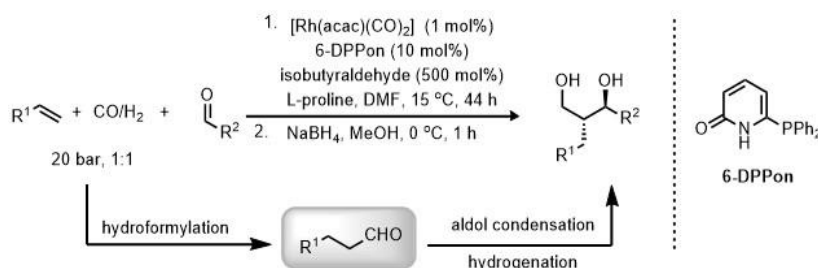
Scheme 19: Domino hydroformylation/enantioselective cross-aldol reaction sequence

Further attempts to develop a domino hydroformylation/aldol condensation/hydrogenation reaction sequence to ketones have been developed in 2014 by our research group (Scheme 20).[30] Various alkenes are efficiently converted into corresponding ketones in good to excellent yields and regioselectivities in the presence of a specific rhodium phosphine/base–acid catalyst system.
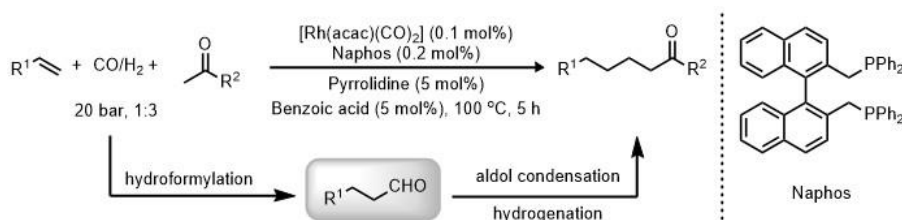
Scheme 20: Domino hydroformylation/aldol condensation/hydrogenation to ketones

Moreover, combination of hydroformylation and benzoin condensation allows for a straightforward and atom-efficient access to a-hydroxy ketones directly from easily available olefins and syngas.

Vorholt and co-workers reported a rhodium/BiPhephos/vitamin catalyst yielding acyloin products in good yields and regioselectivities (Scheme 21).[31]
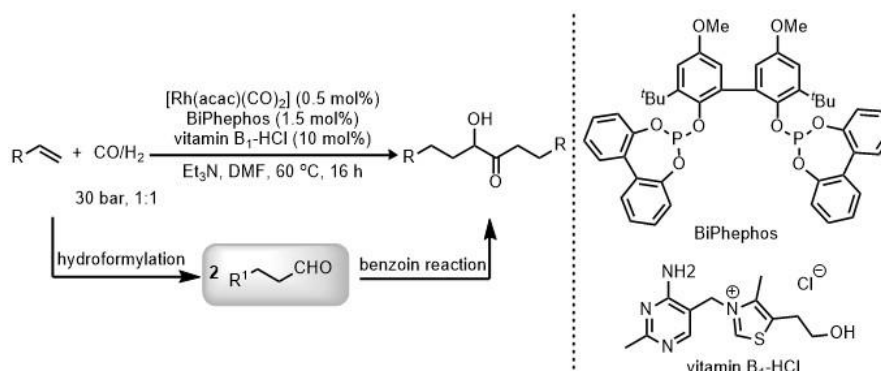
Scheme 21: Domino hydroformylation/acyloin reaction

1.2 Reppe type carbonylation reactions

Reppe carbonylation, named after Walter Reppe, entails the addition of CO and an acidic hydrogen donor (various nucleophiles, such as H_2O, ROH, RNH_2, etc) to the organic substrate (such as alkenes, alkynes, alcohols and so on) (Scheme 22).[7, 32] Today, Reppe carbonylation reaction has become an important rout for the synthesis of all kinds of valuable carboxylic acids and their derivatives.
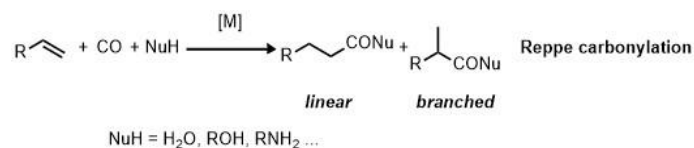
Scheme 22: Reppe type carbonylation

The general accepted reaction mechanism is shown in Scheme 23: the reaction starts with metal-hydride species, which is primarily formed by the reaction of the pre-catalyst with acid additives (TsOH, MSA, HBF_4, etc.) or from the oxidative addition of H-X bond. Subsequent alkene coordination, insertion, and followed by further insertion of carbon monoxide leads to the acyl metal complex. Finally, the catalytic cycle is finished by the nucleophilic attack of the nucleophile on the acylmetal species and the metal-hydride is regenerated.
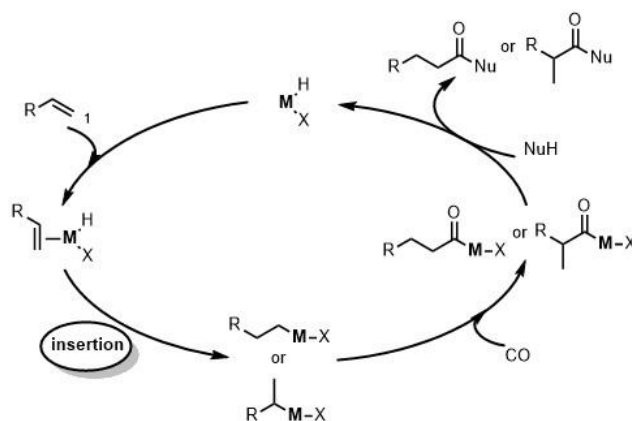
Scheme 23: General reaction mechanism for Reppe carbonylation of alkenes

1.2.1 Carbonylation of alkenes with different nucleophiles

In general, the nucleophiles can be a variety of acidic hydrogen donors, such as H_2O (hydroxycarbonylation), alcohols (alkoxycarbonylation), amines (aminocarbonylation), as well as amides (amidocarbonylation). The original work was reported in the 1950s by Reppe and co-workers using $Ni(CO)_4$ as catalyst under drastic conditions (Scheme 24).[33] However, the highly toxic nickel carbonyl as catalyst great limits its application in industry as well as in laboratory.
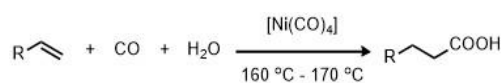
Scheme 24: Ni-catalyzed hydroxycarbonylation

In 1993, Ali and Alper investigated a palladium catalyzed hydroxycarbonylation using a catalytic system comprising Pd/C, a bidentate ligand (dppb), and formic acid or oxalic acid as the additive at 40 bar CO pressure (Scheme 25).[34] Here, linear products were observed as the major products in this transformylation.
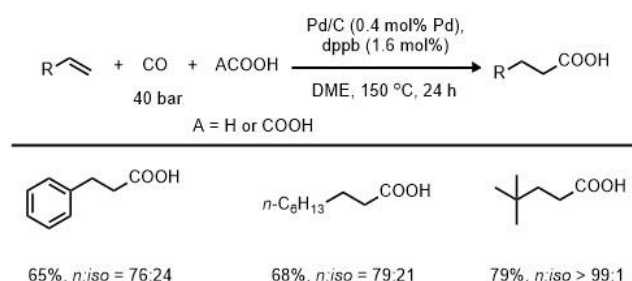
Scheme 25: Palladium catalyzed hydroxycarbonylation

Alkoxycarbonylation also receives a lot attention in the past years. As indicated above, the

development of the alkoxycarbonylation reaction of alkenes is also initiated by Reppe's origin report using $[Ni(CO)_4]$ as the catalyst under harsh conditions. Owing to the great progresses in coordination chemistry, also by the innovation of ligands, palladium catalyst was found to be much more efficient in alkoxycarbonylation later. In general, the use of Pd(0) or Pd(II) precursors in combination with bulky chelating ligands such as d^{t}bpx,[35] Py^{t}bpx,[36] d^{t}bpp,[37] Py^{t}bpf,[38] bis(phosphaadamantyl)diphosphines,[39] or other bidentate phosphines[40] resulted in a greatly improved regioselectivity towards linear esters (Scheme 26).
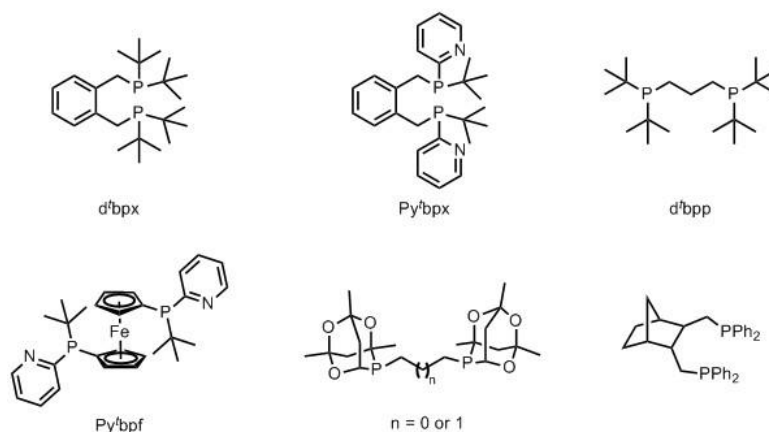
Scheme 26: Various bulky phosphine ligands in alkoxylcarbonylation

The largest application for this type of carbonylation called Lucite α-process (Scheme 27),[35, 41] which consists of methoxycarbonylation of ethylene and subsequent condensation with formaldehyde to form the methyl methacrylate (MMA), a monomer for the manufacture of resins and plastics. This technology was patented in the late 1980s and was commercialized on multi-100.000 ton-scale in Singapore in 2008.
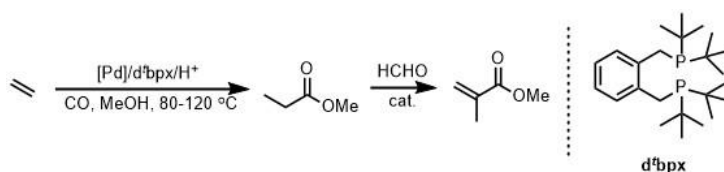
Scheme 27: Lucite α-process

It is noteworthy that the catalytic carbonylation reactivity order of different alkenes is a major problem to be addressed (Scheme 28). Comparing the reactivity of diverse alkenes involving transition metal hydride complexes, it is well known that ethylene shows highest activity and terminal olefins react much faster than internal ones. Hence, the rate of the respective functionalization reaction falls with increasing steric hindrance of alkenes. Recently, a palladium catalyst based on 1,2-bis((tert-butyl(pyridin-2-yl)phosphanyl)methyl)benzene (Py^{t}bpx) is rationally designed and

synthesized by Evonik and our group (Scheme 29).[36] Application of this system allows a general alkoxycarbonylation of sterically hindered and demanding olefins including all kinds of tetra-, tri-, and 1,1-disubstituted alkenes as well as natural products and pharmaceuticals to the desired esters in excellent yield.
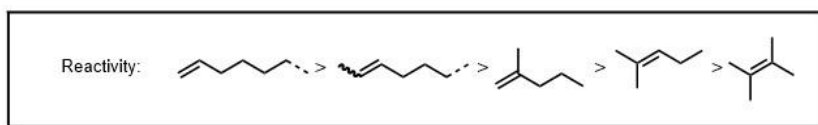
Scheme 28: Reaction rates of alkene carbonylations
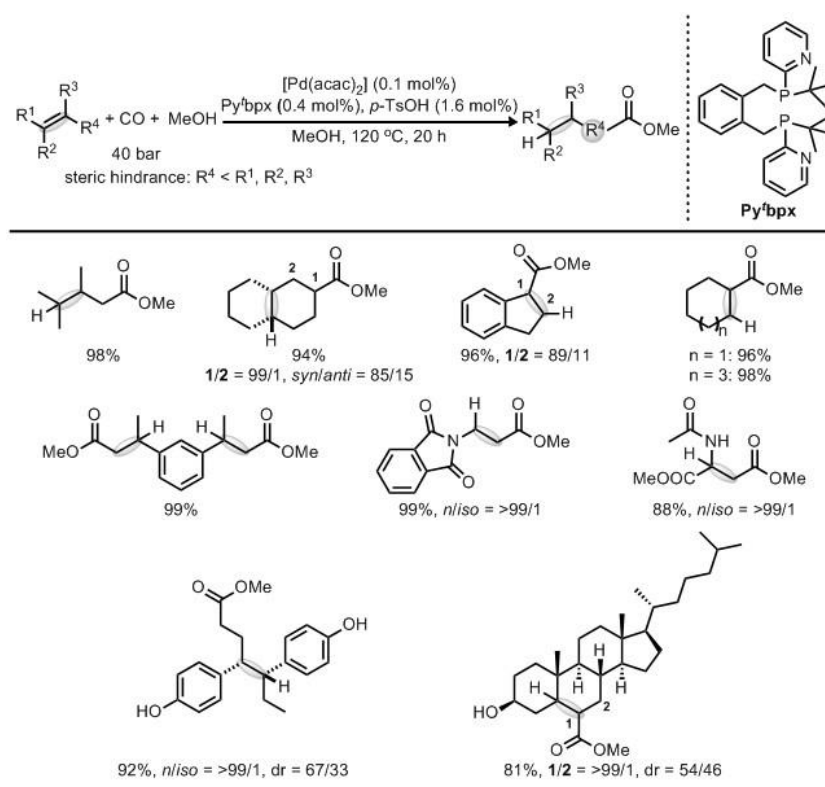
Scheme 29: Methoxycarbonylation of sterically hindered and demanding olefins

Apart from alcohol, amine is also a potential substrate for the Reppe type carbonylation. Recently, palladium-based catalysts for aminocarbonylation of alkenes to linear amides were reported independently by the groups of Cole-Hamilton[42] and our group[43] (Scheme 30).
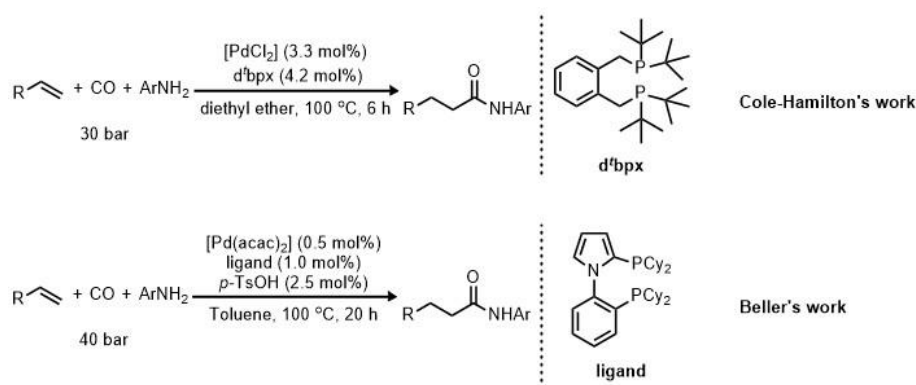
Scheme 30: Pd catalyzed animocarbonylation of aromatic amines

Despite the significant progress in this area, all these methods are limited to aromatic amines as substrates, and carbonylations with aliphatic amines failed. This behavior is simply explained by the stronger basicity of aliphatic amines. Hence, aliphatic amines retard the generation of the active palladium hydride species, which are crucial for catalysis. To overcome this problem, Huang and co-workers developed an elegant strategy to utilize aminals as surrogates of aliphatic amines.[44] Alternatively, our group applied a rhodium catalyst as the solution to this problem (Scheme 31).[45]
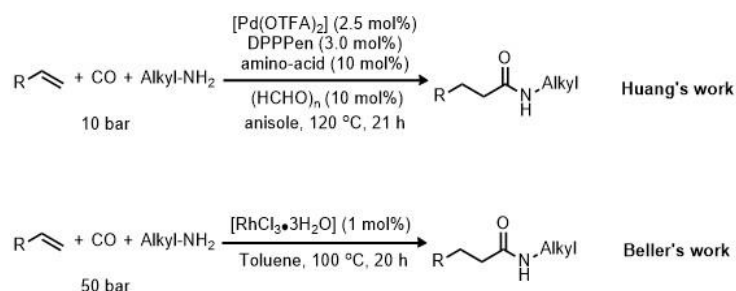
Scheme 31: Pd catalyzed aminocarbonylation of aliphatic amines

Moreover, our group recently reported a novel approach to synthesize imides from alkenes, CO and amides (Scheme 32).[46] The optimal catalyst system (PdI$_2$/DPEPhos) is commercially available and is shown to be efficient and robust at relatively low catalyst loading. Various amides were tested and transformed to the corresponding imides in moderate to excellent yields (64–90%).
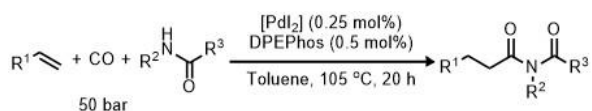
Scheme 32: Pd catalyzed hydroamidocarbonylation of alkenes to imides

1.2.2   Branched selective carbonylation of alkenes

Selectivity consists to be an important issue in homogenous catalysis.[47] The following types of selectivity can be distinguished in a chemical reaction: chemoselectivity, regioselectivity, stereoselectivity and enantioselectivity. In general, the outcome of a reaction is decided by the thermodynamics and the kinetics, which includes the incongruent transition states, thermodynamic stability of products and equilibrium processes. Hence, the catalyst-controlled selectivity is considered to be a challenging topic in organic synthesis.

Taking Reppe carbonylation as an example, it is widely recognized that a number of efficient and highly linear-selective (anti-Markovnikov-selective) systems exist. However, far fewer studies have been reported on the branched-selective (Markovnikov-selective) carbonylation of alkenes. This is because the formation of the branched products from carbonylation reactions is more challenging due to the increase in steric effects for the olefin insertion into the palladium-hydride bond to form the secondary carbon-palladium intermediates (Scheme 33).[48]
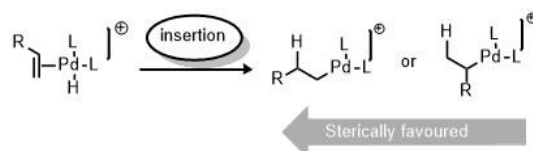
Scheme 33: Two pathways for alkene insertion into the Pd−H bond

The carbonylation of vinylarene is an important reaction for the production 2-arylpropanoic acid and its derivatives, which serves as nonsteroidal anti-inflammatory drugs, such as ibuprofen and naproxen. Due to the significance of these products, numerous examples on this topic have been done. In 1963, BASF first reported branched-selective styrene carbonylation reaction in presence of $[(PPh_3)_2PdCl_2]$, with 95% yield of corresponding branched ester.[49] More recently, Clarke reported the simultaneous control of regioselectivity and enantioselectivity in the hydroxycarbonylation and alkoxycarbonylation of styrene in the presence of a dinuclear palladium complex (Scheme 34).[50]
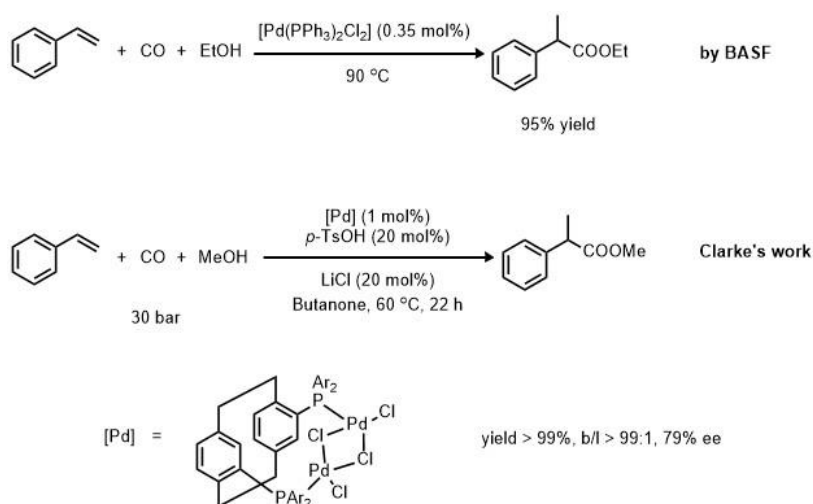
Scheme 34: Branched selective carbonylation of vinylarene

The origin of *iso*-selectivity of carbonylation of vinylarenes could be accounted by the π-benzylic stabilization effect of vinylarene in the palladium hydride insertion step (Scheme 35). In addition, the ligand also plays a key role in this transformation. When monophosphines are used, the branched-product is usually produced as the major product with practically complete regioselectivity. In contrast, when using di-phosphine as ligand, the regioselectivity switches to favor the linear product. Moreover, the activity and selectivity of carbonylation of styrene are also influenced by the nature of anions.
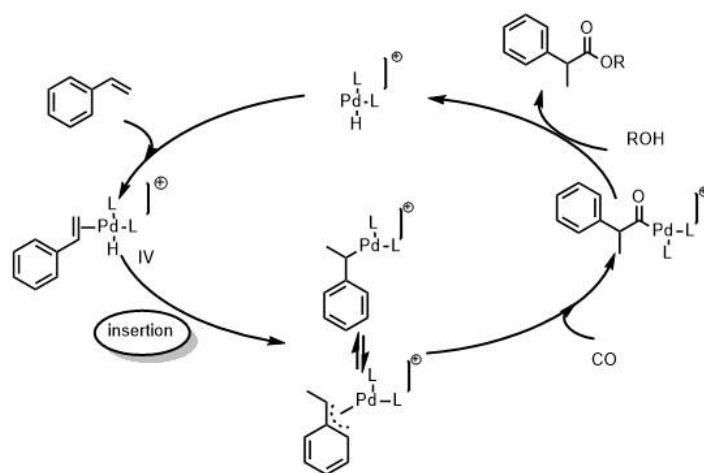
Scheme 35: Proposed mechanism for branched-selective alkoxycarbonylation of vinylarene

Besides alcohol, amine is also a potential substrate for the *iso*-selective carbonylation. In 2014, Dyson, Liu and co-workers described an efficient method for the synthesis of *N*-aryl substituted carboxamides via the palladium-catalyzed aminocarbonylation of alkenes with CO and anilines.[51] Later on, Alper reported a ligand-controlled regioselective Pd-catalyzed carbonylation of styrenes with aminophenols was realized, chemoselectively affording amides (Scheme 36).[52] Despite the significant progress in

this area, all these methods are limited to aromatic amines as substrates and carbonylations with aliphatic amines failed.
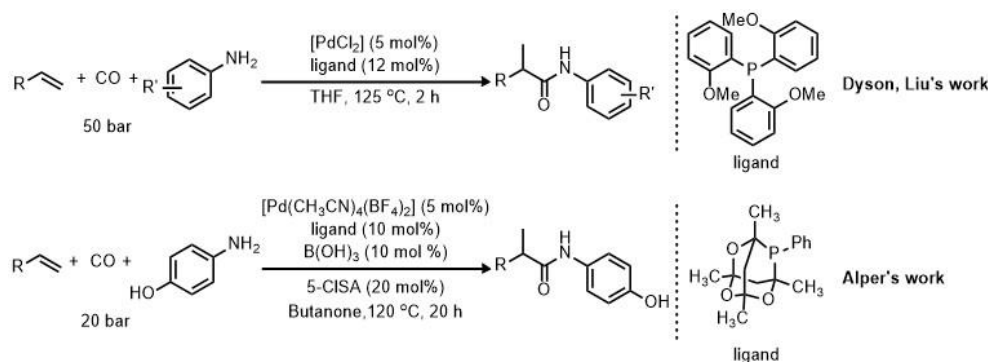
Scheme 36: Branched-selective aminocarbonylation of alkenes

In addition, branched selective carbonylations of vinyl acetate are also reported in the past years. The first example on the alkoxycarbonylation of vinyl acetate dates back to 1992, when Drent reported the methoxycarbonylation of vinyl acetate using [Pd(OAc)$_2$] and d^{t}bpp as catalyst.[37] In 2005, Cole-Hamilton and co-workers described that [(d^{t}bpx)PdH]$^+$ catalyst was also active for the carbonylation of vinyl acetate.[53] The selectivity to branched product achieved as high as 78% at 25°C. The regioselectivity of carbonylation of vinyl acetate is usually explained by the weak coordination of the acetyl group. As depicted in Scheme 37, a five membered palladacycle would form as a stabilized intermediate, which leads to the formation of branched carbonylated product as the major product.
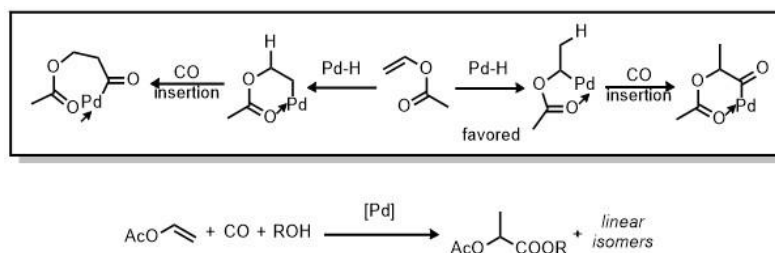
Scheme 37: Branched-selective alkoxycarbonylation of vinylacetate

Generally, if an alkene contains an electron-withdrawing group attached to it, the carbonylation reaction tends to occur at its α-position (Scheme 38). In 1983, alkoxycarbonylation and hydroxycarbonylation of 3,3,3-trifluoropropene and pentafluorostyrene have been reported by Ojima and co-workers.[54] Ethyl 2-methyl-3,3,3-trifluoropropionate was obtained in 96% yield with 79% *iso*-selectivity in the alkoxycarbonylation reaction of 3,3,3-trifluoropropene by using [PdCl$_2$(PPh$_3$)$_2$] as catalyst. Additionally pentafluorostyrene was also alkoxycarbonylated to the corresponding branched ester with 89% yield and 95% regioselectivity using the same catalyst (Scheme 38).

$R_f = CF_3$, 96% yield, b/l = 79:21
$R_f = C_6F_5$, 89% yield, b/l = 95:5
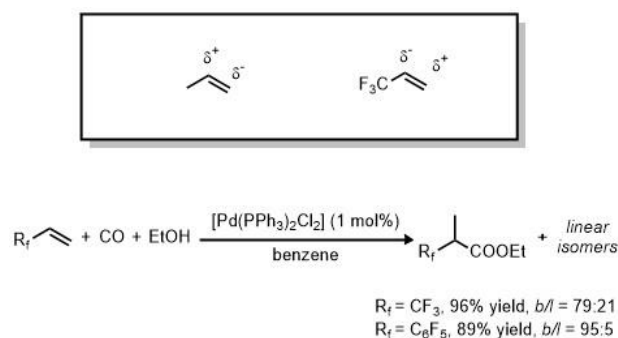
Scheme 38: Branched-selective alkoxycarbonylation of perfluoroalkene

A breakthrough example on this topic was reported in our research group. In 2016, our research group developed an efficient catalyst for Markovnikov-selective alkoxycarbonylation of aliphatic olefins (Scheme 39).[55] In this work, our group showed for the first time that a specific palladium catalyst system consisting of PdX$_2$/N-phenylpyrrole (X = halide) catalyse the alkoxycarbonylation of various alkenes to give the branched esters in high selectivity (b/l up to 91/9). The observed but unexpected selectivity has been rationalized by density functional theory computation including dispersion correction for van der Waals interaction.
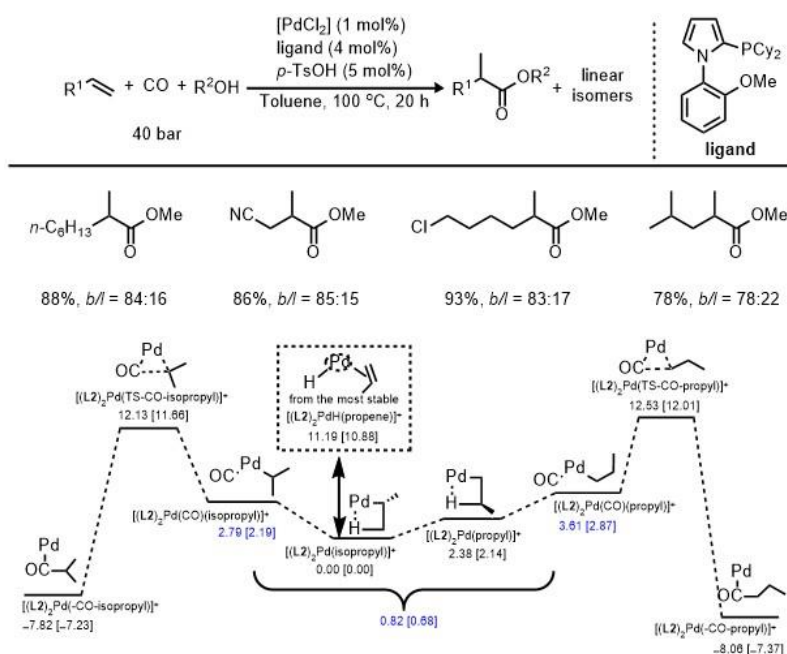
Scheme 39: Mechanistic insight of branched selective alkoxycarbonylation of alkenes by DFT calculation

1.2.3   Carbonylation with different unsaturated compounds

Apart from simple alkenes, other unsaturated compounds such as allylic alcohols, 1,3-dienes and

allenes are also suitable substrates for carbonylation reactions for the synthesis of versatile unsaturated products.

Allylic alcohols are a kind of sustainable organic compounds which already found their broad applications. They are largely used in industry for 1,4-butanediol production by the hydrogenation process of hydroformylation product.[56] Besides hydroformylation reaction, Reppe type carbonylation reactions with different nucleophiles are also reported in the past years.[57] In 2013, a general and practical procedure for the alkoxycarbonylation of allylic alcohol was reported in our research group (Scheme 40).[58] This catalyst system consists of [Pd(OAc)$_2$], phosphine ligand, such as Xantphos or BuPAd$_2$ and trifluoroacetic acid. Interestingly, this reaction proceeds through a novel sequential C-O coupling/carbonylation pathway. A broad scope of allylic alcohols with aliphatic alcohols to produce a variety of synthetically useful β,γ-unsaturated esters was showed in this reaction.
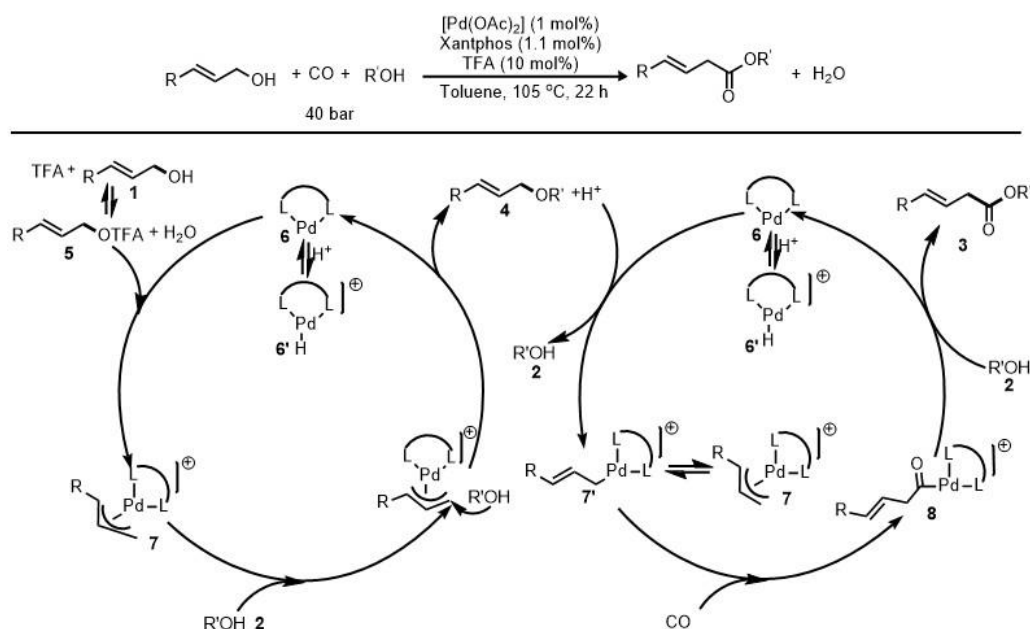
Scheme 40: Pd catalyzed alkoxycarbonylation of allylic alcohols

In addition, carbonylation of allylic alcohols with thiols and amines were also reported by Alper[57] and Beller's group (Scheme 41).[59]
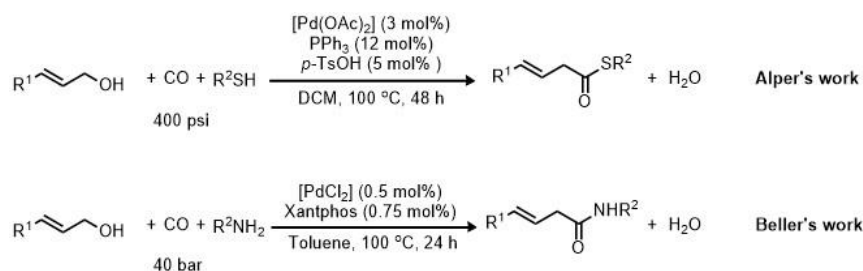
Scheme 41: Carbonylation of allylic alcohols with thiols and amines

1,3-Dienes are largely produced in the bulk and fine chemical industries because of their valuable application to produce synthetic rubber, functional materials, dyes and organic intermediates.[60] Specifically, the selective carbonylation of 1,3-butadiene is of major industrial interests, which give rise to the production of adipic acid and ε-caprolactam via 3-pentenoic acid ester. The early works by DuPont,[61] BASF[62] were based on Co salts as the catalysts, which suffered from harsh conditions (high temperature, high CO pressure and high catalyst loading). In the late 1960s, Tsuji et al. described using PdCl$_2$ as catalyst for the alkoxycarbonylation reaction of 1,3-butadiene, however the productivity was low (at approximately 30% yield).[63] In 2002, our group demonstrated an improved catalyst system for the methoxylcarbonylation of 1,3-butadiene with a TON up to 1200 (Scheme 42).[64] By using palladium catalyst in the presence of dppb and 4-tertbutylbenzoic acid, the telomerization reaction is almost completely suppressed.
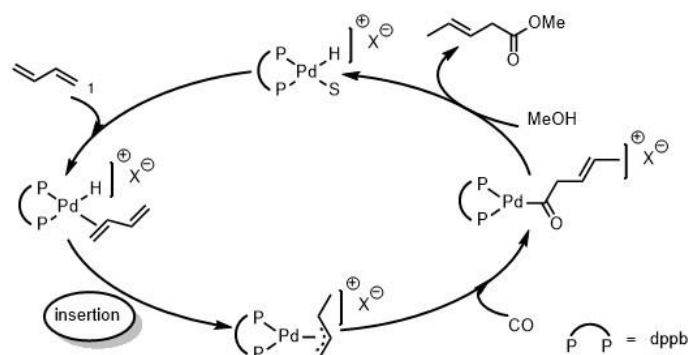
Scheme 42: Mechanistic proposal for palladium-catalyzed alkoxycarbonylation of 1,3-butadiene

Furthermore, recently our group reported various nucleophiles (alcohols,[65] amines,[66] amides[67]) reacted with 1,3-dienes to produce the corresponding β,γ-unsaturated products (Scheme 43).
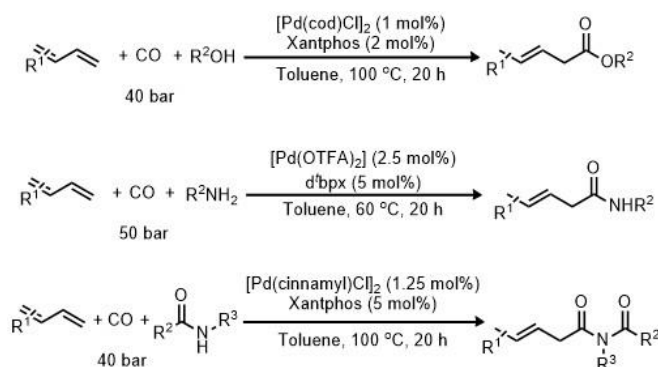
Scheme 43: Carbonylation of 1,3-dienes with other nucleophiles

Compared to other available alkenes, allylic alcohols, 1,3-dienes, the carbonylation of allenes has been

only scarcely investigated over the years. Nevertheless, they have become an important class of synthon in organic synthesis, which can be applied to construct a variety of valuable molecules based on their functionalization. As cumulated unsaturated species, allene is recognized that all the three carbons (C1, C2 and C3 position) on its double bonds can be the potential reaction sites. This allows for various transformations at different positions on allenes. However, it also brings out a challenge to realize regioselective reactions (Scheme 44).[68]
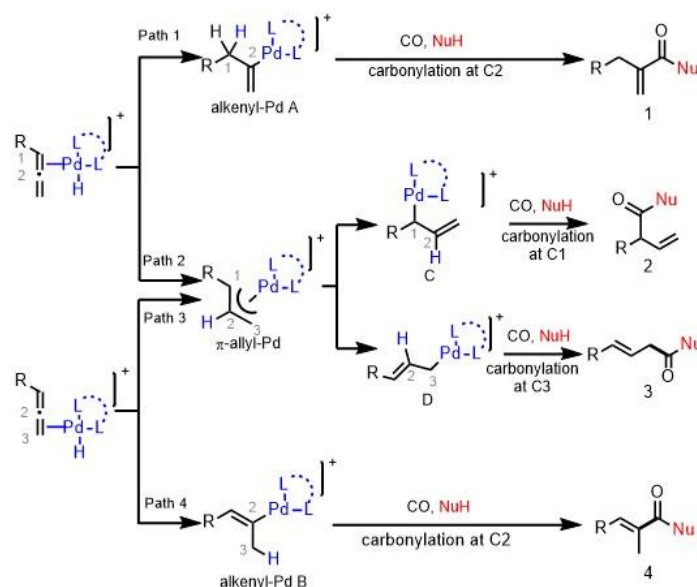
Scheme 44: Possible pathways for palladium-catalyzed allene carbonylation reactions.

In fact, to the best of our knowledge, only one example of Reppe carbonylations of allenes with specific nucleophlic substrates thiols, is reported by Alper and co-workers in 1998 (Scheme 45).[69] Hence, it is highly desirable to develop a more efficient and selective methodology to enrich this class of Reppe carbonylation reactions.
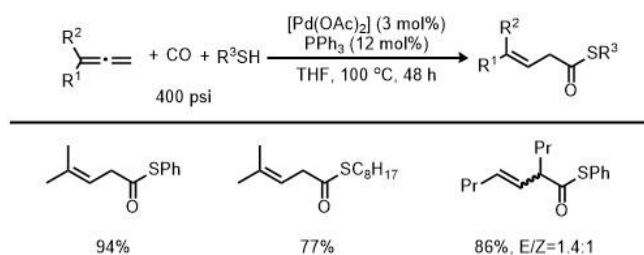
Scheme 45: Carbonylations of allenes with thiols

Recently, Breit and co-workers reported an elegant example on hydroformylation of 1,1-disubstituted allenes (Scheme 46).[70] Applying the self-assembling Rh^I/6-DPPon catalyst system the hydroformylation of 1,1-disubstituted allenes to β,γ-unsaturated aldehydes was achieved in excellent

chemo- and regioselectivity with high yields. When unsymmetrical 1,1-disubstituted allenes are converted, stereoselectivities of more than 95% for the Z-configured product can be reached.
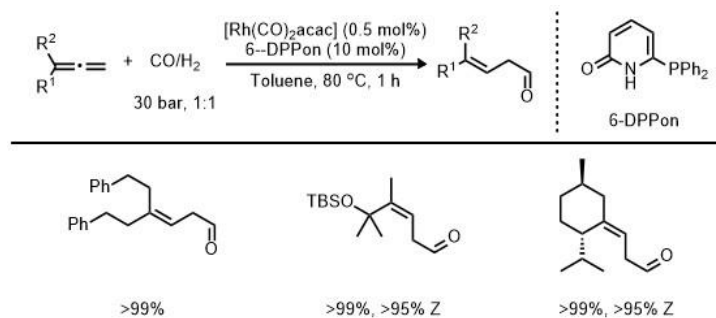
Scheme 46: Rhodium-catalyzed hydroformylation of 1,1-disubstituted allenes

2. Objectives of this work

As described in the introduction part, transition metal catalyzed carbonylation reactions have attracted much research interest both in academics and industries in last 70 years. Although numerous studies have been accomplished in this field, there still are great significance to increase the efficiency and selectivity of the processes through the development of new catalyst systems. The major aim of this work is to develop the novel catalyst systems for selective carbonylation of alkenes to useful bulk and fine chemicals, such as esters, amides and amines.

Due to their bulk availability and relative low price, novel catalytic transformations based on feedstock chemical-alkenes, especially for the internal alkenes, will be expected to complement the current methods for chemical production. Therefore, carbonylative transformations based on these substrates are proved to be highly atom-economic and efficient, which attracts our interest to further discover unknown transformations for sustainable organic synthesis.

In addition to the demand of novel transformations, the catalyst controlled regioselectivity in catalytic transformations is also a challenging work in this field. In this thesis, a novel and efficient catalyst system for branched-selective aminocarbonylation of nonfunctionalized alkenes is also described.

Moreover, the development of general catalytic protocols for more challenging substrates remains an important but challenging goal. Based on our continuous interest in carbonylation reactions, we became attracted by carbonylation of allenes, which represents a straightforward and economic method for the synthesis of versatile building blocks, α, β- and β,γ-unsaturated carbonyl compounds.
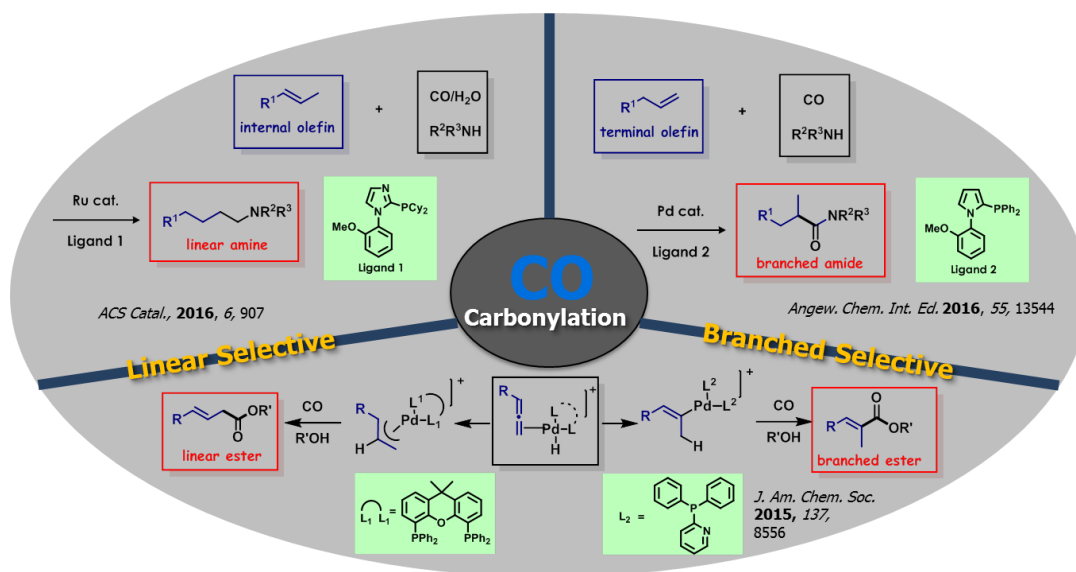
Figure 2: Selective carbonylation of alkenes and allenes

3. Summary of works

3.1 Ruthenium-catalyzed Domino Water-gas Shift/Hydroaminomethylation Sequence

Aliphatic amines are produced as valuable intermediates in the bulk and fine chemical industries. They are used as agrochemicals, pharmaceutical intermediates, solvents, dyes, monomers for polymerization and functional materials.[71] An environmentally benign synthesis of amines from olefins is the so-called hydroaminomethylation reaction.[72] This domino sequence includes hydroformylation of olefins to aldehydes, followed by condensation with amine to imines or enamines and final hydrogenation gives the desired alkylated amines (Scheme 47). A number of protocols for hydroaminomethylation of terminal olefins have been disclosed in recent years.[73] However, more challenging is the synthesis of linear amines from internal olefins. Such reactions are of industrial relevance because mixtures of internal olefins such as butenes, hexenes and octenes are more cost-efficient than the corresponding terminal olefins.
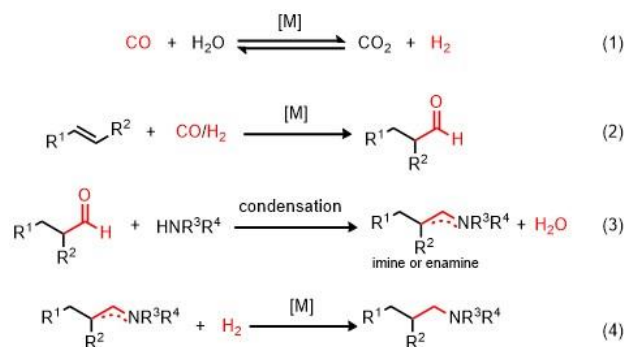
Scheme 47: domino water-gas shift reaction/hydroaminomethylation reaction

Interestingly, most of the known hydroformylation reactions of internal olefins require relatively expensive rhodium catalyst to ensure high activity and selectivity in the carbonylation step. Based on our continuing interest in hydroformylation using so-called "alternative metal" catalysts, our group firstly presented hydrogen-free ruthenium-catalyzed hydroaminomethylation of terminal olefins in 2014 (Scheme 48).[27] Although high yields and regioselectivities were obtained with terminal olefins, unfortunately, internal olefins showed only low activity in this reaction. In addition, recently we showed the catalytic activity of ruthenium catalysts in the presence of 2-phosphino-substituted imidazole ligands in ruthenium catalyzed hydroformylation and hydroaminomethylation reactions.[24-25] These results inspired us to apply such catalytic systems for the selective water-gas shift/hydroaminomethylation of internal olefins.
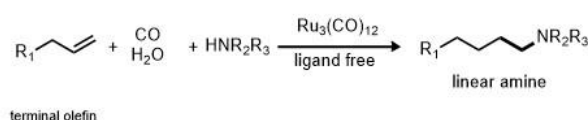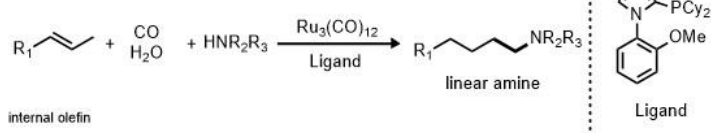
Scheme 48: Ruthenium-catalyzed domino water-gas shift/hydroaminomethylation of internal olefins

Initially, we evaluated the effect of different ligands using 2-octene and piperidine as model substrates (Figure 3). In the absence of ligand, only 13% yield of the desired 1-nonyl piperidine was obtained with a low regioselectivity. Using PPh_3 or PCy_3 as ligands did not improve the activity or selectivity. However, in the presence of L1 (2-(dicyclohexylphosphanyl)-1-phenyl-1H-imidazole) a high yield (93%) and good regioselectivity (n/i = 86:14) was observed. To elaborate the influence of this ligand structure on the catalyst reactivity, more heterocyclic and aromatic phosphine ligands were employed (L2 to L10). To our delight, applying L2 (2-(dicyclohexylphosphanyl)-1-(2-methoxyphenyl)-1H-imidazole) as the most efficient ligand afforded the amine product in 95% yield and good regioselectivity (n/i = 87:13). Notably, L3 with a less basic phenyl substituent on the phosphorus suppressed this reaction. L4 bearing the iPr group on phosphorus also provided good regioselectivity albeit gave slightly lower yield. Other imidazole ligands, such as L5 and L6, displayed high yields, while with moderate regioselectivities were observed. Benzimidazole-type ligand L6 did not present any improvement in this reaction. Other different heterocyclic and aromatic ligands (L8-L10) all gave low catalytically activity and regioselectivity.
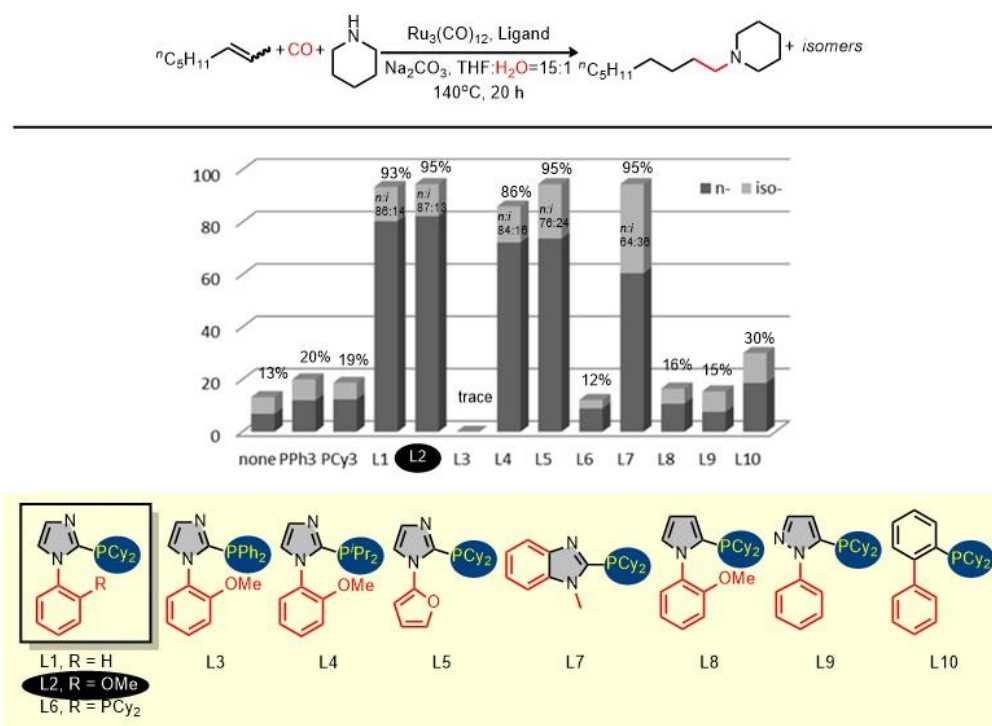
Figure 3: Ligand effects for the water-gas shift / hydroaminomethylation sequence of 2-octene with piperidine. Reaction conditions: 2-octene (1.3 mmol), piperidine (1.0 mmol), $Ru_3(CO)_{12}$ (0.5 mol%), monodentate ligand (1.5 mol%), bidentate ligand (0.75 mol%), Na_2CO_3 (5.0 mol%), CO (40 bar), THF (1.5 mL), H_2O (0.1 mL), 140 °C, 20 h. Yields and selectivity were determined by GC analysis using isooctane as the internal standard.

Then, we investigated the effects of other reaction parameters for the benchmark reaction, and the results are summarized in Table 1. When $[Ru_3(CO)_{12}]$ was replaced by $[Fe_3(CO)_{12}]$, essentially no reaction occurred. Control experiments showed that the ruthenium catalyst and water are essential for this reaction. Decreasing the temperature to 120°C led to significantly slower conversion, affording only 9% yield. As to the solvent, toluene also gave good regioselectivity albeit lower yield was obtained, while dipolar aprotic NMP showed less efficiency in terms of chemical yield. Notably, the reaction without base demonstrated lower yield, but still significant activity. Addition of benzoic acid instead of Na_2CO_3 led to no improvement for this transformation.

Table 1: Effects of reaction parameters:
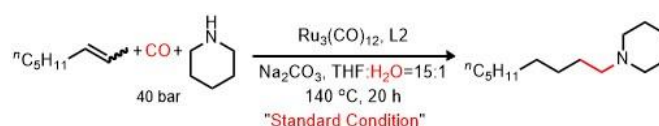
Entry	Variation from "Standard Condition"	Yield [%]	*n:i*
1	None	95	87:13
2	$Fe_3(CO)_{12}$ instead of $Ru_3(CO)_{12}$	0	-
3	Without $Ru_3(CO)_{12}$	0	-
4	Without water	0	-
5	120 ^{o}C instead of 140 ^{o}C	9	87:13
6	Toluene instead of THF	65	87:13
7	NMP instead of THF	33	85:15
8	Without Na_2CO_3	71	87:13
9	Benzoic acid instead of Na_2CO_3	73	87:13

Standard reaction conditions: 2-octene (1.3 mmol), piperidine (1.0 mmol), $Ru_3(CO)_{12}$ (0.5 mol%), L_2 (1.5 mol%), Na_2CO_3 (5.0 mol%), CO (40 bar), THF (1.5 mL), H_2O (0.1 mL), 140 ^{o}C, 20 h. Yield and selectivity were determined by GC analysis.

Applying optimized conditions good to excellent yields and selectivities towards the linear amines can be obtained from various aromatic and aliphatic alkynes as shown in Scheme 49. We were pleased to find that related internal olefins (2-octene, 3-hexene) reacted well to give the corresponding linear amines in good yield and regioselectivity. Functionalized 4-hexen-1-ol also reacted smoothly with a good yield (77%) and high regioselectivity (*n:I* = 91:9). Interestingly, cyclic olefins including cyclohexene, norbornene were found to be suitable substrates to afford the corresponding amines in high yields. Furthermore, the reactivity of different amines was investigated using 2-octene as substrate. With cyclic secondary amines like morpholine and 1-phenylpiperazine, good yields and regioselectivities were achieved. Acyclic amines such as di-*n*-butylamine, and (2-methylamino)ethanol also underwent this transformation smoothly in moderate and high yields and regioselectivities. Secondary benzylic amines were found to be suitable substrates, too; however product yields were only moderate.
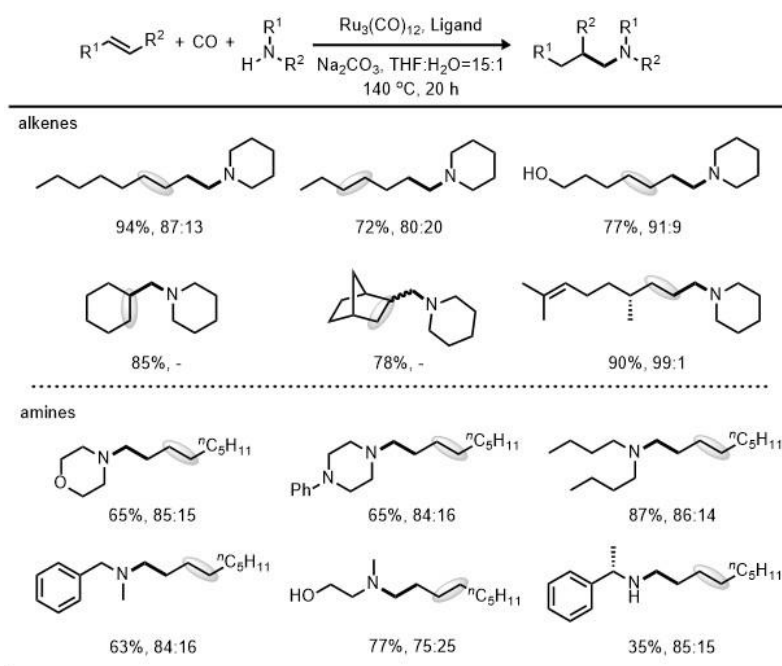
Scheme 49: Substrates scope. Reaction conditions: olefin (1.3 mmol), amine (1.0 mmol), $Ru_3(CO)_{12}$ (0.5 mol%), L2 (1.5 mol%), Na_2CO_3 (5.0 mol%), CO (40 bar), THF (1.5 mL), H_2O (0.1 mL), 140 °C, 20 h. Isolated yield. Selectivity was determined by GC analysis.

Furthermore, we were interested in demonstrating the utility of this method for the hydroaminomethylation of industrially important building blocks (Scheme 50). Here, crack C4, a mixture including 1-butene, 2-butenes, isobutene and butanes, which is a product from cracking of naphtha (light gasoline), reacted to the corresponding linear amines in high yield and regioselectivity with only 0.2 mol% $[Ru_3(CO)_{12}]$. Additionally, a mixture of octenes, which is mainly manufactured by oligomerization of ethylene, was also applied to this reaction and gave 81% yield with a selectivity of *n:i*=81:19.
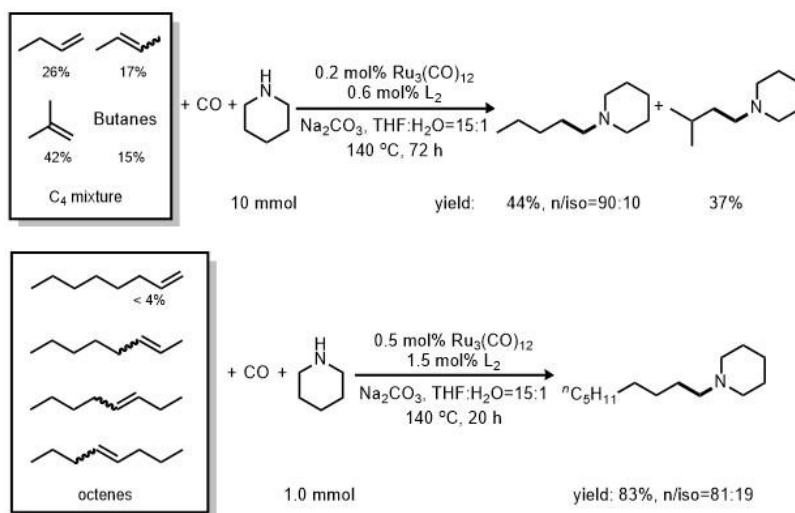
Scheme 50: Hydroaminomethylation of industrially important building blocks. Reaction conditions: For crack C4 (0.72 g), piperidine (10 mmol), $Ru_3(CO)_{12}$ (0.2 mol%), L2 (0.6 mol%), Na_2CO_3 (5.0 mol%), CO (50 bar), THF (15 mL), H2O (1 mL), 140 ^{o}C, 72 h. Isolated yield. Selectivity was determined by GC analysis. For octenes (1.3 mmol), piperidine (1.0 mmol), $Ru_3(CO)_{12}$ (0.5 mol%), L2 (1.5 mol%), Na_2CO_3 (5.0 mol%), CO (40 bar), THF (1.5 mL), H_2O (0.1 mL), 140 ^{o}C, 20 h. Isolated yield. Selectivity was determined by GC analysis.

Investigations into the coordination chemistry under hydro-formylation conditions in toluene by in situ FTIR-spectroscopy showed that a complex of the type $[Ru(CO)_4L2]$ (ν (CO) = 1946, 1977 and 2053 cm^{-1}) with trigonal-bipyramidal structure functions as a resting state (Figure 4). The monophosphine coordinates in the axial position. Even though the imine nitrogen of the imidazolyl moiety does not substitute a carbonyl ligand in the resting state, its presence seems to be essential for the outstanding activity. FTIR-experiments with the pyrrol derivative showed that a same type of complex $[Ru(CO)_4L8]$ with ν (CO) = 1943, 1976 and 2054 cm^{-1} was formed, but the catalytic performance was declined. This difference in activity can be perhaps attributed to a subtle interaction between the imine nitrogen of the imidazolyl unit and the ruthenium center in respective 16-electron complexes in the case of Ru/L2. A hemilabile behaviour was reported for heteroarylphosphines structurally similar to imidazole-substuted monophosphines.
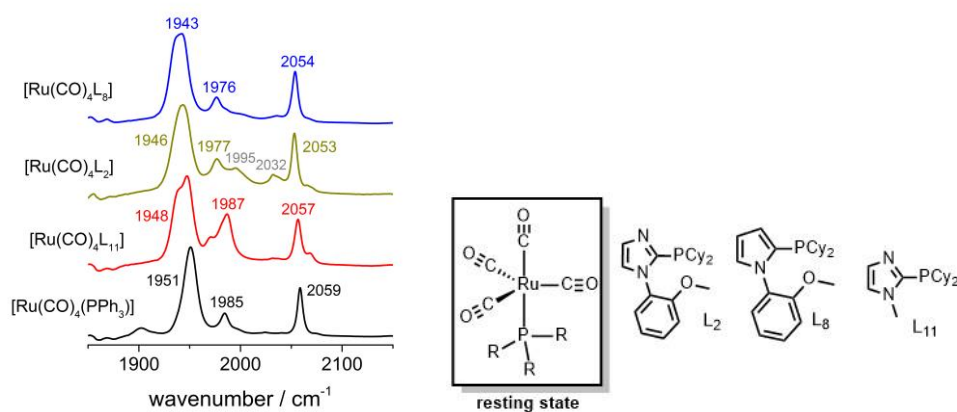
Figure 4: IR-spectra for [Ru(CO)4L] (L = PPh$_3$, L11, L2, L8) after the preformation from $[Ru_3(CO)_{12}]$/L. Bands at ν (CO) = 1995 and 2032 cm^{-1} can be attributed to $[Ru(CO)_5]$. Experimental conditions: T = 100 °C, p(CO) = 2.0 MPa, p(H$_2$) = 4.0 MPa, [Ru] = 4 × 10-3 mol L^{-1}, [L] = 4.4 × 10-3 mol L^{-1}, solvent = toluene.
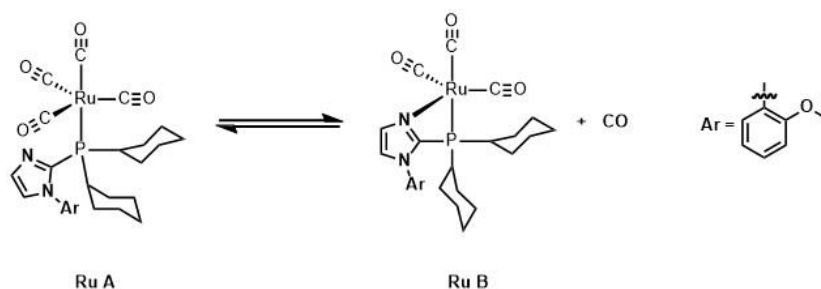
Scheme 51: Equilibrium between Ru A and Ru B

Actually, we think there is an equilibrium between $Ru(CO)_4L$ and $Ru(CO)_3L$ (Scheme 51). Under the high pressure of CO, the Ru A, $[Ru(CO)_4L]$ was observed as the major species in situ FTIR-spectroscopy. Additionally, the equivalent experiments of $Ru_3(CO)_{12}$ and L_2 was also done under syn gas (40 bar) for 2 hours. The ^{31}P NMR spectra and HRMS data were fast collected from reaction solutions after pressure release at room temperature under Ar (Scheme 52). To our delight, the Ru B, $Ru(CO)_3L$ was confirmed by MS (Scheme 53). We attempted to perform an X-ray analysis of Ru B, however, the crystallization was not successful because of the instability of this complex. Although currently we do not have very solid evidence to support our experimental results, this interesting finding intrigued us to further investigate the mechanism of this reaction in our future work.
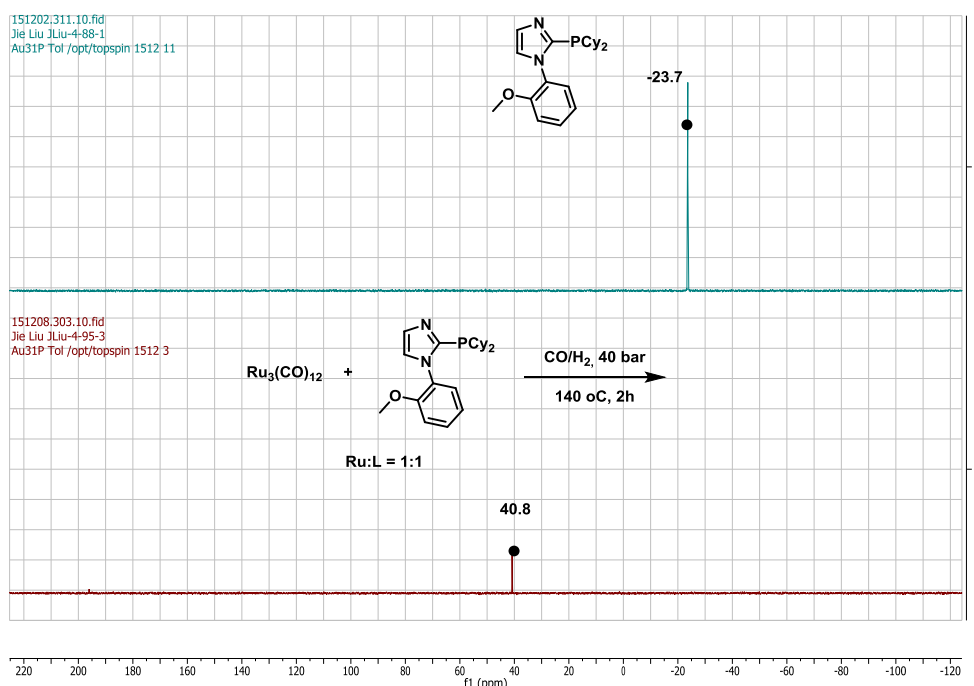
Scheme 52: ^{31}P NMR spectra

33
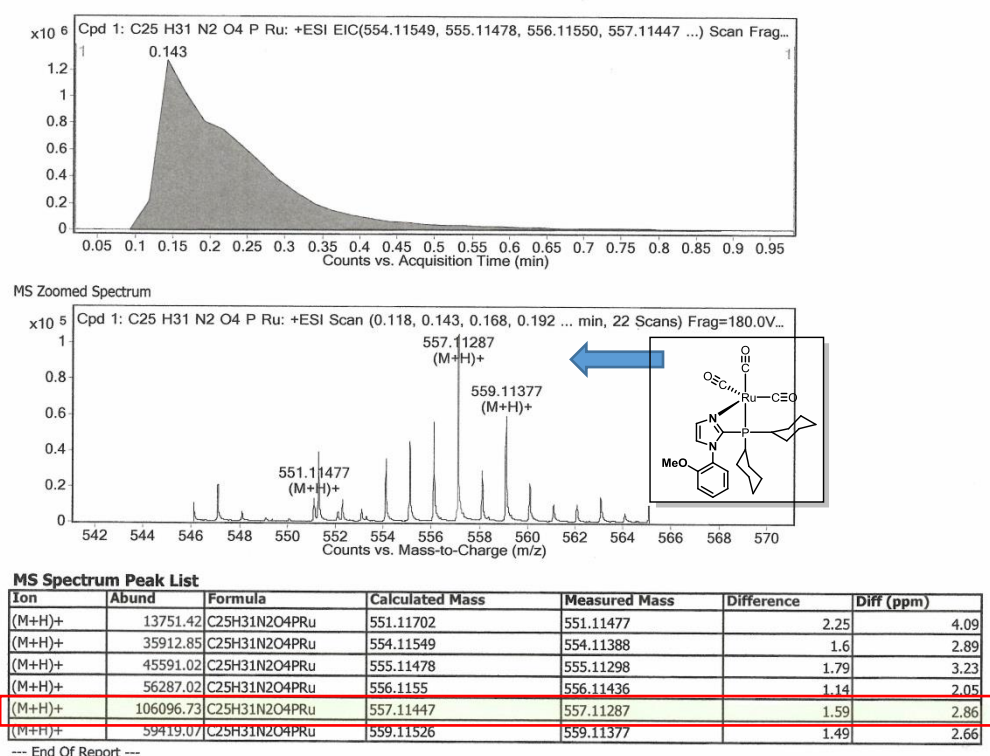
Scheme 53: HRMS spectra

In order to test the stability of the ruthenium catalyst, after 24 h of reaction, cooling to room temperature, and releasing the pressure, a new portion of substrate and gases was added and the reaction mixture was heated back to 140 $^{\circ}$C (Figure 5). Notably, the reaction took place, however, at a much slower rate. Stopping the reaction after additional 24 h, the products were obtained in 57% overall yield. This result demonstrated that this catalyst system seems not very stable in the absence of high CO pressure, which is consistent with our mechanistic finding.
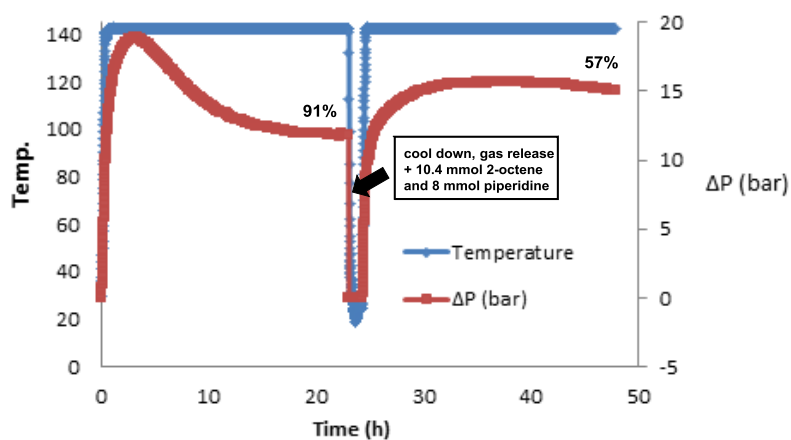
Figure 5: Gas consumption for catalyst stability test

Finally, the reaction progress of this ruthenium-catalyzed water-gas shift/hydroformylation of 2-octene and piperidine was examined in more detail. As depicted in Figure 6, the gas consumption started only after 2.5 hours and within this time only small amounts of E/Z isomerization of 2-octene were observed. Then, 2-octene was consumed slowly and at the same time, the corresponding amine and other internal octenes (3-octene and 4-octene) were formed (Figure 6). It is noteworthy that 1-octene, which is proposed as the intermediate in this transformation, was not accumulated during the reaction. In agreement with our previous work, this result is attributed to the faster hydroformylation of terminal olefins. In addition, neither aldehyde, enamine nor imine were detected during the whole reaction time, which illustrates a fast process of the aldehyde with the amine and subsequent hydrogenation reaction.
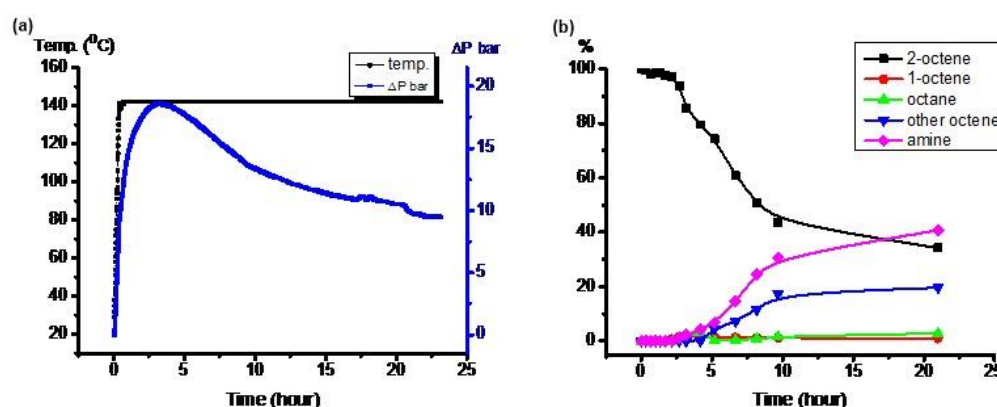
Figure 6: (a) Δp (Pressure change compared to initial pressure) curve and temperature curve. (b) Composition of the reaction mixture.

In conclusion, we demonstrate a novel domino sequence for the conversion of internal olefins to linear amines via catalytic water-gas shift reaction, subsequent olefin isomerization, followed by hydroformylation and reductive amination. Comparing with expensive rhodium catalyst, as a less costly alternative metal, ruthenium shows good reactivity and selectivity in this reaction. More importantly, in the presence of a special imidazole phosphine ligand, the corresponding linear amines are obtained in general in moderate to good yields and regioslectivity. This procedure is expected to complement the current methods for hydroaminomethylation reactions in organic synthesis.

3.3 Selective Palladium-Catalyzed Aminocarbonylation of Olefins to Branched Amides

Carbonylation reactions are widely used for the industrial production of fine and bulk chemicals, especially to produce valuable monomers for polymers.[74] Due to the versatility of the carbonyl group and the possibility to easily expand carbon chains they find also increasing applications in organic synthesis. Within this class of reactions, transition metal catalyzed aminocarbonylations, also called hydroamidations, represent a straightforward method for the conversion of available olefins, CO and

amines into the corresponding amides, which represent important intermediates, building blocks and functional molecules in organic synthesis, the chemical industry as well as biological systems.

Since the original work of Reppe and co-workers in the 1950s,[7] numerous catalytic systems based on Co,[75] Ni,[76] Fe,[77] Ru[78] complexes have been developed, which allow for the aminocarbonylation of olefins with amines. However, the severe reaction conditions (high temperature and CO pressure), unavoidable byproducts formamide and limited substrates scope impeded further applications of these processes. Although palladium-based catalysts for aminocarbonylation of olefins were reported independently by several groups recently, however, all these methods are limited to aromatic amines as substrates and carbonylations with aliphatic amines failed. This behavior is simply explained by the stronger basicity of aliphatic amines (Scheme 54):[79] For example, alanine ester (pK_b=4.87), benzylamine (pK_b=4.66), piperidine (pK_b=2.78) are much more basic than aniline (pK_b=9.37). Hence, aliphatic amines retard the generation of active Pd-H species, which are crucial for catalysis.
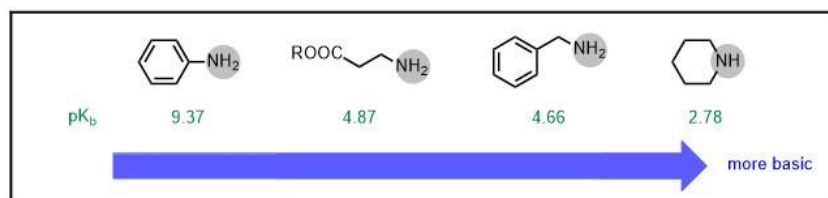
Scheme 54: The pK_b of various amines

To overcome this, Huang developed an elegant strategy to utilize aminals as surrogates of aliphatic amines.[44] Alternatively, our group applied a rhodium catalyst as the solution to this problem.[45] Noteworthy both catalyst systems favor the formation of the linear amides from olefins and aliphatic amines. In contrast, the formation of the branched amides from carbonylation reactions is more challenging due to the increase in steric effects for the olefin insertion into the palladium-hydride bond to form the secondary carbon-palladium intermediates (Scheme 55).
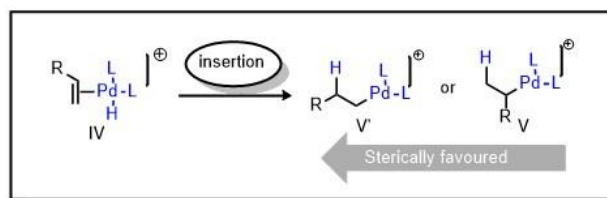
Scheme 55: Two pathways for olefin insertion into the Pd−H bond

Herein, we report for the first time the development of a general and efficient palladium catalyst for the aminocarbonylation of olefins with aliphatic amines giving selectively branched products (Scheme 56).
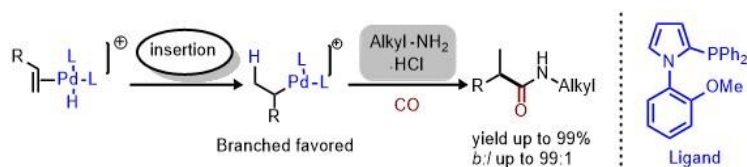
Scheme 56: Branched selective aminocarbonylation

In order to prevent the deactivation of the palladium hydride catalyst by the strongly basic aliphatic amine, we investigated the reaction of benzylamine with 1-octene in the presence of different acidic additives including Brønsted acids and Lewis acids. Based on our recent work on the alkoxylcarbonylation of olefins,[55] we used a combination of PdCl$_2$, CataCXium® POMeCy (2-(dicyclohexylphosphino)-1-(2-methoxyphenyl)-1H-pyrrole, L1) under 40 bar CO in THF at 100 $^{\circ}$C. As shown in Table 2, when BnNH$_2$ was used without any additives, no desired product was observed at all. Similarly, attempts to adjust the pH in reaction solution by adding hydrochloride salts like NEt$_3$·HCl did not give any product in this reaction. Other acidic additives, like Brønsted acids and Lewis acids all turned out to be ineffective. However, when applying BnNH$_2$·HCl instead of BnNH$_2$, the branched amide was formed with high selectivity (85:15) albeit moderate yield (48%) was achieved.

Table 2: Selective aminocarbonylation of 1-octene and benzylamine: Effect of additives.

Entry	Additive	Yield [%]	*b:l*
1	none	0	-
2	NEt$_3$·HCl (1.0 equiv.)	0	-
3	HOAc (1.0 equiv.)	0	-
4	HCl (10 mol%)	0	-
5	Zn(OTf)$_2$ (5 mol%)	0	-
6	Sc(OTf)$_3$ (5 mol%)	0	-
7	Yb(OTf)$_3$ (5 mol%)	0	-
8	**BnNH$_2$·HCl instead of BnNH$_2$**	**48**	**85:15**

Reaction conditions: 1-octene (2.0 mmol), BnNH$_2$ (1.0 mmol), PdCl$_2$ (1.0 mol%), ligand 1 (2.0 mol%), additive, CO (40 bar), THF (2.0 mL), 100 $^{\circ}$C, 20 h. Yields (*linear* & branched product) and regioselectivity were determined by GC analysis using isooctane as the internal standard.

It is interested that the amine hydrochloride salt is important to the successful aminocarbonylation. How about amine salt with other strong acid? Then we carefully examined the effect of amine salts in this transformation. We tried different acids, like HBr, sulfuric acid, MSA, TFA, and TfOH in this transformation, from the results in Table 3, only $BnNH_2 \cdot HCl$ gave the best yield and regioselectivity.

Table 3: Variation of different amine salts
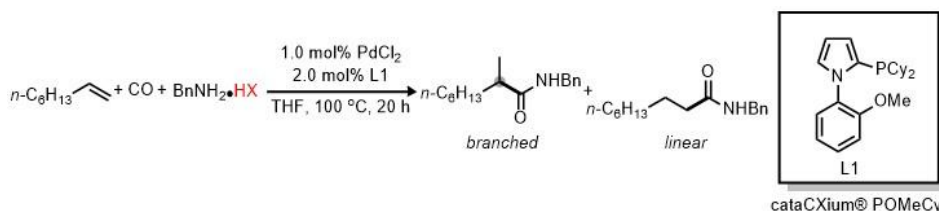
Entry	HX	Yield [%]	b:l
1	**HCl**	**48**	**85:15**
2	HBr	48	67:33
3	H_2SO_4 (0.5 equiv.)	3	-
4	CH_3SO_3H	2	-
5	CF_3COOH	0	-
6	CF_3SO_3H	0	-

Reaction conditions: 1-octene (2.0 mmol), $BnNH_2 \cdot HX$ (1.0 mmol), $PdCl_2$ (1.0 mol%), ligand 1 (2.0 mol%), CO (40 bar), THF (2.0 mL), 100 $^{\circ}$C, 20 h. Yields (*linear* & *branched* product) and regioselectivity were determined by GC analysis using isooctane as the internal standard.

It should be noted that the observed regioselectivity is unexpected, which intrigued us to further investigate this reaction. Hence, we examined the benchmark reaction in the presence of a series of phosphines (Figure 7). When PPh_3 was used as ligand, good yield (69%) was obtained while moderate regioselectivity was observed (b/l = 68:32). To elaborate the influence of the ligand structure on the catalyst reactivity, more (hetero)arylphosphine ligands were employed (L2 to L6). To our delight, when applying L2 (2-(diphenylphosphino)-1-(2-methoxyphenyl)-1H-pyrrole) the yield increased to 61% with a good branched-selectivity (b/l = 88:12). Notably, L3 bearing the tBu group on phosphorus suppressed this reaction. The modification of substitution at N on pyrrole from aryl to alkyl group (L4), did not present any improvement in this reaction. Notably, changing the pyrrole moiety to imidazolyl and phenyl (L5 and L6), the catalytic performance of the corresponding catalysts declined. Interestingly, bidentate ligands such as L7-L10 gave the linear amide as the major product. Finally, using 1.5 mol% Pd catalyst at 125 $^{\circ}$C led to the desired product in 81% yield and good regioselectivity (*b/l* = 88:12).
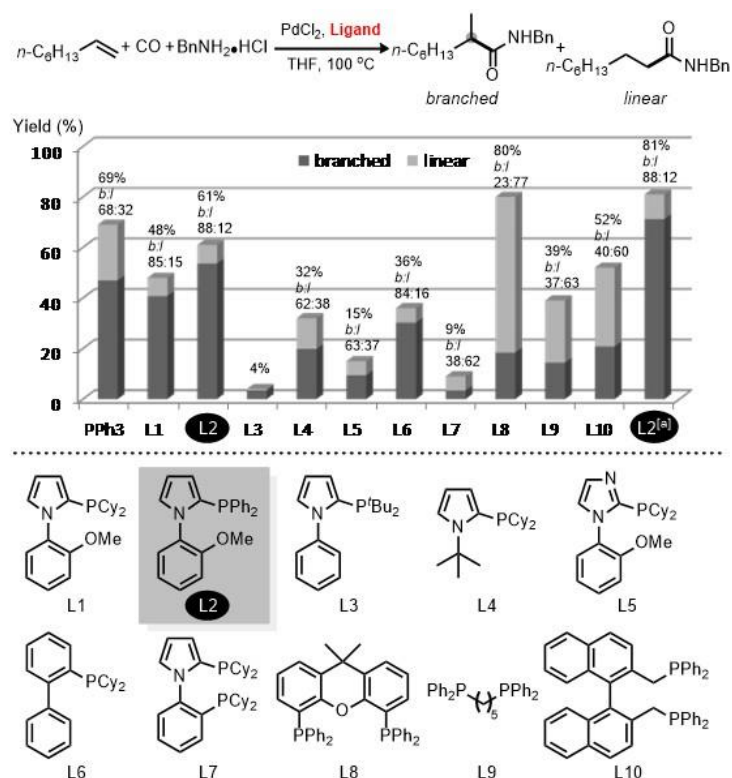
Figure 7: Ligand effect for branched selective aminocarbonylation of 1-octene with benzylamine hydrochloride. Reaction conditions: 1-octene (2.0 mmol), benzylamine hydrochloride (1.0 mmol), PdCl$_2$ (1.0 mol%), monodentate ligand (2.0 mol%), or bidentate ligand (1.0 mol%), CO (40 bar), THF (2.0 mL), 100 °C, 20 h. Yields and regioselectivity were determined by GC analysis using isooctane as the internal standard. [a] 1.5 mol% PdCl$_2$, 3.0 mol% L2 was added, 125 °C, 24 h.
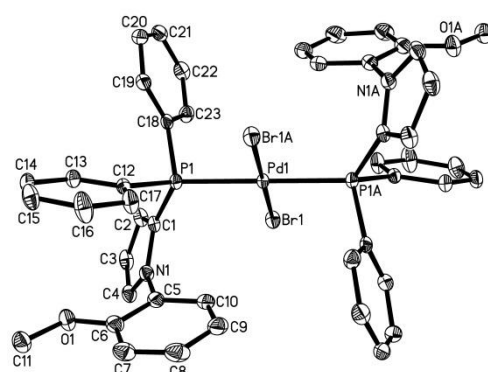
Figure 8: X-ray structure of Pd(L2)$_2$Br$_2$. Hydrogen atoms are omitted for clarity. Displacement ellipsoids correspond to 30% probability. Operator for generating equivalent atoms: -x+1, -y, -z+1.

Theoretically, simple 1-octene might form 4 different regioisomeric C9-amides because of the olefin

isomerization reaction and then followed by carbonylation of different internal olefins (Scheme 57). In the presence of our catalyst system, products at C2 and C1 postion were mainly obtained and only trace of other internal isomeric amides were observed in GC.
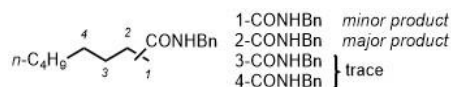
Scheme 57: Possible products of aminocarbonylation

With the optimized reaction conditions in hand, we explored the substrate scope. At first, the reactions of various aliphatic amines hydrochloride with 1-octene were studied (Scheme 58). With primary amines like benzylamine, isobutylamine, α-methylbenzylamine, as starting material good yields (70-80%) and regioselectivities (b-selectivity up to 87%) were achieved. More bulky substituted amines such as isopropylamine also underwent this transformation smoothly in moderate to good yields. Moreover, aromatic amine like aniline was selectively carbonylated to the branch amide in excellent yields and selectivity. On the other hand, this novel methodology allows to functionalize a series of amino acid derivatives in a straightforward manner. Here, several natural α-amino acids derivatives such as glycine methyl ester, and (S)-(+)-2-phenylglycine methyl ester hydrochloride participated efficiently in this process without racemization. Additionally, β-amino acids derivatives like β-alanine ethyl ester hydrochloride also reacted smoothly to give the corresponding amide 3al selectively.

Then, reactions of $BnNH_2 \cdot HCl$ with bulk industrial as well as functionalized olefins were studied. For example, industrially important propene gave *N*-benzyl isobutyric amide with only 0.2 mol% Pd catalyst in excellent yield. 4-methyl-1-pentene also furnished the desired aminocarbonylation products in moderate yields and branched selectivities. Olefins containing nitrile- , halogen- , ester-groups were efficiently converted to the branched amines (41-86%) with good regioselectivities. Allylbenzene also demonstrated excellent reactivity and high regioselectivity. Gratifyingly, aromatic olefins like styrene led to the corresponding amide in high yield with excellent *b*-selectivity (>99%). When (−)-β-citronellene was used as the substrates, the internal bond remained intact and only the double bond in the terminal position was selectively carbonylated to the branched amide.
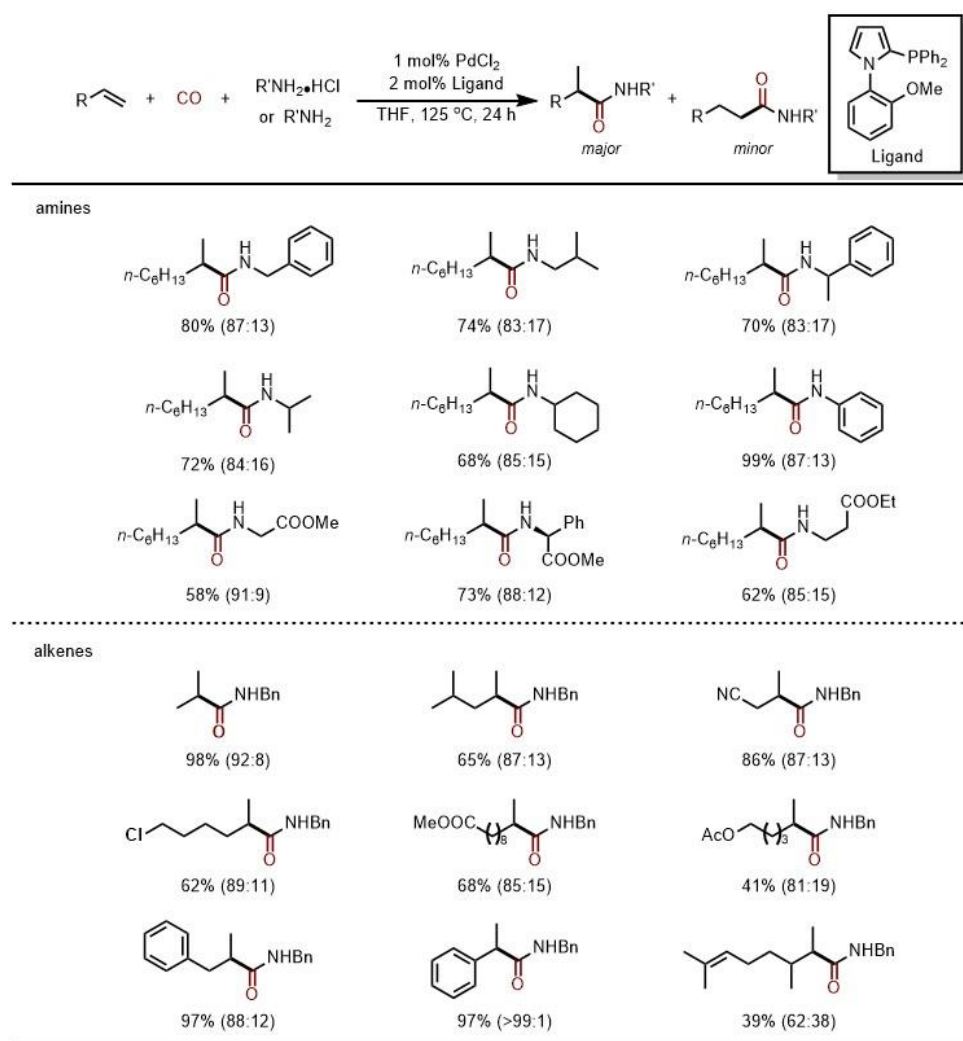
Scheme 58: Substrates scope. Reaction conditions: alkene (2.0 mmol), amine (1.0 mmol), PdCl$_2$ (1.5 mol%), L2 (3.0 mol%), CO (40 bar), THF (2.0 mL), 125 °C, 24 h. Yield of isolated mixture of *branched* (major) and *linear* (minor) amides. Regioselectivity was determined by GC analysis.

Additionally, in order to explore the enantioselectivity in this reaction, a chiral phosphine ligand and a chiral phosphinic acid were applied in this reaction (Table 4). To simplify the reaction condition, we choose styrene and aniline as the model substrate, with 1 mol% PdI$_2$ as catalyst, THF as solvent under 10 bar CO for 20 h. From the results above, chiral P-ligands and chiral phosphinic acid did not give enantioseletivity for the chiral α-methyl amides.

Table 4: Enantioselective aminocabonylation of styrene
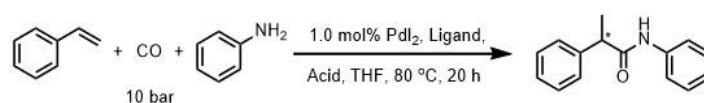
Entry	(chiral) Ligand	(chiral) Acid	Yield (b:l)	ee%
1		H_2O	99% (81:19)	0
2			78% (90:10)	0
3		H_2O	21% (83:17)	0
4			17% (88:12)	0

Reaction condition: styrene (2.0 mmol), PhNH$_2$ (1.0 mmol), PdI$_2$ (1.0 mol%), ligand (2.0 mol%), CO (10 bar), THF (2.0 mL), 80 ^{o}C, 20 h. Yields and regioselectivity were determined by GC analysis using isooctane as the internal standard. The enantioselectivity was determined by chiral HPLC analysis.

The following mechanism is proposed for the synthesis of branched amides (Scheme 59). Initially, Pd(II) catalyst precursor is in-situ reduced to Pd(0) species **II** in the presence of excess amount of phosphine ligands. In the presence of acid, Pd(0) is in an equilibrium with the corresponding Pd(II) hydride complex **III**. In the presence of this pyrrole ligand, the alkene substrate coordinates to Pd-H species, and consequent insertion of double bond will give secondary alkyl-Pd intermediates **V**. Then, Pd complex **V** undergoes a facile CO insertion process to give the corresponding acyl Pd species **VI**. Finally, amines attacking of intermediate VI generates the desired product branched amides **3** and closes the catalytic cycle.
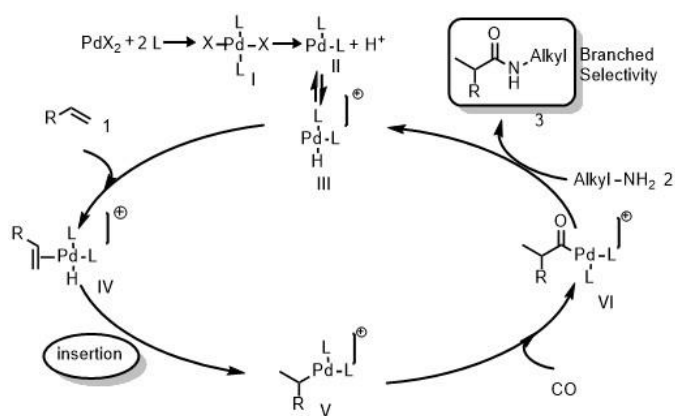
Scheme 59: Proposed mechanism for the synthesis of branched amides

42

In summary, we developed the first palladium catalyst system for a general and selective aminocarbonylation of olefins with aliphatic amines. Applying a special pyrrole type ligand, a wide range of aliphatic amines and olefins are efficiently transformed to the corresponding branched amides in good yields and often with high regioselectivity. Apart from simple aliphatic and aromatic amines, this procedure allows the efficient and selective aminocarbonylation of amino acids derivatives, too. In view of the easy availability of the substrates, the efficiency and the good regioselectivity, this method is expected to complement the current methods for carbonylations in organic synthesis

3.3 Ligand-controlled palladium-catalyzed alkoxycarbonylation of allenes

Transition metal catalyzed alkoxycarbonylations, also called hydroesterifications, represent a straightforward method for the conversion of widely available unsaturated compounds, CO and alcohols into the corresponding esters.[80] In this respect, catalytic alkoxycarbonylation is also of considerable interests for the synthesis of α,β- and β,γ-unsaturated carboxylic acid derivatives, which represent important intermediates, building blocks and functional molecules in organic synthesis, the chemical industry as well as biological systems.[81] Since the original work of Reppe in the past century,[7] alkoxycarbonylations of π-unsaturated compounds such as alkenes,[36, 38] 1,3-dienes,[65] and allylic alcohols[58] have been extensively studied and improved in our group. Despite all these works, it is still highly desirable to develop catalytic systems for the straightforward, convenient, and regioselective synthesis of α,β- and β,γ-unsaturated carboxylic acid derivatives from other easily accessible start materials. Key requirements for the applicability of such methodologies are high atom-economy, broad substrate scope as well as chemo- and regioselectivity.

Compared to other available olefins, the functionalization of allenes has been only scarcely investigated over the years.[82] Nevertheless, they have become an important class of synthon in organic synthesis, which can be applied to construct a variety of valuable molecules based on their functionalization. As cumulated unsaturated species, allene is recognized that all the three carbons (C1, C2 and C3 position) on its double bonds can be the potential reaction sites (Scheme 60). This allows for various transformations at different positions on allenes. However, it also brings out a challenge to realize regioselective reactions. Although allenes functionalizations including addition reactions, cyclizations, oxidation and reduction reactions are well developed in recent years,[82-83] however, the carbonylation of allenes is still challenging and very few examples are known.[69, 84] We herein present the first example of palladium-catalyzed alkoxycarbonylation of allenes to synthesize α,β- and β,γ-unsaturated esters regioselectively promoted by two different ligands.
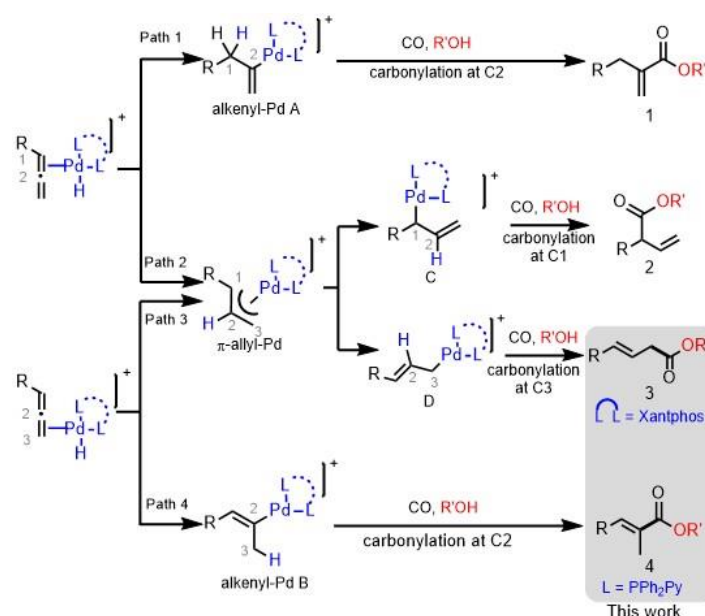
Scheme 60: Selective alkoxycarbonylation of allene

Initially, we investigated the Pd-catalyzed alkoxycarbonylation of conveniently available propa-1,2-dienylbenzene and *n*-butanol as a model reaction. It is noteworthy that three products were detected in this reaction: β,γ-unsaturated esters, α,β-unsaturated esters and direct C-O coupling product. In order to improve the selectivity, we firstly studied the ligand effect using $Pd(OAc)_2$ as the catalyst precursor and *p*-TsOH as the acid co-catalyst (Figure 9). The application of monodentate ligands, such as PPh_3, PCy_3, P^tBu_3 and $PAd_2{}^nBu$, all gave quite low catalytic activity with less than 10% yield of carbonylative products. Interestingly, when PPh_2Py was applied as the ligand, α,β-unsaturated ester was formed with high selectivity albeit only 18% yield was gained. Then, a serial of bidentate ligands were also tested. DPEphos and DPPF exhibited low reactivity for the carbonylation process which mainly led to the C-O coupling product. The application of DPPB, gave worse result with less than 5% yield of the desired product. To our delight, using d^tbpx and Xantphos as ligands, the desired product was not observed and Xantphos was identified as the most effective ligand to afford 90% yield with excellent selectivity.
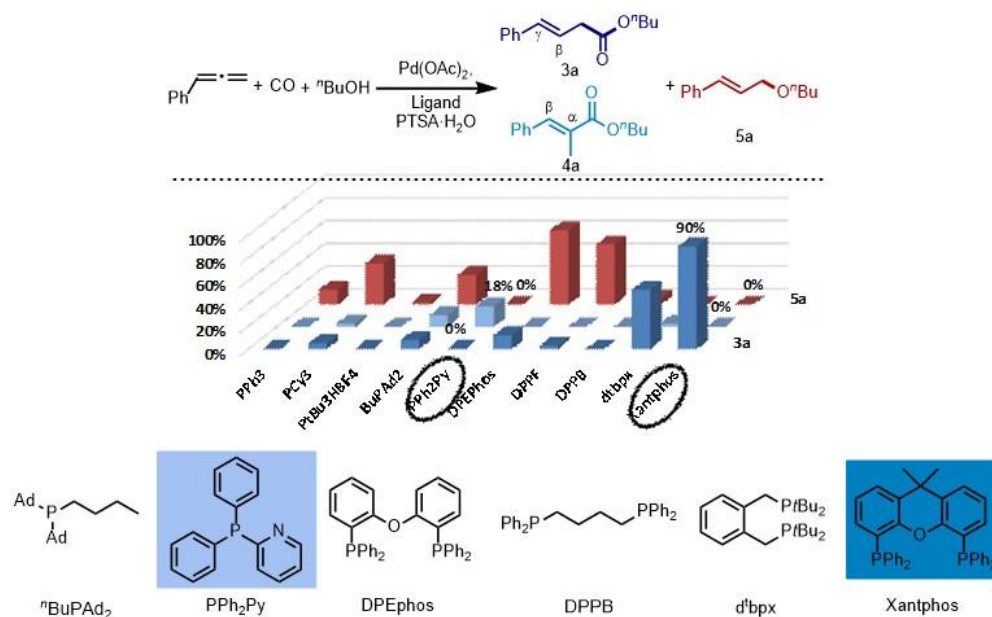
Figure 9: Ligand effect for the palladium-catalyzed alkoxycarbonylation of propa-1,2-dienylbenzene and n-butanol. Reaction conditions: allene (1.0 mmol), n-butanol (1.2 mmol), Pd(OAc)$_2$ (1.0 mol%), monodentate ligand (4.0 mol%), bidentate ligand (2.0 mol%), PTSA·H$_2$O (4.0 mol%), CO (40 bar), toluene (2 mL), 110 $^\circ$C, 20 h. Yields were determined by GC analysis using isooctane as the internal standard.

After optimizing the reaction conditions for the synthesis of butyl 4-phenyl-3-butenoate, we continued to explore the scope of different allenes (Scheme 61). To our delight, the catalytic system can be applied in a straightforward manner to a series of aryl-substituted allenes, and good yields were obtained with substrates bearing halogen or alkyl groups at both *para*, *meta* and *ortho* positions. In all these cases exclusive formation of the *E*-regioisomers took place. Notably, aliphatic allenes were found to be suitable substrates under similar conditions to afford the corresponding carbonylative products in moderate to good yields. As an example, cyclohexylallene participated in this carbonylation reaction with high reactivity. Moreover, electron-deficient allenes, e.g. ethyl 2,3-butadienoate, reacted smoothly and furnished a moderate yield of the desired product. Gratifyingly, the reaction of 1,1-disubstituted allene such as 3-methyl-1,2-butadiene also furnished the desired carbonylation product in moderate yield.

Furthermore, the reactivity of different alcohols was also investigated. Firstly, a variety of simple primary and secondary aliphatic alcohols were tested under the optimal reaction conditions. The corresponding esters were generated in good yields. It is noteworthy that by tuning the amount of allenes, the mono- and di-carbonylation products of diols can be selectively formed, respectively. Interestingly, bio-active alcohols such as amino acid derivatives and carbohydrates can be used in this transformation and synthetically useful yields were obtained. Last but not the least, some natural and

functionalized alcohols showed good reactivity as well. For instance, (-)-nopol, bearing a C=C bond, proved to be suitable. Notably, secondary natural alcohols, such as menthol (-)-borneol, and cholesterol participated in this transformation efficiently highlighting the broad substrate scope of this protocol and its potential utility in organic synthesis.
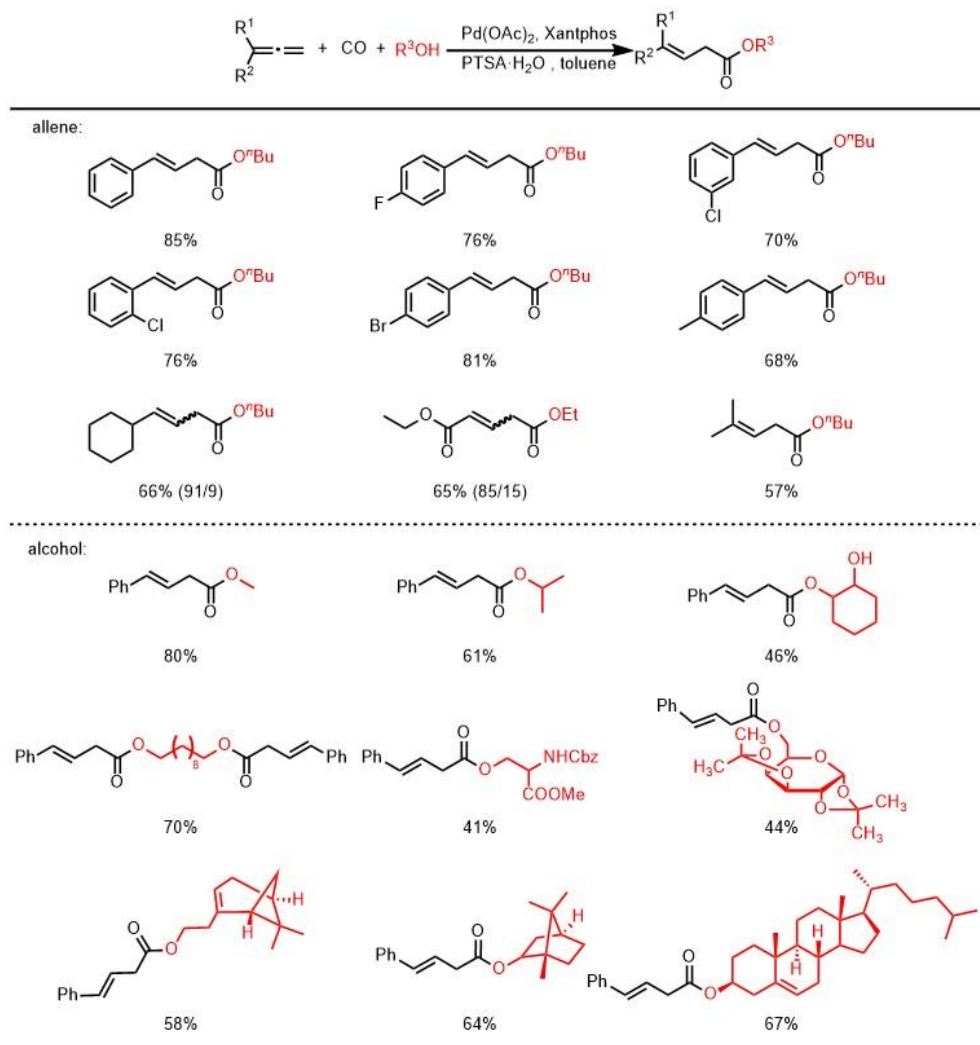
Scheme 61: Linear selective alkoxycarbonylation of allenes. Reaction conditions: allene (1.0 mmol), alcohol (1.2 mmol), Pd(OAc)$_2$ (1.0 mol%), Xantphos (2.0 mol%), PTSA·H$_2$O (4.0 mol%), CO (40 bar), toluene (2 mL), 110 ^{o}C, 20 h. Isolated yields. *E/Z* ratio is shown in the parentheses and determined by GC.

Furthermore, we were interested in demonstrating the utility of this method for the synthesis of an industrially important building block. 1,2-Butadiene is a minor product from oil cracking which is available from industry on multi-tons-scale. To the best of our knowledge no catalytic applications have been described of this feedstock in the open literature. Indeed, we succeeded to convert 1,2-butadiene into dimethyl adipate, which is a valuable start material for polymer and plasticizer

synthesis, in two steps (Scheme 62). The first alkoxycarbonylation reaction takes place with only 0.1 mol% Pd catalyst loading to give the β,γ-unsaturated esters with a TON of 820. Further decrease of the Pd catalyst loading led to a TON of even 2240. Subsequent transformation gave selectively dimethyl adipate in high yield via the second alkoxycarbonylation step based on a known isomerization carbonylation catalyst system.
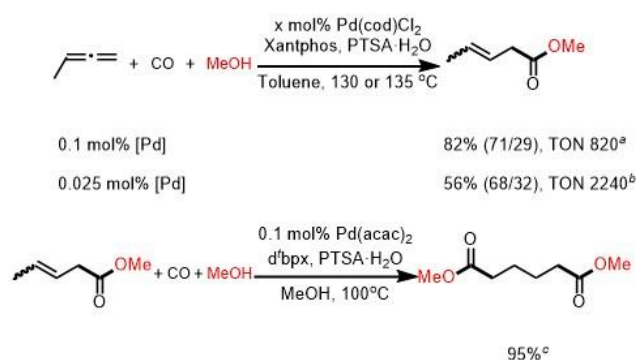
Scheme 62: Synthetic application by using 1,2-butadiene as the substrate. Reaction conditions: [a] 1,2-butadiene (20-25 mmol), methanol (20 mmol), Pd(cod)Cl$_2$ (0.1 mol%), Xantphos (0.2 mol%), PTSA·H$_2$O (0.4 mol%), CO (80 bar), toluene (10 mL), 130 ^{o}C, 20 h. GC yield. *E/Z* ratio is shown in the parentheses and determined by GC. [b] 1,2-butadiene (20-25 mmol), methanol (20 mmol), Pd(cod)Cl$_2$ (0.025 mol%), Xantphos (0.05 mol%), PTSA·H$_2$O (0.1 mol%), CO (80 bar), toluene (10 mL), 135 ^{o}C, 72 h. GC yield. *E/Z* ratio is shown in the parentheses and determined by GC. [c] Methyl 3-pentenoate (10 mmol), methanol (10 mL), Pd(acac)$_2$ (0.1 mol%), d^{t}bpx (0.4 mol%), PTSA·H$_2$O (0.8 mol%), CO (40 bar), 100 ^{o}C, 20 h. GC yield.

Next, the kinetic progress of the reaction between propa-1,2-dienylbenzene and *n*-butanol was examined under the optimal conditions (Figure 10a). It is shown that allene is initially converted into the C-O coupling product. Then, the β,γ-unsaturated ester is generated at a lower reaction rate along with the consumption of the reaction intermediate C-O coupling product. It illustrates that a common reaction intermediate, π-allyl-Pd species, is involved in these two reactions, which is more prone to undergo nucleophilic addition with aliphatic alcohols compared to the slow CO insertion step. In order to confirm whether the C-O coupling product is an intermediate in this carbonylation reaction, it was applied to the standard conditions and the corresponding β,γ-unsaturated ester was obtained with 76% yield (Figure 10b). To further verify that the direct C-O coupling process is catalyzed by palladium and acid co-catalyst, three control experiments were carried out. As shown in Figure 10c, under the standard conditions, the direct C-O coupling product is obtained in 77% yield after 15 min. However, in the absence of either Pd catalyst or PTSA·H$_2$O, there was no conversion of starting material at all.
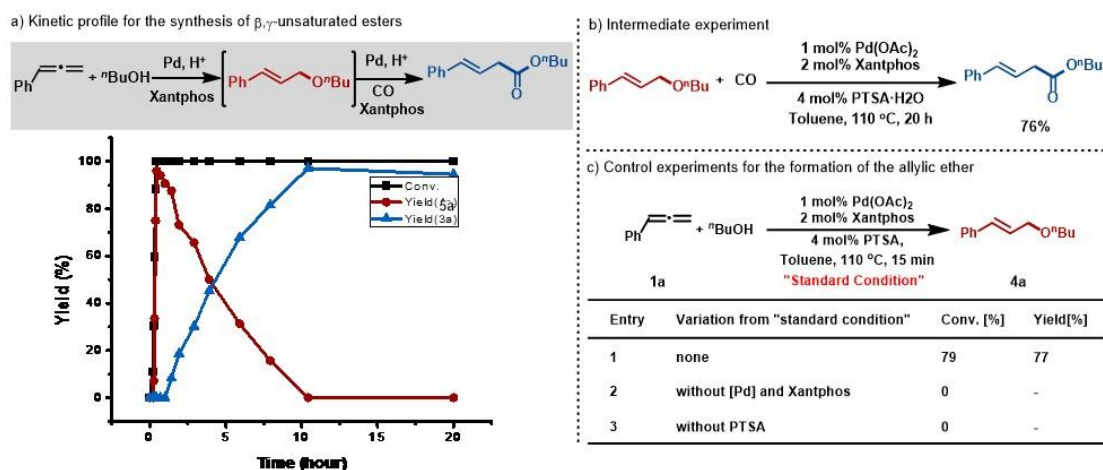
Figure 10: Mechanistic insights

In order to gain some mechanistic insights into this reaction, a deuterium labelling experiment was carried out. When methanol-d4 was applied in this transformation, 68% of the ester product was D-labelled only at the β-position along with 32% non-labelled product (Eq.1). The proton at the β-position in non-labelled product might be introduced from acid co-catalyst and trace amount of water in the solvent. Therefore, deuterated acid TsOD·D$_2$O was employed as well, and 8% of deuterated ester product at C2 position was obtained (Eq. 2) which indicates a partial scrambling process. Nevertheless, these results demonstrate a selective insertion of the double bond between C2 and C3 positions of allene into the Pd-D or Pd-H bond and the β,γ-unsaturated ester products were not generated via isomerization of preformed α,β-unsaturated isomers.
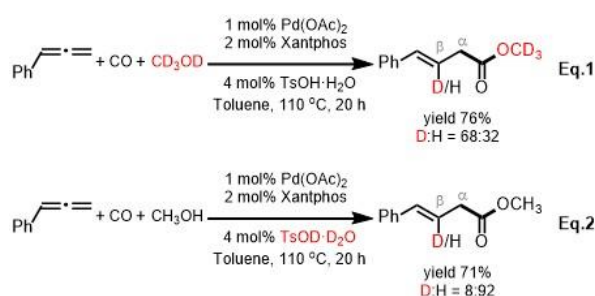
On the basis of all these experimental findings, the following mechanism is proposed for the synthesis of β,γ-unsaturated esters (Scheme 63). Initially, Pd(II) catalyst precursor is in-situ reduced to Pd(0) species I in the presence of excess amount of phosphine ligands. In the presence of acid, Pd(0) is in an equilibrium with the corresponding Pd(II) hydride complex II, which are both key catalytically active species to initiate the following domino catalytic cycles. The allene substrate coordinates to Pd-H species, and consequent insertion of C2-C3 double bond will give σ- and π-allyl-Pd intermediates. These intermediates undergo a fast nucleophilic substitution by the aliphatic alcohol at the less sterically hindered terminal position to afford the C-O coupling product and regenerate Pd hydride

species to finish cycle A. Subsequently, in the presence of acid, the ether is activated and reacts with Pd(0) species via oxidative addition to form σ- and π-allyl-Pd complex again. Then, CO insertion, the alcoholysis of intermediate VII provides the desired carbonylation product β,γ-unsaturated esters and regenerates Pd hydride species.
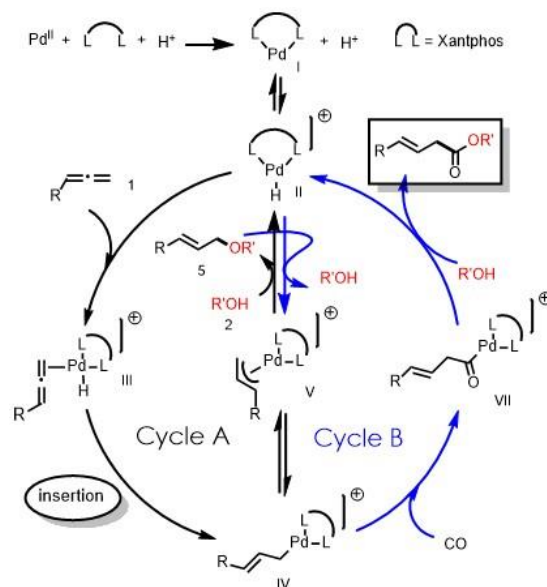
Scheme 63: Proposed mechanism for the synthesis of β,γ-unsaturated esters. (L,L = Xantphos)

As we discussed above (Figure 9), it is interesting to note that in the presence of PPh$_2$Py as ligand a good selectivity for the synthesis of the branched ester is observed, albeit in a low yield. This result intrigued us to vary the reaction conditions to improve the yield of this transformation. As shown in Table 5 the performance of the catalyst is influenced by the different acid co-catalysts. TFA (trifluoroacetic acid) showed superior reaction activity compared to other tested acid co-catalysts including PTSA·H$_2$O, CH$_3$SO$_3$H and CF$_3$SO$_3$H. Then, the effects of ligand and co-catalyst concentrations were investigated as well. Actually, both the concentrations of the acid co-catalyst TFA and the ligand have a profound influence on the yield of branched ester. To our delight, under optimized conditions the desired product is obtained in 75% yield along with 7% of linear product as by-product.

Table 5: Effect of acid co-catalyst and ligand for the synthesis of branched product.
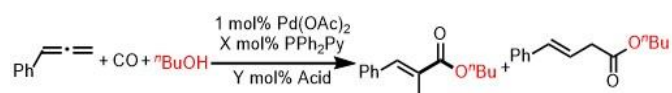
Entry	Acid	X:Y	Yield *(branched)* [%]	Yield *(linear)* [%]
1	PTSA·H$_2$O	4:4	18	Trace
2	CH$_3$SO$_3$H	4:4	20	Trace

3	CF$_3$SO$_3$H	4:4	4	Trace
4	TFA	4:4	44	4
5	TFA	4:5	43	5
6	TFA	4:6	49	5
7	TFA	6:6	56	7
8	**TFA**	**6:8**	**75**	**7**
9	TFA	6:10	66	11

Reaction conditions: allene (1.0 mmol), *n*-butanol (1.2 mmol), Pd(OAc)$_2$ (1.0 mol%), PPh$_2$Py (X mol%), Acid (Y mol%), CO (40 bar), toluene (2.0 mL), 110 $^{\circ}$C, 20 h. GC yield.

With the optimal conditions established, various alcohols were employed to react with allenes to produce the corresponding α,β-unsaturated esters (Scheme 64). All tested primary aliphatic alcohols gave the desired carbonylation product in good yields. Interestingly, some bio-active secondary alcohols were also compatible in this transformation and moderate yields were obtained. Then, different allenes were investigated in this transformation as well: 4-methyl phenyl substituted allene worked well under the standard conditions; remarkably, aliphatic allenes including cyclohexylallene, and 1,2-butadiene gave the corresponding ester product in moderate to good yields. Finally, a functionalized substrate, ethyl 2,3-butadienoate, underwent this transformation smoothly as well.
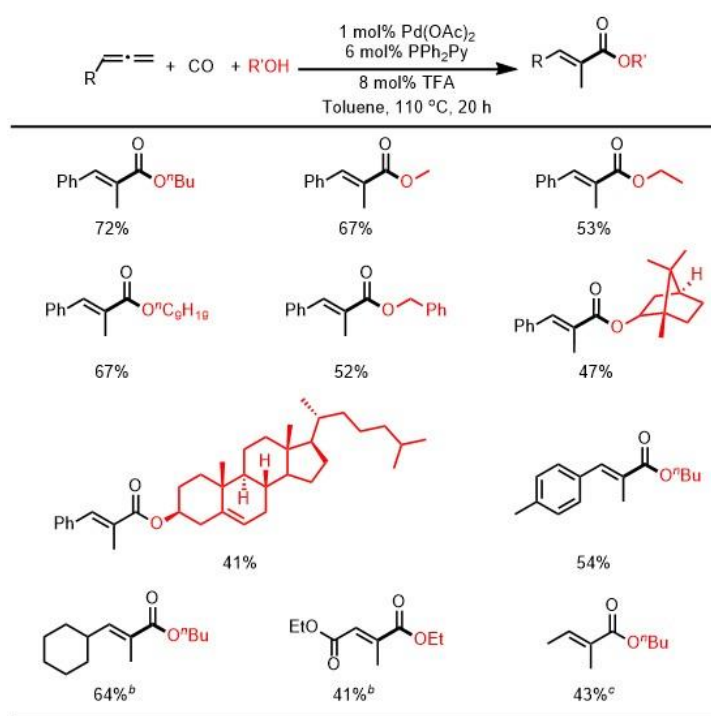
Scheme 64: Scope of different allenes and alcohols for the synthesis of α,β-unsaturated esters. Reaction conditions: allene (1.0 mmol), alcohol (1.2 mmol), Pd(OAc)$_2$ (1.0 mol%), PPh$_2$Py (6.0 mol%), TFA (8.0 mol%), CO (40 bar), toluene (2 mL), 110 $^{\circ}$C, 20 h. Isolated yields. [b] allene (1.0 mmol), alcohol

(4.0 mmol), Pd(OAc)$_2$ (1.0 mol%), PPh$_2$Py (6.0 mol%), TFA (8.0 mol%), CO (40 bar), toluene (2 mL), 110 ^{o}C, 20 h. Isolated yields. ^{c}allene (18 mmol), alcohol (20 mmol), Pd(cod)Cl$_2$ (0.2 mol%), PPh$_2$Py (1.2 mol%), TFA (1.6 mol%), CO (80 bar), toluene (10 mL) in a 25 mL autoclave, 130 ^{o}C, 20 h. Isolated yields.

In order to confirm whether the C-O coupling reaction intermediate is involved in this transformation, the kinetic progress was also examined under the optimal conditions. As is shown in Figure 11, the corresponding C-O coupling product was not observed during the whole reaction process. The carbonylation product was accumulated from the very beginning along with the gradual consumption of the allene substrate. This result proves that this reaction undergoes a mechanistically different reaction pathway compared to the synthesis of the β,γ-unsaturated esters.
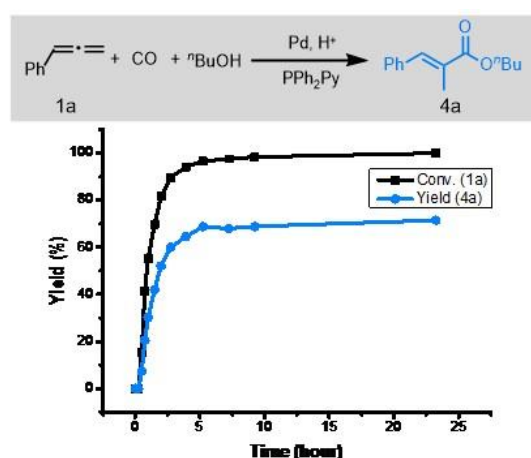
Figure 11: Kinetic profile for the synthesis of α,β-unsaturated esters.

Regarding the mechanism a similar deuterium labelling experiment was carried out. When methanol-d4 was applied to this reaction, 76% of the ester product was deuterated only at C3 position along with 24% non-labelled product (Eq. 3). Additionally, using TFA-*d* instead of TFA gave 6% of deuterated ester product at C3 position (Eq. 4). These results indicate that the double bond between C2 and C3 positions inserts into the Pd-D or Pd-H bond in a reverse manner compared to the synthesis of β,γ-unsaturated esters and the carbonylation products are not generated via the isomerization of other isomers as well.
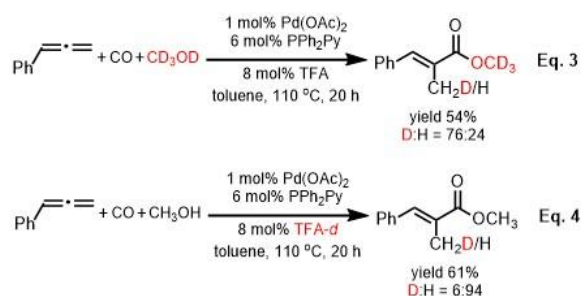
Based on this experimental observations, a possible reaction pathway is proposed for the synthesis of α,β-unsaturated esters. As shown in Scheme 65, the catalyst precursor leads to an equilibrium of the active Pd(0) species **I** with the Pd(II) hydride complex **II**. Then, allene coordinates to Pd to form the complex **III**, and subsequent double bond insertion in a reverse manner affords the alkenyl-Pd intermediate **VIII** instead of π-allyl-Pd intermediate formed in the previous example. Therefore, in contrast to the reaction pathway for the formation of β,γ-unsaturated esters, the direct C-O coupling product was not observed in this case as the reaction intermediate. Then, Pd complex **VIII** directly undergoes a facile CO insertion process to give the corresponding acyl Pd species **IX**. Finally, alcoholysis of intermediate **IX** generates the desired product α,β-unsaturated esters and closes the catalytic cycle.
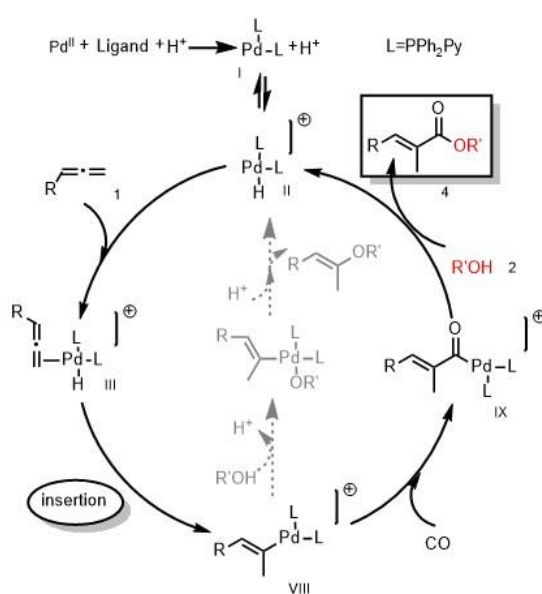
Scheme 65: Proposed mechanism for the synthesis of α,β-unsaturated esters.

In summary, we have developed the first general carbonylation reaction of allenes with aliphatic alcohols to produce a variety of synthetically useful unsaturated esters. Depending on the ligand present α,β- and β,γ-unsaturated esters are selectively formed. Interestingly, these two catalytic reactions proceeded via different reaction pathways supported by mechanistic studies. Moreover, the first catalytic reactions of the industrially available 1,2-butadiene are described. The valuable building block dimethyl adipate was obtained in high yield at low catalyst loadings. These procedures are expected to complement the current methods for carbonylation reactions in organic synthesis.

4. References

[1]   C. C. I. http://www.cefic.org/Facts-and-Figures/.

[2]   M. Beller, A. Renken, R. A. van Santen, *Catalysis: From Principles to Applications*, Wiley-VCH, **2012**.

[3]   M. Appl, *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, **2000**.

[4]   A. d. Klerk, *Fischer-Tropsch Refining*, **2011**.

[5]   M. Beller, *Catalytic Carbonylation Reactions*, Springer Berlin Heidelberg, **2006**.

[6]   R. Franke, D. Selent, A. Börner, *Chem. Rev.* **2012**, *112*, 5675-5732.

[7]   W. Reppe, H. Kröper, *Justus Liebigs Annalen der Chemie* **1953**, *582*, 38-71.

[8]   a) O. Roelen, *Chem. Abstr.* **1944**, *38*, 550, (DE 849548; US 1217066); b) B. Cornils, W. A. Herrmann, M. Rasch, *Angew. Chem. Int. Ed* **1994**, *33*, 2144-2163.

[9]   E. F. Lutz, *J. Chem. Educ.* **1986**, *63*, 202.

[10]   R. F. Heck, D. S. Breslow, *J. Am. Chem. Soc.* **1961**, *83*, 4023-4027.

[11]   a) J. A. Osborn, G. Wilkinson, J. F. Young, *Chem. Commun.* **1965**, 17-17; b) D. Evans, J. A. Osborn, G. Wilkinson, *Journal of the Chemical Society A: Inorganic, Physical, Theoretical* **1968**, 3133-3142.

[12]   A. Seayad, M. Ahmed, H. Klein, R. Jackstell, T. Gross, M. Beller, *Science* **2002**, *297*, 1676-1678.

[13]   a) G. D. Cuny, S. L. Buchwald, *J. Am. Chem. Soc.* **1993**, *115*, 2066-2068; b) M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje, *Organometallics* **1995**, *14*, 3081-3089; c) L. A. van der Veen, M. D. K. Boele, F. R. Bregman, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje, H. Schenk, C. Bo, *J. Am. Chem. Soc.* **1998**, *120*, 11616-11626; d) L. A. van der Veen, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Angew. Chem. Int. Ed.* **1999**, *38*, 336-338; e) D. Selent, K.-D. Wiese, D. Röttger, A. Börner, *Angew. Chem. Int. Ed.* **2000**, *39*, 1639-1641; f) J. J. Carbó, F. Maseras, C. Bo, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2001**, *123*, 7630-7637; g) H. Klein, R. Jackstell, K.-D. Wiese, C. Borgmann, M. Beller, *Angew. Chem. Int. Ed.* **2001**, *40*, 3408-3411; h) M. Ahmed, A. M. Seayad, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2003**, *42*, 5615-5619; i) D. Sémeril, C. Jeunesse, D. Matt, L. Toupet, *Angew. Chem. Int. Ed.* **2006**, *45*, 5810-5814; j) Y. Yan, X. Zhang, X. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 16058-16061; k) X. Jia, Z. Wang, C. Xia, K. Ding, *Chem. Eur. J.* **2012**, *18*, 15288-15295.

[14]   J. Pospech, I. Fleischer, R. Franke, S. Buchholz, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 2852-2872.

[15]   D. Evans, J. A. Osborn, F. H. Jardine, G. Wilkinson, *Nature* **1965**, *208*, 1203-1204.

[16]   K. Takahashi, M. Yamashita, Y. Tanaka, K. Nozaki, *Angew. Chem. Int. Ed.* **2012**, *51*, 4383-4387.

[17]   I. Piras, R. Jennerjahn, R. Jackstell, A. Spannenberg, R. Franke, M. Beller, *Angew. Chem. Int. Ed.* **2011**, *50*, 280-284.

[18]   L. Wu, Q. Liu, A. Spannenberg, R. Jackstell, M. Beller, *Chem. Commun.* **2015**, *51*, 3080-3082.

[19]   R. Jennerjahn, I. Piras, R. Jackstell, R. Franke, K.-D. Wiese, M. Beller, *Chem. Eur. J.* **2009**, *15*, 6383-6388.

[20]   L. F. Tietze, G. Brasche, K. M. Gericke, in *Domino Reactions in Organic Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, **2006**, pp. I-XIV.

[21]   K. Takahashi, M. Yamashita, K. Nozaki, *J. Am. Chem. Soc.* **2012**, *134*, 18746-18757.

[22] I. Fleischer, K. M. Dyballa, R. Jennerjahn, R. Jackstell, R. Franke, A. Spannenberg, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 2949-2953.

[23] I. Fleischer, L. Wu, I. Profir, R. Jackstell, R. Franke, M. Beller, *Chem. Eur. J.* **2013**, *19*, 10589-10594.

[24] L. Wu, I. Fleischer, R. Jackstell, I. Profir, R. Franke, M. Beller, *J. Am. Chem. Soc.* **2013**, *135*, 14306-14312.

[25] L. Wu, I. Fleischer, R. Jackstell, M. Beller, *J. Am. Chem. Soc.* **2013**, *135*, 3989-3996.

[26] A. Ambrosi, S. E. Denmark, *Angew. Chem. Int. Ed.* **2016**, *55*, 12164-12189.

[27] S. Gülak, L. Wu, Q. Liu, R. Franke, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2014**, *53*, 7320-7323.

[28] K. Dong, X. Fang, R. Jackstell, M. Beller, *Chem. Commun.* **2015**, *51*, 5059-5062.

[29] O. Abillard, B. Breit, *Adv. Synth. Catal.* **2007**, *349*, 1891-1895.

[30] X. Fang, R. Jackstell, A. Börner, M. Beller, *Chem. Eur. J.* **2014**, *20*, 15692-15696.

[31] K. A. Ostrowski, T. A. Faßbach, A. J. Vorholt, *Adv. Synth. Catal.* **2015**, *357*, 1374-1380.

[32] G. Kiss, *Chem. Rev.* **2001**, *101*, 3435-3456.

[33] W. Reppe, *Justus Liebigs Annalen der Chemie* **1953**, *582*, 1-37.

[34] B. El Ali, G. Vasapollo, H. Alper, *J. Org. Chem.* **1993**, *58*, 4739-4741.

[35] C. Jimenez Rodriguez, D. F. Foster, G. R. Eastham, D. J. Cole-Hamilton, *Chem. Commun.* **2004**, 1720-1721.

[36] K. Dong, X. Fang, S. Gülak, R. Franke, A. Spannenberg, H. Neumann, R. Jackstell, M. Beller, *Nature Commun.* **2017**, *8*, 14117.

[37] E. Drent, E. Kragtwijk*, Vol. EP 495548*, **1992**.

[38] K. Dong, R. Sang, X. Fang, R. Franke, A. Spannenberg, H. Neumann, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2017**, *10.1002/anie.201700317*.

[39] R. I. Pugh, E. Drent, P. G. Pringle, *Chem. Commun.* **2001**, 1476-1477.

[40] R. I. Pugh, E. Drent, *Adv. Synth. Catal.* **2002**, *344*, 837-840.

[41] G. R. Eastham, C. Jimenez, D. Cole-Hamilton,   (Ed.: LUCITE), WO/2004/014834, **2004**.

[42] C. Jimenez-Rodriguez, A. A. Nunez-Magro, T. Seidensticker, G. R. Eastham, M. R. L. Furst, D. J. Cole-Hamilton, *Cat. Sci. Tech.* **2014**, *4*, 2332-2339.

[43] X. Fang, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 14089-14093.

[44] G. Zhang, B. Gao, H. Huang, *Angew. Chem. Int. Ed.* **2015**, *54*, 7657-7661.

[45] K. Dong, X. Fang, R. Jackstell, G. Laurenczy, Y. Li, M. Beller, *J. Am. Chem. Soc.* **2015**, *137*, 6053-6058.

[46] H. Li, K. Dong, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2015**, *54*, 10239-10243.

[47] J. Mahatthananchai, A. M. Dumas, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, *51*, 10954-10990.

[48] J. Liu, H. Li, A. Spannenberg, R. Franke, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2016**, *55*, 13544-13548.

[49] K. Bittler, N. V. Kutepow, D. Neubauer, H. Reis, *Angew. Chem. Int. Ed* **1968**, *7*, 329-335.

[50] T. M. Konrad, J. T. Durrani, C. J. Cobley, M. L. Clarke, *Chem. Commun.* **2013**, *49*, 3306-3308.

[51] H. Liu, N. Yan, P. J. Dyson, *Chem. Commun.* **2014**, *50*, 7848-7851.

[52] T. Xu, F. Sha, H. Alper, *J. Am. Chem. Soc.* **2016**, *138*, 6629-6635.

[53] A. J. Rucklidge, G. E. Morris, D. J. Cole-Hamilton, *Chem. Commun.* **2005**, 1176-1178.

[54] T. Fuchikami, K. Ohishi, I. Ojima, *J. Org. Chem.* **1983**, *48*, 3803-3807.

[55] H. Li, K. Dong, H. Jiao, H. Neumann, R. Jackstell, M. Beller, *Nat. Chem.* **2016**, *8*, 1159-1166.

[56]   J. C. Pittman, W. Honnick, *J. Org. Chem.* **1980**, *45*, 2132-2139.

[57]   W.-J. Xiao, H. Alper, *J. Org. Chem.* **1998**, *63*, 7939-7944.

[58]   Q. Liu, L. Wu, H. Jiao, X. Fang, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 8064-8068.

[59]   H. Li, H. Neumann, M. Beller, *Chem. Eur. J.* **2016**, *22*, 10050-10056.

[60]   H. N. Sun, J. P. Wristers, in *Kirk-Othmer Encyclopedia of Chemical Technology*, John Wiley & Sons, Inc., **2000**.

[61]   W. F. Gresham, R. E. Brooks*, Vol. USP 2542767*, **1951, DU Pont**.

[62]   R. Kummer, F. J. Weiss, H. W. Schneider, V. Taglieber*, Vol. USP 4316047*, **1982, BASF**.

[63]   J. Tsuji, J. Kiji, S. Hosaka, *Tetrahedron Lett.* **1964**, *5*, 605-608.

[64]   M. Beller, A. Krotz, W. Baumann, *Adv. Synth. Catal.* **2002**, *344*, 517-524.

[65]   X. Fang, H. Li, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2014**, *53*, 9030-9034.

[66]   X. Fang, H. Li, R. Jackstell, M. Beller, *J. Am. Chem. Soc.* **2014**, *136*, 16039-16043.

[67]   H. Li, X. Fang, R. Jackstell, H. Neumann, M. Beller, *Chem. Commun.* **2016**, *52*, 7142-7145.

[68]   J. Liu, Q. Liu, R. Franke, R. Jackstell, M. Beller, *J. Am. Chem. Soc.* **2015**, *137*, 8556-8563.

[69]   W.-J. Xiao, G. Vasapollo, H. Alper, *J. Org. Chem.* **1998**, *63*, 2609-2612.

[70]   A. Köpfer, B. Breit, *Angew. Chem. Int. Ed.* **2015**, *54*, 6913-6917.

[71]   S. A. Lawrence, *Amines: Synthesis, Properties and Applications*, Cambridge University Press, Cambridge, **2006, November**.

[72]   T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795-3892.

[73]   a) M. Ahmed, C. Buch, L. Routaboul, R. Jackstell, H. Klein, A. Spannenberg, M. Beller, *Chem.–Eur. J.* **2007**, *13*, 1594-1601; b) M. Ahmed, A. M. Seayad, R. Jackstell, M. Beller, *J. Am. Chem. Soc.* **2003**, *125*, 10311-10318; c) B. Hamers, E. Kosciusko-Morizet, C. Müller, D. Vogt, *ChemCatChem* **2009**, *1*, 103-106; d) G. Liu, K. Huang, C. Cai, B. Cao, M. Chang, W. Wu, X. Zhang, *Chem.–Eur. J.* **2011**, *17*, 14559-14563.

[74]   a) P. W. N. M. Van Leeuwen, C. Claver, *Rhodium Catalyzed Hydroformylation, Vol. 22*, Springer Netherlands, **2002**; b) in *Catalytic Carbonylation Reactions* (Ed.: M. Beller), Springer Berlin Heidelberg, **2006**; c) B. Breit, in *Metal Catalyzed Reductive C–C Bond Formation: A Departure from Preformed Organometallic Reagents* (Ed.: M. J. Krische), Springer Berlin Heidelberg, Berlin, Heidelberg, **2007**, pp. 139-172.

[75]   a) P. Pino, P. Paleari, *Gazz. Chim. Ital.* **1951**, *81*, 64; b) P. Pino, R. Magri, *Chim. Ind.* **1952**, *34*, 511; c) S. I. Lee, S. U. Son, Y. K. Chung, *Chem. Commun.* **2002**, 1310-1311.

[76]   W. Reppe, H. Main, *Chem. Abstr.* **1953**, *47*, 5428.

[77]   A. Striegler, J. Weber, *Journal für Praktische Chemie* **1965**, *29*, 281-295.

[78]   Y. Tsuji, T. Ohsumi, T. Kondo, Y. Watanabe, *J. Organomet. Chem.* **1986**, *309*, 333-344.

[79]   a) H. K. Hall, *J. Am. Chem. Soc.* **1957**, *79*, 5441-5444; b) E. Folkers, O. Runquist, *J. Org. Chem.* **1964**, *29*, 830-832.

[80]   G. Kiss, *Chemical Reviews* **2001**, *101*, 3435-3456.

[81]   in *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals* (Eds.: M. Beller, C. Bolm), WILEY-VCH Verlag GmbH & Co. KGaA, **2008**.

[82]   D. J. Pasto, *Tetrahedron* **1984**, *40*, 2805-2827.

[83]   a) M. A. Tius, in *Modern Allene Chemistry*, Wiley-VCH Verlag GmbH, **2008**, pp. 817-845; b) M. Murakami, T. Matsuda, in *Modern Allene Chemistry*, Wiley-VCH Verlag GmbH, **2008**, pp. 727-815; c) A. Horváth, J.-E. Bäckvall, in *Modern Allene Chemistry*, Wiley-VCH Verlag GmbH,

2008, pp. 973-994; d) *Modern Allene Chemistry*, Wiley-VCH Verlag GmbH, **2008**; e) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067-3126; f) H. E. Schuster, G. M. Coppola, *Allenes in Organic Synthesis*, Wiley, New York, **1984**.

[84]   A. Nomoto, A. Ogawa, in *Modern Carbonylation Methods*, Wiley-VCH Verlag GmbH & Co. KGaA, **2008**, pp. 291-300.

5. Publications

5.1 From Internal Olefins to Linear Amines: Ruthenium-Catalyzed Domino Water-Gas Shift/Hydroaminomethylation Sequence

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Author contributions:

Prof. Matthias Beller and Jie Liu conceived and developed this project. Dr. Christoph Kubis performed the mechanistic study (in situ IR). Prof. Matthias Beller and Jie Liu wrote the manuscript with revisions provided by Dr. Ralf Jackstell and Prof. Robert Franke. My contribution as co-author of this paper is approximately 75%.

From Internal Olefins to Linear Amines: Ruthenium-Catalyzed Domino Water−Gas Shift/Hydroaminomethylation Sequence

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Ⓢ *Supporting Information*

ABSTRACT: A selective ruthenium-catalyzed water−gas shift/hydroformylation of internal olefins and olefin mixtures is reported. This novel domino reaction takes place through a catalytic water−gas shift reaction, subsequent olefin isomerization, followed by hydroformylation and reductive amination. Key to the success for the efficient one-pot process is the use of a specific 2-phosphino-substituted imidazole ligand and triruthenium dodecacarbonyl as precatalyst. Industrially important internal olefins react with various amines to give the corresponding tertiary amines generally in good yield and selectivity. This reaction sequence constitutes an economically attractive and environmentally favorable process for the synthesis of linear amines.

KEYWORDS: *internal olefin, linear amine, ruthenium, water−gas shift, hydroaminomethylation, domino reaction*
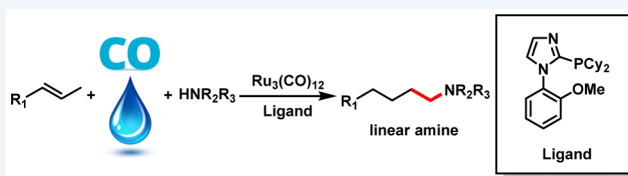
■ INTRODUCTION

Aliphatic amines are produced as valuable intermediates in the bulk and fine chemical industries.[1] They are used as agrochemicals, pharmaceutical intermediates, solvents, dyes, monomers for polymerization, and functional materials.[2] Nowadays, methods such as reductive amination of carbonyl compounds,[3] amination of alcohols,[4] and hydrogenation of the respective nitriles,[5] prevail in industry. In addition, a plethora of less atom-efficient methodologies such as classical nucleophilic substitution of alkyl halides[3a] and cross coupling reactions,[6] or less general methods like hydroamination of alkenes,[3a,7] are continuously being investigated for laboratory scale synthesis. Despite all these known processes, there is still considerable interest to develop improved routes to this class of compounds. An environmentally benign synthesis of amines from olefins is the so-called hydroaminomethylation reaction.[8] This domino sequence includes hydroformylation of olefins to aldehydes, followed by condensation with amine to imines or enamines and final hydrogenation gives the desired alkylated amines (Scheme 1, (2) to (4)). A number of protocols for hydroaminomethylation of terminal olefins have been disclosed in recent years;[9] however, more challenging is the synthesis of linear amines from internal olefins. Such reactions are of industrial relevance because mixtures of internal olefins such as butenes, hexenes, and octenes are more cost-efficient than the corresponding terminal olefins. Thus, our group developed the first general catalyst system for linear amine synthesis from internal olefins in 2002 (Scheme 2, (1)).[10] This work was inspired by related hydroformylations of internal olefins to give linear products.[11]

Scheme 1. Domino Water−Gas Shift/Hydroaminomethylation Sequence[a]

$$CO + H_2O \underset{[M]}{\rightleftharpoons} CO_2 + H_2 \qquad (1)$$

$$R^1\text{-olefin} + CO/H_2 \xrightarrow{[M]} R^1\text{-aldehyde} \qquad (2)$$

$$\text{aldehyde} + HNR^3R^4 \xrightarrow{condensation} \text{imine or enamine} + H_2O \qquad (3)$$

$$\text{imine/enamine} + H_2 \xrightarrow{[M]} R^1\text{-NR}^3R^4 \qquad (4)$$
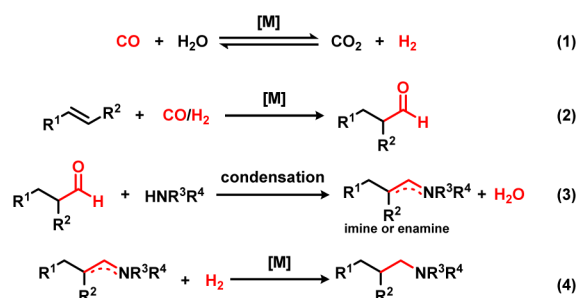
[a](1) Metal catalyzed water−gas shift reaction. (2) Hydroformylation of olefins. (3) Condensation of aldehyde and amine. (4) Hydrogenation of imine or enamine.

Interestingly, most of the known hydroformylation reactions of internal olefins require relatively expensive rhodium/ligand catalyst systems to ensure high activity and selectivity in the carbonylation step.[12] Hence, it is highly desirable to apply less costly alternative metals to realize this process.[13] In this regard, it is noteworthy that recently the groups of Nozaki,[14] Krische,[15] Ding,[16] Ackermann,[17] Sanford,[18] and others[19] as well as ourselves[20] have reported ruthenium-catalyzed C−C and C-hetero bond formation reactions and demonstrated their potential and application to hydroformylation reactions. Moreover, in the 1970s, homogeneous ruthenium,[21] as well

Scheme 2. Hydroaminomethylation of Olefins for the Synthesis of Linear Amines[a]
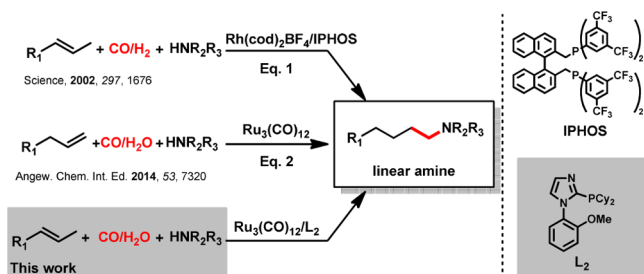
[a]Equation 1, rhodium catalyzed hydroaminomethylation of internal olefins. Equation 2, ruthenium catalyzed water–gas shift/hydroaminomethylation of terminal olefins.

as rhodium[22] and platinum[23] catalysts were found to demonstrate good activity for water gas shift reaction (Scheme 1 (1)), then these catalytic systems were further applied to hydrofomylation and hydrogenation reactions.[24] In this context, our group first presented hydrogen-free ruthenium-catalyzed hydroaminomethylation of terminal olefins in 2014 (Scheme 2, eq 2).[25] Although high yields and regioselectivities were obtained with terminal olefins, unfortunately, internal olefins showed only low activity in this reaction. These results intrigued us to develop a more general, practical and complementary ruthenium-catalyzed hydroaminomethylation of industrial importantly internal olefins.

In order to produce linear amines from internal olefins via hydroaminomethylation, a suitable catalytic system should fulfill several requirements: (1) This domino sequence consists of water–gas shift reaction, olefin isomerization, hydroformylation, condensation, and final hydrogenation (Scheme 1), and the catalyst system should be compatible with all these steps. (2) To selectively produce linear amines, the hydroformylation of the terminal olefin must occur much faster and with high regioselectivity compared with the reaction of the internal olefin. (3) The catalyst must be active, selective for the hydrogenation step of imine or enamine under CO pressure.

On the basis of our continuing interest in hydroformylation using so-called "alternative metal" catalysts, recently we showed the catalytic activity of ruthenium catalysts in the presence of 2-phosphino-substituted imidazole ligands in hydroformylation and hydroaminomethylation reactions.[26] These results inspired us to apply such catalytic systems for the selective water–gas shift/hydroaminomethylation of internal olefins.

■ RESULTS AND DISCUSSION

At the start of this project, we evaluated the effect of different ligands using 2-octene **1a** and piperidine **2a** as model substrates (Figure 1). In the absence of any ligand, only 13% yield of the desired 1-nonyl piperidine **3a** was obtained with a low regioselectivity. Using PPh$_3$ or PCy$_3$ as ligands did not improve the activity or selectivity. However, in the presence of L$_1$ (2-(dicyclohexylphosphanyl)-1-phenyl-1H-imidazole) a high yield of **3a** (93%) and good regioselectivity (n/i = 86:14) was observed. To elaborate the influence of this ligand structure on the catalyst reactivity, more heterocyclic and aromatic phosphine ligands were employed (L$_2$ to L$_{10}$). To our delight, applying L$_2$ (2-(dicyclohexylphosphanyl)-1-(2-methoxyphenyl)-1H-imidazole) as the most efficient ligand afforded **3a** in 95% yield and good regioselectivity (n/i = 87:13). Notably, L$_3$
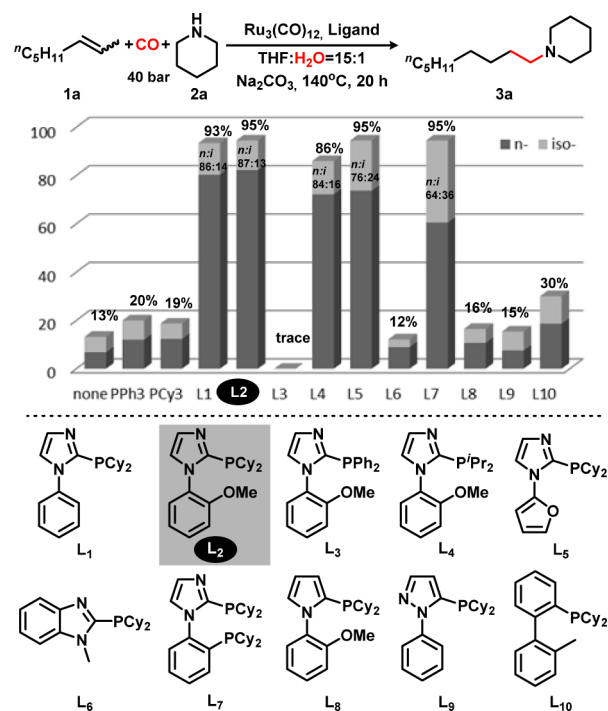
Figure 1. Ligand effects for the water–gas shift/hydroaminomethylation sequence of 2-octene with piperidine. Reaction conditions: **1a** (1.3 mmol), **2a** (1.0 mmol), Ru$_3$(CO)$_{12}$ (0.5 mol %), monodentate ligand (1.5 mol %), bidentate ligand (0.75 mol %), Na$_2$CO$_3$ (5.0 mol %), CO (40 bar), THF (1.5 mL), H$_2$O (0.1 mL), 140 °C, 20 h. Yields and selectivity were determined by GC analysis using isooctane as the internal standard.

with a less basic phenyl substituent on the phosphorus suppressed this reaction. L$_4$ bearing the ^{i}Pr group on phosphorus also provided good regioselectivity albeit gave slightly lower yield. Other imidazole ligands, such as L$_5$ and L$_6$, displayed high yields, while with moderate regioselectivities were observed. Benzimidazole-type ligand L$_6$ did not present any improvement in this reaction. Changing the imidazolyl moiety to pyrrol, pyrazol, and aromatic type ligands (L$_8$–L$_{10}$), the catalytic performance declined. These results demonstrate that a hemilabile behavior[27] between the imine nitrogen of the imidazolyl unit and the ruthenium center may play an important role in this catalytic transformation.[28]

Then, we investigated the effects of other reaction parameters for the benchmark reaction, and the results are summarized in Table 1. When Ru$_3$(CO)$_{12}$ was replaced by Fe$_3$(CO)$_{12}$, essentially no reaction occurred (entry 2). Control experiments showed that the ruthenium catalyst and water are essential for this reaction (entries 3 and 4). Decreasing the temperature to 120 °C led to significantly slower conversion, affording only 9% yield of **3a** (entry 5). As to the solvent, toluene also gave good regioselectivity albeit lower yield was obtained (entry 6), while dipolar aprotic NMP showed less efficiency in terms of chemical yield (entry 7). Notably, the reaction without base demonstrated lower yield, but still significant activity (entry 8). Addition of benzoic acid instead of Na$_2$CO$_3$ led to no improvement for this transformation (entry 9).

With the optimized reaction conditions in hand, we explored the substrate scope. At first, the reactions of various internal olefins **1** with piperidine **2a** were studied. We were pleased to find that related internal olefins (2-hexene, 3-hexene) reacted

Table 1. Domino Water−Gas Shift/Hydroaminomethylation of 2-Octene 1a with Piperidine 2a: Effects of Reaction Parameters[a]

entry	variation from "standard condition"[a]	yield [%]	n:i
1	none	95	87:13
2	Fe₃(CO)₁₂ instead of Ru₃(CO)₁₂	0	
3	without Ru₃(CO)₁₂	0	
4	without water	0	
5	120 °C instead of 140 °C	9	87:13
6	toluene instead of THF	65	87:13
7	NMP instead of THF	33	85:15
8	without Na₂CO₃	71	87:13
9	benzoic acid instead of Na₂CO₃	73	87:13

[a]Standard reaction conditions: **1a** (1.3 mmol), **2a** (1.0 mmol), Ru₃(CO)₁₂ (0.5 mol %), L₂ (1.5 mol %), Na₂CO₃ (5.0 mol %), CO (40 bar), THF (1.5 mL), H₂O (0.1 mL), 140 °C, 20 h. Yield and selectivity were determined by GC analysis.

well to give the corresponding linear amines in good yield and regioselectivity (Table 2, entries 1−3). On the other hand, 4-octene gave only 22% yield with moderate regioselectivity (Table 2, entry 4). Functionalized 4-hexen-1-ol also reacted smoothly with good yield (77%) and high regioselectivity ($n:i$ = 91:9) (Table 2, entry 5). Interestingly, cyclic olefins including cyclohexene, norbornene, and indene were found to be suitable substrates to afford the corresponding amines in high yields (Table 2, entries 6−8). 2,3-Dihydrofuran, which represents an enol ether substrate, provided a good yield but poor regioselectivity (Table 2, entry 9). With (1E)-1-propenylbenzene, a mixture of three different amines was obtained (Table 2, entry 10). When limonene and (−)-β-citronellene were used as the substrates, the internal bond remained intact and only the double bond in the terminal positions were selectively hydroformylated to the corresponding amines with moderate to good results (Table 2, entries 11−12).

Furthermore, the reactivity of different amines was investigated using 2-octene as substrate (Table 3). With cyclic secondary amines like morpholine and 1-phenylpiperazine, good yields and regioselectivities were achieved (Table 3, entries 1 and 2). Acyclic amines such as di-n-butylamine and (2-methylamino)ethanol also underwent this transformation smoothly in moderate and high yields and regioselectivities (Table 3, entries 3 and 4). Secondary benzylic amines were found to be suitable substrates, too; however, product yields were only moderate (Table 3, entries 5−6). Finally, indoline was alkylated under the reaction conditions, albeit in low yield (Table 3, entry 7).

Next, we were interested in demonstrating the utility of this method for the hydroaminomethylation of industrially important building blocks (Scheme 3). Here, crack C₄, a mixture including 1-butene, 2-butenes, isobutene, and butanes, which is a product from cracking of naphtha (light gasoline), reacted to the corresponding linear amines **3r** and **3r′** in high yield and regioselectivity with only 0.2 mol % Ru₃(CO)₁₂. Additionally, a mixture of octenes, which is mainly manufactured by oligomerization of ethylene, was also applied to this reaction and gave 81% yield of **3a** with a selectivity of $n:i$ = 81:19.

Table 2. Variation of Different Internal Olefins for the Synthesis of Amines[a]

Entry	Olefin	Major product	Yield [%]	n:i
1		3a	94	87:13
2		3b	85	89:11
3		3b	72[b]	80:20
4		3a	22[b]	65:35
5		3c	77	91:9
6		3d	85	-
7		3e	78	-
8		3f₁ + 3f₂	81	3f₁:3f₂ 87:13
9		3g₁ + 3g₂	71	3g₁:3g₂ 59:41
10		3h₁ + 3h₂ + 3h₃	53	3h₁:3h₂:3h₃ 34:8:58
11		3i	58	99:1
12		3j	90	99:1

[a]Reaction conditions: **1** (1.3 mmol), **2a** (1.0 mmol), Ru₃(CO)₁₂ (0.5 mol %), L₂ (1.5 mol %), Na₂CO₃ (5.0 mol %), CO (40 bar), THF (1.5 mL), H₂O (0.1 mL), 140 °C, 20 h. Isolated yield. Selectivity was determined by GC analysis. [b]Reaction conditions: **1** (1.3 mmol), **2a** (1.0 mmol), Ru₃(CO)₁₂ (1.0 mol %), L₂ (3.0 mol %), Na₂CO₃ (5.0 mol %), CO (40 bar), THF (1.5 mL), H₂O (0.1 mL), 140 °C, 20 h. Yield and selectivity was determined by GC analysis.

Finally, the reaction progress of this ruthenium-catalyzed water−gas shift/hydroformylation of 2-octene **1a** and piperidine **2a** was examined in more detail. As depicted in Figure 2a, the gas consumption started only after 2.5 h and within this time only small amounts of E/Z isomerization of 2-octene were observed. Then, 2-octene **1a** was consumed slowly and at the same time, the corresponding amine **3a** and other internal octenes (3-octene and 4-octene) were formed (Figure 2b). It is noteworthy that 1-octene, which is proposed as the intermediate in this transformation, was not accumulated

Table 3. Substrates Scope for Different Amines[a]

Entry	Amine	Major product	Yield [%]	n:i
1	morpholine	3k	65	85:15
2	Ph-piperazine	3l	65	84:16
3	dibutylamine	3m	87	86:14
4	HO-methylamine	3n	77	75:25
5	N-methylbenzylamine	3o	63	84:16
6	α-methylbenzylamine	3p	35	85:15
7	indoline	3q	18	86:14

[a]Reaction conditions: **1a** (1.3 mmol), **2** (1.0 mmol), Ru$_3$(CO)$_{12}$ (0.5 mol %), L$_2$ (1.5 mol %), Na$_2$CO$_3$ (5.0 mol %), CO (40 bar), THF (1.5 mL), H$_2$O (0.1 mL), 140 °C, 20 h. Isolated yield. Selectivity was determined by GC analysis.

Scheme 3. Synthetic Applications by Using Crack C$_4$ and a Mixture of Octenes[a]
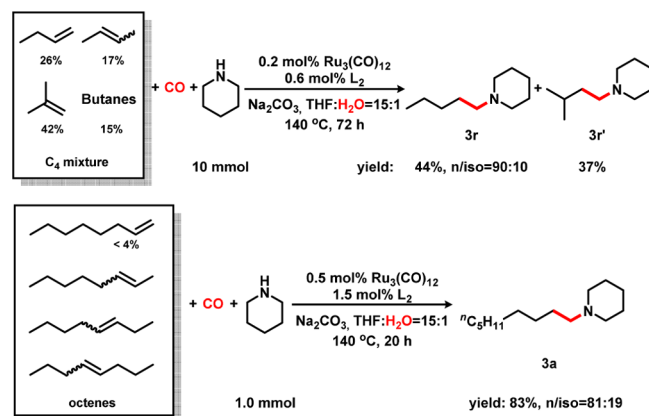
[a]Reaction conditions: For crack C$_4$ (0.72 g), **2a** (10 mmol), Ru$_3$(CO)$_{12}$ (0.2 mol %), L$_2$ (0.6 mol %), Na$_2$CO$_3$ (5.0 mol %), CO (50 bar), THF (15 mL), H$_2$O (1 mL), 140 °C, 72 h. Isolated yield. Selectivity was determined by GC analysis. For octenes (1.3 mmol), **2a** (1.0 mmol), Ru$_3$(CO)$_{12}$ (0.5 mol %), L$_2$ (1.5 mol %), Na$_2$CO$_3$ (5.0 mol %), CO (40 bar), THF (1.5 mL), H$_2$O (0.1 mL), 140 °C, 20 h. Isolated yield. Selectivity was determined by GC analysis.

during the reaction. In agreement with our previous work,[26a,b] this result is attributed to the faster hydroformylation of terminal olefins. In addition, neither aldehyde, enamine nor imine were detected during the whole reaction time, which illustrates a fast process of the aldehyde with the amine and subsequent hydrogenation reaction.
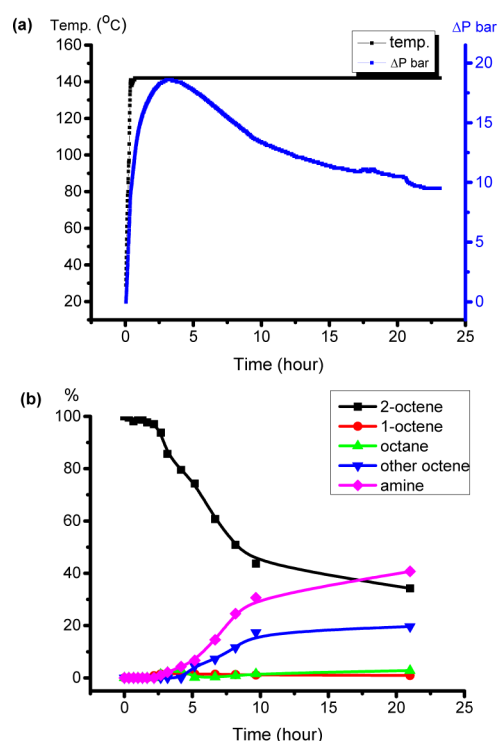
Figure 2. (a) Δp (pressure change compared to initial pressure) curve and temperature curve. (b) Composition of the reaction mixture.

CONCLUSIONS

In summary, we have developed a novel domino sequence for the conversion of internal olefins to linear amines via catalytic water−gas shift reaction, subsequent olefin isomerization, followed by hydroformylation and reductive amination. Comparing with expensive rhodium catalyst, as a less costly alternative metal, ruthenium also demonstrates good reactivity and selectivity in this reaction. More importantly, in the presence of a special imidazole ligand, the corresponding linear amines are obtained in general in moderate to good yields and regioslectivity. Interestingly, the conversion of industrially available bulk mixtures of olefins such as crack C$_4$ and octenes proceed in excellent yields considering the number of reaction steps. This procedure is expected to complement the current methods for hydroaminomethylation reactions in organic synthesis.

ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b02457.

General considerations, experimental sections, substrate information, general procedure for the synthesis of 3, kinetic progress measurement, mechanistic insights, stability of catalyst, characterization of products, reference, spectra of products (PDF)

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Notes
The authors declare no competing financial interest.

■ REFERENCES

(1) Amines Market by Amine Type−Global Trends and Forecast to 2020. marketsandmarkets.com (accessed December 2015).

(2) Lawrence, S. A. *Amines: Synthesis, Properties and Applications*; Cambridge University Press: Cambridge, 2006; November.

(3) (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−704. (b) Gross, T.; Seayad, A. M.; Ahmad, M.; Beller, M. *Org. Lett.* **2002**, *4*, 2055−2058. (c) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84−86. (d) Ricci, A. *Modern Amination Methods*; Wiley-VCH: Weinheim, Germany, 2007. (e) Lee, O.-Y.; Law, K.-L.; Yang, D. *Org. Lett.* **2009**, *11*, 3302−3305.

(4) (a) Trost, B. *Science* **1991**, *254*, 1471−1477. (b) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555−1575. (c) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681−703. (d) Guillena, G.; J. Ramón, D.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611−1641. (e) Watson, A. J. A.; Williams, J. M. J. *Science* **2010**, *329*, 635−636. (f) Bähn, S.; Imm, S.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. *ChemCatChem* **2011**, *3*, 1853−1864. (g) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 1229712.

(5) (a) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; John Wiley & Sons, 2001. (b) Gomez, S.; Peters, J. A.; Maschmeyer, T. *Adv. Synth. Catal.* **2002**, *344*, 1037−1057. (c) Bini, L.; Müller, C.; Wilting, J.; von Chrzanowski, L.; Spek, A. L.; Vogt, D. *J. Am. Chem. Soc.* **2007**, *129*, 12622−12623. (d) Enthaler, S.; Addis, D.; Junge, K.; Erre, G.; Beller, M. *Chem. - Eur. J.* **2008**, *14*, 9491−9494. (e) Göthlich, A. P. V.; Tensfeldt, M.; Rothfuss, H.; Tauchert, M. E.; Haap, D.; Rominger, F.; Hofmann, P. *Organometallics* **2008**, *27*, 2189−2200. (f) Reguillo, R.; Grellier, M.; Vautravers, N.; Vendier, L.; Sabo-Etienne, S. *J. Am. Chem. Soc.* **2010**, *132*, 7854−7855. (g) Bornschein, C.; Werkmeister, S.; Wendt, B.; Jiao, H.; Alberico, E.; Baumann, W.; Junge, H.; Junge, K.; Beller, M. *Nat. Commun.* **2014**, *5*, 4111.

(6) (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348−1350. (b) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133−1135. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (d) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860. (e) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (f) Hartwig, J. F. *Nature* **2008**, *455*, 314−322.

(7) (a) Kaspar, L. T.; Fingerhut, B.; Ackermann, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 5972−5974. (b) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795−3892.

(8) (a) Reppe, W.; Vetter, H. *Justus Liebigs Annalen der Chemie* **1953**, *582*, 133−161. (b) Laine, R. M. *J. Org. Chem.* **1980**, *45*, 3370−3372. (c) Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329−3366. (d) Crozet, D.; Urrutigoïty, M.; Kalck, P. *ChemCatChem* **2011**, *3*, 1102−1118. (e) Raoufmoghaddam, S. *Org. Biomol. Chem.* **2014**, *12*, 7179−7193.

(9) (a) Ahmed, M.; Seayad, A. M.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* **2003**, *125*, 10311−10318. (b) Koç, F.; Wyszogrodzka, M.; Eilbracht, P.; Haag, R. *J. Org. Chem.* **2005**, *70*, 2021−2025. (c) Ahmed, M.; Buch, C.; Routaboul, L.; Jackstell, R.; Klein, H.; Spannenberg, A.; Beller, M. *Chem. - Eur. J.* **2007**, *13*, 1594−1601. (d) Vieira, T. O.; Alper, H. *Chem. Commun.* **2007**, 2710−2711. (e) Hamers, B.; Bäuerlein, P. S.; Müller, C.; Vogt, D. *Adv. Synth. Catal.* **2008**, *350*, 332−342. (f) Vieira, T. O.; Alper, H. *Org. Lett.* **2008**, *10*, 485−487.

(g) Hamers, B.; Kosciusko-Morizet, E.; Müller, C.; Vogt, D. *ChemCatChem* **2009**, *1*, 103−106. (h) Subhani, M. A.; Müller, K.-S.; Eilbracht, P. *Adv. Synth. Catal.* **2009**, *351*, 2113−2123. (i) Kubiak, R.; Prochnow, I.; Doye, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 2626−2629. (j) Liu, G.; Huang, K.; Cai, C.; Cao, B.; Chang, M.; Wu, W.; Zhang, X. *Chem. - Eur. J.* **2011**, *17*, 14559−14563. (k) Crozet, D.; Gual, A.; McKay, D.; Dinoi, C.; Godard, C.; Urrutigoïty, M.; Daran, J.-C.; Maron, L.; Claver, C.; Kalck, P. *Chem. - Eur. J.* **2012**, *18*, 7128−7140. (l) Dong, K.; Fang, X.; Jackstell, R.; Beller, M. *Chem. Commun.* **2015**, *51*, 5059−5062.

(10) Seayad, A.; Ahmed, M.; Klein, H.; Jackstell, R.; Gross, T.; Beller, M. *Science* **2002**, *297*, 1676−1678.

(11) (a) van der Veen, L. A.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 336−338. (b) Selent, D.; Wiese, K.-D.; Röttger, D.; Börner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1639−1641. (c) Klein, H.; Jackstell, R.; Wiese, K.-D.; Borgmann, C.; Beller, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3408−3411. (d) Ahmed, M.; Bronger, R. P. J.; Jackstell, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Beller, M. *Chem. - Eur. J.* **2006**, *12*, 8979−8988. (e) Liu, G.; Huang, K.; Cao, B.; Chang, M.; Li, S.; Yu, S.; Zhou, L.; Wu, W.; Zhang, X. *Org. Lett.* **2012**, *14*, 102−105.

(12) (a) van Leeuwen, P. W. N. M.; Claver, C. *Rhodium Catalyzed Hydroformylation*; Springer: Netherlands, 2002; Vol. 22. (b) Franke, R.; Selent, D.; Börner, A. *Chem. Rev.* **2012**, *112*, 5675−5732.

(13) Pospech, J.; Fleischer, I.; Franke, R.; Buchholz, S.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2852−2872.

(14) (a) Takahashi, K.; Yamashita, M.; Nozaki, K. *J. Am. Chem. Soc.* **2012**, *134*, 18746−18757. (b) Takahashi, K.; Yamashita, M.; Tanaka, Y.; Nozaki, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 4383−4387.

(15) (a) Zbieg, J. R.; Yamaguchi, E.; McInturff, E. L.; Krische, M. J. *Science* **2012**, *336*, 324−327. (b) Sam, B.; Breit, B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 3267−3274.

(16) (a) Han, Z.; Rong, L.; Wu, J.; Zhang, L.; Wang, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 13041−13045. (b) Zhao, B.; Han, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4744−4788. (c) Zhang, L.; Han, Z.; Zhao, X.; Wang, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 6186−6189.

(17) (a) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792−9826. (b) Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877−5884. (c) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281−295.

(18) (a) Huff, C. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18122−18125. (b) Rezayee, N. M.; Huff, C. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 1028−1031.

(19) (a) Isnard, P.; Denise, B.; Sneeden, R. P. A.; Cognion, J. M.; Durual, P. *J. Organomet. Chem.* **1982**, *240*, 285−288. (b) Kondo, T.; Akazome, M.; Tsuji, Y.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 1286−1291. (c) Omura, S.; Fukuyama, T.; Horiguchi, J.; Murakami, Y.; Ryu, I. *J. Am. Chem. Soc.* **2008**, *130*, 14094−14095.

(20) (a) Liu, Q.; Wu, L.; Fleischer, I.; Selent, D.; Franke, R.; Jackstell, R.; Beller, M. *Chem. - Eur. J.* **2014**, *20*, 6888−6894. (b) Pospech, J.; Tlili, A.; Spannenberg, A.; Neumann, H.; Beller, M. *Chem. - Eur. J.* **2014**, *20*, 3135−3141. (c) Wu, L.; Liu, Q.; Fleischer, I.; Jackstell, R.; Beller, M. *Nat. Commun.* **2014**, *5*, 3091. (d) Wu, L.; Liu, Q.; Jackstell, R.; Beller, M. *Org. Chem. Front.* **2015**, *2*, 771−774.

(21) (a) Laine, R. M.; Rinker, R. G.; Ford, P. C. *J. Am. Chem. Soc.* **1977**, *99*, 252−253. (b) King, R. B. *J. Organomet. Chem.* **1999**, *586*, 2−17.

(22) Cheng, C.-H.; Hendriksen, D. E.; Eisenberg, R. *J. Am. Chem. Soc.* **1977**, *99*, 2791−2792.

(23) Cheng, C.-H.; Eisenberg, R. *J. Am. Chem. Soc.* **1978**, *100*, 5968−5970.

(24) (a) Kang, H. C.; Mauldin, C. H.; Cole, T.; Slegeir, W.; Cann, K.; Pettit, R. *J. Am. Chem. Soc.* **1977**, *99*, 8323−8325. (b) Okano, T.; Kobayashi, T.; Konishi, H.; Kiji, J. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3799−3805.

(25) Gülak, S.; Wu, L.; Liu, Q.; Franke, R.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 7320−7323.

(26) (a) Wu, L.; Fleischer, I.; Jackstell, R.; Profir, I.; Franke, R.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 14306−14312. (b) Wu, L.; Fleischer, I.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 3989−3996. (c) Fleischer, I.; Wu, L.; Profir, I.; Jackstell, R.; Franke, R.; Beller, M. *Chem. - Eur. J.* **2013**, *19*, 10589−10594. (d) Fleischer, I.; Dyballa, K. M.; Jennerjahn, R.; Jackstell, R.; Franke, R.; Spannenberg, A.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2949−2953.

(27) (a) Braunstein, P.; Naud, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 680−699. (b) Grotjahn, D. B.; Gong, Y.; Zakharov, L.; Golen, J. A.; Rheingold, A. L. *J. Am. Chem. Soc.* **2006**, *128*, 438−453. (c) Díez, V.; Espino, G.; Jalón, F. A.; Manzano, B. R.; Pérez-Manrique, M. *J. Organomet. Chem.* **2007**, *692*, 1482−1495. (d) Grotjahn, D. B.; Zeng, X.; Cooksy, A. L.; Kassel, W. S.; DiPasquale, A. G.; Zakharov, L. N.; Rheingold, A. L. *Organometallics* **2007**, *26*, 3385−3402. (e) Grotjahn, D. B. *Dalton Transactions* **2008**, 6497−6508. (f) Hintermann, L.; Dang, T. T.; Labonne, A.; Kribber, T.; Xiao, L.; Naumov, P. *Chem. - Eur. J.* **2009**, *15*, 7167−7179. (g) Grotjahn, D. B. *Pure Appl. Chem.* **2010**, *82*, 635−647. (h) Kubis, C.; Profir, I.; Fleischer, I.; Baumann, W.; Selent, D.; Fischer, C.; Spannenberg, A.; Ludwig, R.; Hess, D.; Franke, R.; Börner, A. *Chem.—Eur. J.* **2015**, accepted.

(28) For some preliminary mechanistic studies for the interaction of this imidazole-type ligand and Ru center, please see the Supporting Information, Scheme S1−S3.

5.2 Selective Palladium-Catalyzed Aminocarbonylation of Olefins to Branched Amides

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Author contributions:

Prof. Matthias Beller and Jie Liu conceived and developed this project. Dr. Anke Spannenberg performed the X-ray experiments. Prof. Matthias Beller and Jie Liu wrote the manuscript with revisions provided by Dr. Haoquan Li, Dr. Ralf Jackstell and Prof. Robert Franke. My contribution as co-author of this paper is approximately 80%.

Selective Palladium-Catalyzed Aminocarbonylation of Olefins to Branched Amides

Jie Liu, Haoquan Li, Anke Spannenberg, Robert Franke, Ralf Jackstell, and Matthias Beller*

Abstract: *A general and efficient protocol for iso-selective aminocarbonylation of olefins with aliphatic amines has been developed for the first time. Key to the success for this process is the use of a specific 2-phosphino-substituted pyrrole ligand in the presence of PdX₂ (X = halide) as a pre-catalyst. Bulk industrial and functionalized olefins react with various aliphatic amines, including amino-acid derivatives, to give the corresponding branched amides generally in good yields (up to 99%) and regioselectivities (b/l up to 99:1).*

Carbonylation reactions are widely used for the industrial production of fine and bulk chemicals, especially to produce valuable monomers for polymers.[1] Because of the versatility of the carbonyl group and the possibility to easily expand carbon chains, they also find increasing applications in organic synthesis.[2] Within this class of reactions, transition metal catalyzed aminocarbonylations, also called hydroamidations, represent a straightforward method for the conversion of available olefins, CO, and amines into the corresponding amides, which represent important intermediates, building blocks, and functional molecules in organic synthesis, the chemical industry, as well as biological systems.[3]

Since the original work of Reppe and co-workers in the 1950s,[4] numerous catalytic systems based on cobalt,[5] nickel,[6] iron,[7] and ruthenium[8] complexes have been developed, and allow aminocarbonylation of olefins with amines. However, the severe reaction conditions (high temperature and CO pressure), unavoidable byproducts (formamide), and limited substrate scope impeded further applications of these processes. Recently, palladium-based catalysts for aminocarbonylation of olefins were reported independently by the groups of Cole-Hamilton,[9] Liu,[10] and Alper,[11] as well as our group.[12] Despite the significant progress in this area, all these methods are limited to aromatic amines as substrates, and carbonylations with aliphatic amines failed. This behavior is simply explained by the stronger basicity of aliphatic amines: For example, alanine

ester (pK_b = 4.87), benzylamine (pK_b = 4.66), and piperidine (pK_b = 2.78) are much more basic than aniline (pK_b = 9.37; Scheme 1a).[13] Hence, aliphatic amines retard the generation of the active palladium hydride species **C**, which are crucial for catalysis (Scheme 1c). To overcome this problem, Huang
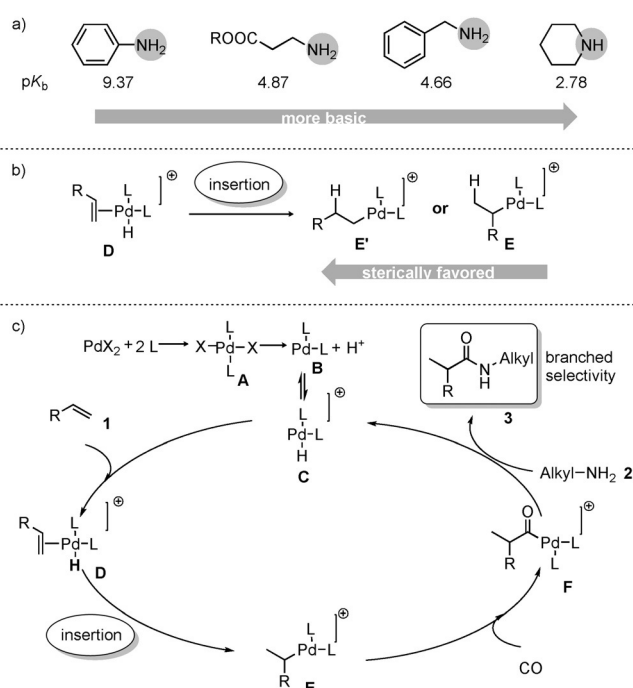
Scheme 1. a) The pK_b of various amines. b) Two pathways for olefin insertion into the Pd—H bond. c) Catalytic cycle for palladium-catalyzed branched-selective carbonylation of olefins with aliphatic amines.

and co-workers developed an elegant strategy to utilize aminals as surrogates of aliphatic amines.[14] Alternatively, our group applied a rhodium catalyst as the solution to this problem.[15] Notably, both catalyst systems favor the formation of the linear amides from olefins and aliphatic amines. In contrast, the formation of the branched amides from carbonylation reactions is more challenging because of the increase in steric effects for the olefin insertion into the palladium–hydride bond to form the secondary carbon palladium intermediates **E** (Scheme 1b).[16] Although a few examples of branched-selective functionalization of olefins, such as hydroformylation,[17] hydroamination,[18] hydroacylation,[19] and hydrocyanation,[20] etc.,[16b] have been developed in recent years, such carbonylations of aliphatic amines with olefins, especially for industrially available bulk olefins such as propene, hexene, octene, etc., are basically unknown and

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continue to be a challenging goal in homogeneous catalysis. Herein, we report for the first time the development of a general and efficient palladium catalyst for the aminocarbonylation of olefins with aliphatic amines giving selectively branched products.

To prevent the deactivation of the palladium hydride catalyst by the strongly basic aliphatic amine, we investigated the reaction of benzylamine with 1-octene (**1a**) in the presence of different acidic additives including, Brønsted acids and Lewis acids. Based on our recent work on the alkoxylcarbonylation of olefins,[21] we used a combination of PdCl₂ and CataCXium® POMeCy (2-(dicyclohexylphosphino)-1-(2-methoxyphenyl)-1*H*-pyrrole; **L1**)[22] under 40 bar of CO in THF at 100°C. As shown in Table 1, when

Table 1: Selective aminocarbonylation of 1-octene (**1a**) and benzylamine: Effect of additives.[a]

Entry	Additive	Yield [%]	*b/l*
1	none	0	–
2	NEt₃·HCl (1.0 equiv)	0	–
3	HOAc (1.0 equiv)	0	–
4	HCl (10 mol%)	0	–
5	Zn(OTf)₂ (5 mol%)	0	–
6	Sc(OTf)₃ (5 mol%)	0	–
7	Yb(OTf)₃ (5 mol%)	0	–
8	BnNH₂·HCl instead of BnNH₂	48	85:15

[a] Reaction conditions: **1a** (2.0 mmol), BnNH₂ (1.0 mmol), PdCl₂ (1.0 mol%), ligand **1** (2.0 mol%), additive, CO (40 bar), THF (2.0 mL), 100°C, 20 h. Yields (**3aa**+**3aa'**) and regioselectivities were determined by GC analysis using isooctane as the internal standard. Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

BnNH₂ was used without any additives, no desired product was observed at all (entry 1). Similarly, attempts to adjust the pH of the reaction solution by adding hydrochloride salts, like NEt₃·HCl, did not give any product in this reaction (entry 2). Other acidic additives, like Brønsted acids (entries 3 and 4) and Lewis acids (entries 5–7), all turned out to be ineffective. However, when applying BnNH₂·HCl instead of BnNH₂, the branched amide (**3aa**) was formed with high selectivity (85:15) albeit in moderate yield (48%) was achieved (entry 8).

It should be noted that the observed regioselectivity is unexpected, and it intrigued us to further investigate this reaction. Hence, we examined the benchmark reaction in the presence of a series of phosphines (Figure 1). When PPh₃ was used as ligand, good yield (69%) was obtained while moderate regioselectivity was observed (*b/l* = 68:32). To elaborate the influence of the ligand structure on the catalyst reactivity, more (hetero)arylphosphine ligands were employed (**L2** to **L6**). To our delight, when applying **L2** [2-(diphenylphosphino)-1-(2-methoxyphenyl)-1*H*-pyrrole] the yield of **3aa** increased to 61% with a good branched selectivity (*b/l* = 88:12).[23] Notably, **L3**, bearing the *t*Bu group on phosphorus, suppressed this reaction. The modification of
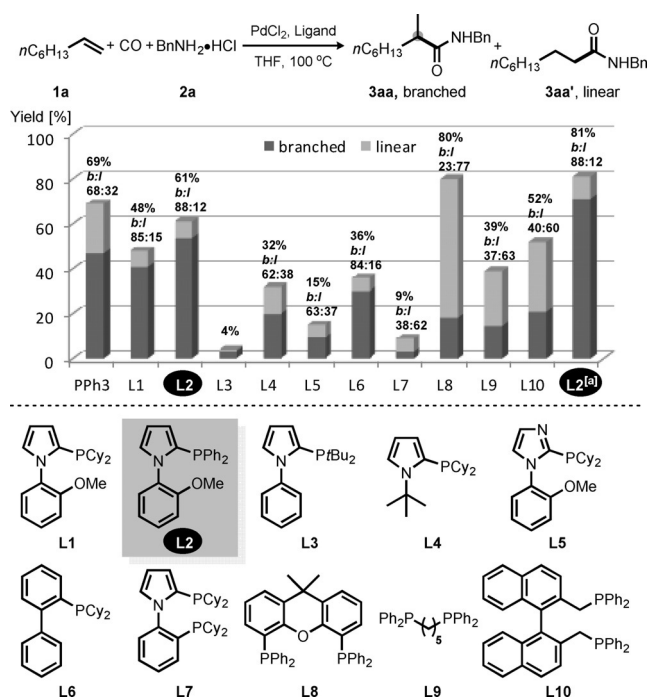
Figure 1. Ligand effect for branched selective aminocarbonylation of **1a** with **2a**. Reaction conditions: **1a** (2.0 mmol), **2a** (1.0 mmol), PdCl₂ (1.0 mol%), monodentate ligand (2.0 mol%), or bidentate ligand (1.0 mol%), CO (40 bar), THF (2.0 mL), 100°C, 20 h. Yields and regioselectivities were determined by GC analysis using isooctane as the internal standard. [a] 1.5 mol% PdCl₂, 3.0 mol% **L2** was added, 125°C, 24 h.

substitution, at N on the pyrrole, from an aryl to alkyl group (**L4**), did not present any improvement in this reaction. Notably, changing the pyrrole moiety to imidazolyl and phenyl (**L5** and **L6**), the catalytic performance of the corresponding catalysts declined. Interestingly, bidentate ligands such as **L7**–**L10** gave the linear amide as the major product.[16a] Finally, using 1.5 mol% palladium catalyst at 125°C led to the desired product in 81% yield and good regioselectivity (*b/l* = 88:12)[24] (for detailed optimization of the reaction conditions, see the Supporting Information; Table S1–S6.)

With the optimized reaction conditions in hand, we explored the substrate scope. At first, the reactions of various aliphatic amine hydrochlorides (**2**) with 1-octene (**1a**) were studied (Table 2). With primary amines such as benzylamine (**2a**), isobutylamine (**2b**), α-methylbenzylamine (**2c**), and hexylamine (**2d**) as starting materials, good yields (72–80%) and regioselectivities (*b* selectivity up to 88%) were achieved (entries 1–4). More bulky substituted amines, such as isopropylamine (**2e**) and cyclohexylamine (**2f**), also underwent this transformation smoothly in moderate to good yields (entries 5 and 6). The reaction of piperidine (**2g**), as an example of a secondary amine, provided the corresponding product in moderate yield (entry 7).

Moreover, aromatic amines such as aniline were selectively carbonylated to the branch amide in excellent yields and selectivities (Table 2, entry 8). In contrast, this novel methodology allows functionalization of a series of amino-

Table 2: Palladium-catalyzed aminocarbonylation with the aliphatic amine salts **2**.[a]

Entry	Amine·HCl	Major product	Yield [%][b]	b/l[c]
1	**2a** (benzylamine·HCl)	**3aa**	80	88:12
2	**2b** (isobutylamine·HCl)	**3ab**	74	83:17
3	**2c** (1-phenylethylamine·HCl)	**3ac**	70	83:17
4	**2d**	**3ad**	76	82:18
5	**2e** (isopropylamine·HCl)	**3ae**	72	84:16
6	**2f** (cyclohexylamine·HCl)	**3af**	68	85:15
7[d]	**2g** (piperidine·HCl)	**3ag**	42	82:18
8[e]	**2h** (aniline)	**3ah**	99 (99[f])	87:13
9[g]	**2i** (H₂N–CH₂–COOMe·HCl)	**3ai**	58	91:9
10[g]	**2j** (COOMe, NH₂·HCl)	**3aj**	68	88:12
11[g]	**2k** (Ph, COOMe, NH₂·HCl)	**3ak**	73	88:12
12[g]	**2l** (H₂N–CH₂CH₂–COOEt·HCl)	**3al**	62	85:15

[a] Reaction conditions: **1a** (2.0 mmol), **2** (1.0 mmol), PdCl₂ (1.5 mol%), L2 (3.0 mol%), CO (40 bar), THF (2.0 mL), 125 °C, 24 h. [b] Yield of isolated amides as a mixture of branched (major) and linear (minor) products. [c] Regioselectivity was determined by GC analysis. [d] Reaction at 110 °C for 36 h. [e] **1a** (2.0 mmol), aniline (1.0 mmol), H₂O (5 μL), PdBr₂ (1.5 mol%), L2 (3.0 mol%), CO (40 bar), THF (2.0 mL), 125 °C, 24 h. [f] With 1.5 mol% [Pd(**L2**)₂Br₂] pre-catalyst (complex **A**) as catalyst precursor. [g] Reaction at 125 °C for 36 h.

acid derivatives in a straightforward manner. Here, several natural α-amino-acid derivatives, such as glycine methyl ester (**2i**), L-alanine methyl ester (**2j**), and (S)-(+)-2-phenylglycine

methyl ester hydrochloride (**2k**), participated efficiently in this process without racemization (entries 9–11). Additionally, the β-amino-acid derivative β-alanine ethyl ester hydrochloride (**2l**) also reacted smoothly to give the corresponding amide (**3al**) selectively (entry 12).

Next, reactions of BnNH₂·HCl (**2a**) with bulk industrial, as well as functionalized olefins (**1**), were studied. For example, industrially important propene (**1b**) gave *N*-benzyl isobutyric amide, in the presence of only 0.2 mol% of the catalyst, in excellent yield (Table 3, entry 1). 1-Hexene (**1c**) and 4-methyl-1-pentene (**1d**) also furnished the desired aminocarbonylation products in moderate yields and branched selectivities (entries 2 and 3). Olefins containing

Table 3: Palladium-catalyzed aminocarbonylation with different olefins (**1**).[a]

Entry	Olefin	Major product	Yield [%][b]	b/l[c]
1[d]	**1b** (propene)	**3ba**	98	92:8
2	**1c** (1-hexene)	**3ca**	74	90:10
3[e]	**1d** (4-methyl-1-pentene)	**3da**	65	87:13
4	**1e** (NC–)	**3ea**	86	87:13
5	**1f** (Cl–)	**3fa**	62	89:11
6	**1g** (MeOOC–)	**3ga**	68	85:15
7[e]	**1h** (AcO–)	**3ha**	41	81:19
8	**1i**	**3ia**	97	88:12
9	**1j** (styrene)	**3ja**	97	>99:1
10[e]	**1k**	**3ka**	39	62:38

[a] Reaction conditions: **1** (2.0 mmol), **2a** (1.0 mmol), PdCl₂ (1.5 mol%), L2 (3.0 mol%), CO (40 bar), THF (2.0 mL), 125 °C, 24 h. [b] Yield of isolated amides as a mixture of branched (major) and linear (minor) products. [c] Regioselectivity was determined by GC analysis. [d] **1b** (20 mmol), **2a** (5.0 mmol), PdCl₂ (0.2 mol%), L2 (0.8 mol%), CO (40 bar), THF (6.0 mL), 130 °C, 36 h. [e] Reaction time of 36 h.

nitrile (**1e**), halogen (**1f**), and ester groups (**1g** and **1h**) were efficiently converted into the branched amines (41–86%) with good regioselectivities (entries 4–7). Allylbenzene (**1i**) also demonstrated excellent reactivity and high regioselectivity (entry 8). Gratifyingly, aromatic olefins like styrene (**1j**) led to the corresponding amide in high yield with excellent *b* selectivity (>99%; entry 9). When (−)-β-citronellene (**1k**) was used as the substrate, the internal bond remained intact and only the double bond in the terminal position was selectively carbonylated to the branched amide (entry 10).

In summary, we developed the first palladium catalyst system for a general and selective aminocarbonylation of olefins with aliphatic amines. By applying a special pyrrole-type ligand, a wide range of aliphatic amines and olefins are efficiently transformed into the corresponding branched amides in good yields and often with high regioselectivity. Apart from simple aliphatic and aromatic amines, this procedure allows the efficient and selective aminocarbonylation of amino acids derivatives, too. In view of the easy availability of the substrates, the efficiency, and the good regioselectivity, this method is expected to complement the current methods for carbonylations in organic synthesis.

Acknowledgments

[1] a) P. W. N. M. van Leeuwen, C. Claver, *Rhodium Catalyzed Hydroformylation, Vol. 22*, Springer, Netherlands, **2002**; b) *Catalytic Carbonylation Reactions* (Ed.: M. Beller), Springer, Berlin Heidelberg, **2006**; c) B. Breit, in *Metal Catalyzed Reductive C−C Bond Formation: A Departure from Preformed Organometallic Reagents* (Ed.: M. J. Krische), Springer, Berlin, Heidelberg, **2007**, pp. 139–172; d) *Modern Carbonylation Methods*, Wiley-VCH, Weinheim, **2008**; e) *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2008**; f) R. Franke, D. Selent, A. Börner, *Chem. Rev.* **2012**, *112*, 5675–5732.

[2] a) Q. Liu, H. Zhang, A. Lei, *Angew. Chem. Int. Ed.* **2011**, *50*, 10788–10799; *Angew. Chem.* **2011**, *123*, 10978–10989; b) X.-F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986–5009; c) L. Wu, X. Fang, Q. Liu, R. Jackstell, M. Beller, X.-F. Wu, *ACS Catal.* **2014**, *4*, 2977–2989; d) X.-F. Wu, X. Fang, L. Wu, R. Jackstell, H. Neumann, M. Beller, *Acc. Chem. Res.* **2014**, *47*, 1041–1053; e) B. Sam, B. Breit, M. J. Krische, *Angew. Chem. Int. Ed.* **2015**, *54*, 3267–3274; *Angew. Chem.* **2015**, *127*, 3317–3325.

[3] a) P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp, T. Skrydstrup, *J. Am. Chem. Soc.* **2011**, *133*, 6061–6071; b) T. Xu, H. Alper, *Tetrahedron Lett.* **2013**, *54*, 5496–5499; c) W. Li, C. Liu, H. Zhang, K. Ye, G. Zhang, W. Zhang, Z. Duan, S.

You, A. Lei, *Angew. Chem. Int. Ed.* **2014**, *53*, 2443–2446; *Angew. Chem.* **2014**, *126*, 2475–2478; d) T. Xu, H. Alper, *J. Am. Chem. Soc.* **2014**, *136*, 16970–16973; e) T. L. Andersen, S. D. Friis, H. Audrain, P. Nordeman, G. Antoni, T. Skrydstrup, *J. Am. Chem. Soc.* **2015**, *137*, 1548–1555; f) J. Cheng, X. Qi, M. Li, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2015**, *137*, 2480–2483; g) K. T. Neumann, A. T. Lindhardt, B. Bang-Andersen, T. Skrydstrup, *Org. Lett.* **2015**, *17*, 2094–2097; h) R. Shi, H. Zhang, L. Lu, P. Gan, Y. Sha, H. Zhang, Q. Liu, M. Beller, A. Lei, *Chem. Commun.* **2015**, *51*, 3247–3250; i) H. Yu, G. Zhang, H. Huang, *Angew. Chem. Int. Ed.* **2015**, *54*, 10912–10916; *Angew. Chem.* **2015**, *127*, 11062–11066.

[4] W. Reppe, H. Kroper, *Ger. Pat.* **1951**, *149*, 868.

[5] a) P. Pino, P. Paleari, *Gazz. Chim. Ital.* **1951**, *81*, 64; b) P. Pino, R. Magri, *Chim. Ind.* **1952**, *34*, 511; c) S. I. Lee, S. U. Son, Y. K. Chung, *Chem. Commun.* **2002**, 1310–1311.

[6] W. Reppe, H. Main, *Chem. Abstr.* **1953**, *47*, 5428.

[7] A. Striegler, J. Weber, *J. Prakt. Chem.* **1965**, *29*, 281–295.

[8] Y. Tsuji, T. Ohsumi, T. Kondo, Y. Watanabe, *J. Organomet. Chem.* **1986**, *309*, 333–344.

[9] C. Jiménez-Rodriguez, A. A. Núñez-Magro, T. Seidensticker, G. R. Eastham, M. R. L. Furst, D. J. Cole-Hamilton, *Catal. Sci. Technol.* **2014**, *4*, 2332–2339.

[10] H. Liu, N. Yan, P. J. Dyson, *Chem. Commun.* **2014**, *50*, 7848–7851.

[11] T. Xu, F. Sha, H. Alper, *J. Am. Chem. Soc.* **2016**, *138*, 6629–6635.

[12] X. Fang, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 14089–14093; *Angew. Chem.* **2013**, *125*, 14339–14343.

[13] a) H. K. Hall, *J. Am. Chem. Soc.* **1957**, *79*, 5441–5444; b) E. Folkers, O. Runquist, *J. Org. Chem.* **1964**, *29*, 830–832.

[14] a) G. Zhang, B. Gao, H. Huang, *Angew. Chem. Int. Ed.* **2015**, *54*, 7657–7661; *Angew. Chem.* **2015**, *127*, 7767–7771; Vorholt and co-workers reported a palladium-catalyzed aminocarbonylation of aliphatic alkenes with DMF as an in situ source of CO to produce linear amides, see: b) T. Seidensticker, M. R. L. Furst, R. Frauenlob, J. Vondran, E. Paetzold, U. Kragl, A. J. Vorholt, *ChemCatChem* **2015**, *7*, 4085–4090.

[15] a) K. Dong, X. Fang, R. Jackstell, G. Laurenczy, Y. Li, M. Beller, *J. Am. Chem. Soc.* **2015**, *137*, 6053–6058; Behr and co-workers reported a rhodium-catalyzed aminocarbonylation of dienes. See: b) A. Behr, D. Levikov, E. Nurenberg, *Catal. Sci. Technol.* **2015**, *5*, 2783–2787.

[16] a) G. Kiss, *Chem. Rev.* **2001**, *101*, 3435–3456; b) M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem. Int. Ed.* **2004**, *43*, 3368–3398; *Angew. Chem.* **2004**, *116*, 3448–3479; c) P. Roesle, C. J. Dürr, H. M. Möller, L. Cavallo, L. Caporaso, S. Mecking, *J. Am. Chem. Soc.* **2012**, *134*, 17696–17703; d) J. T. Christl, P. Roesle, F. Stempfle, P. Wucher, I. Göttker-Schnetmann, G. Müller, S. Mecking, *Chem. Eur. J.* **2013**, *19*, 17131–17140.

[17] For selected examples for branched-selective hydroformylation, see: a) N. Sakai, S. Mano, K. Nozaki, H. Takaya, *J. Am. Chem. Soc.* **1993**, *115*, 7033–7034; b) M. Diéguez, O. Pàmies, A. Ruiz, S. Castillón, C. Claver, *Chem. Commun.* **2000**, 1607–1608; c) B. Breit, *Acc. Chem. Res.* **2003**, *36*, 264–275; d) T. P. Clark, C. R. Landis, S. L. Freed, J. Klosin, K. A. Abboud, *J. Am. Chem. Soc.* **2005**, *127*, 5040–5042; e) Y. Yan, X. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 7198–7202; f) B. Zhao, X. Peng, Z. Wang, C. Xia, K. Ding, *Chem. Eur. J.* **2008**, *14*, 7847–7857; g) S. Allmendinger, H. Kinuta, B. Breit, *Adv. Synth. Catal.* **2015**, *357*, 41–45; h) C. U. Grünanger, B. Breit, *Angew. Chem. Int. Ed.* **2008**, *47*, 7346–7349; *Angew. Chem.* **2008**, *120*, 7456–7459.

[18] For selected examples for branched-selective hydroamination, see: a) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675–704; b) J. F. Hartwig, *Pure Appl. Chem.* **2004**, *76*, 507; c) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795–3892; d) Y. Yang, S.-L. Shi, D. Niu, P. Liu, S. L. Buchwald, *Science* **2015**, *349*, 62–66.

[19] For selected examples for branched-selective hydroacylation, see: a) R. T. Stemmler, C. Bolm, *Adv. Synth. Catal.* **2007**, *349*, 1185–1198; b) K. Hirano, A. T. Biju, I. Piel, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 14190–14191; c) M. C. Willis, *Chem. Rev.* **2010**, *110*, 725–748; d) I. Piel, M. Steinmetz, K. Hirano, R. Fröhlich, S. Grimme, F. Glorius, *Angew. Chem. Int. Ed.* **2011**, *50*, 4983–4987; *Angew. Chem.* **2011**, *123*, 5087–5091; e) J. C. Leung, M. J. Krische, *Chem. Sci.* **2012**, *3*, 2202–2209; f) J. S. Bandar, E. Ascic, S. L. Buchwald, *J. Am. Chem. Soc.* **2016**, *138*, 5821–5824; g) L.-J. Xiao, X.-N. Fu, M.-J. Zhou, J.-H. Xie, L.-X. Wang, X.-F. Xu, Q.-L. Zhou, *J. Am. Chem. Soc.* **2016**, *138*, 2957–2960.

[20] For selected examples for branched-selective hydrocyanation, see: a) P. Arthur, D. C. England, B. C. Pratt, G. M. Whitman, *J. Am. Chem. Soc.* **1954**, *76*, 5364–5367; b) C. A. Tolman, W. C. Seidel, J. D. Druliner, P. J. Domaille, *Organometallics* **1984**, *3*, 33–38; c) B. Gaspar, E. M. Carreira, *Angew. Chem. Int. Ed.* **2007**, *46*, 4519–4522; *Angew. Chem.* **2007**, *119*, 4603–4606; d) L. Bini, C. Muller, D. Vogt, *Chem. Commun.* **2010**, *46*, 8325–8334.

[21] H. Li, K. Dong, H. Jiao, H. Neumann, R. Jackstell, M. Beller, *Nat. Chem.* **2016**, DOI: 10.1038/nchem.2586.

[22] A. Zapf, R. Jackstell, F. Rataboul, T. Riermeier, A. Monsees, C. Fuhrmann, N. Shaikh, U. Dingerdissen, M. Beller, *Chem. Commun.* **2004**, 38–39.

[23] The molecular structure of the [Pd(**L2**)$_2$Br$_2$] pre-catalyst (CCDC 1480945) is given in supporting information (Figure S1). CCDC 1480945 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[24] Theoretically, simple 1-octene might form four different regio-isomeric C9-amides because of the olefin isomerization reaction and then followed by carbonylation of different internal olefins. In the presence of our catalyst system, **3aa** and **3aa′** were mainly obtained and only trace amounts of other internal isomeric amides were observed by GC.

5.3 Ligand-Controlled Palladium-Catalyzed Alkoxycarbonylation of Allenes: Regioselective Synthesis of α,β- and β,γ-Unsaturated Esters

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Author contributions:

Prof. Matthias Beller, Dr. Qiang Liu and Jie Liu conceived and developed this project. Prof. Matthias Beller, Dr. Qiang Liu and Jie Liu wrote the manuscript with revisions provided by Dr. Ralf Jackstell and Prof. Robert Franke. My contribution as co-author of this paper is approximately 75%.

Ligand-Controlled Palladium-Catalyzed Alkoxycarbonylation of Allenes: Regioselective Synthesis of α,β- and β,γ-Unsaturated Esters

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S *Supporting Information*

ABSTRACT: The palladium-catalyzed regioselective alkoxycarbonylation of allenes with aliphatic alcohols allows to produce synthetically useful α,β- and β,γ-unsaturated esters in good yields. Efficient selectivity control is achieved in the presence of appropriate ligands. Using Xantphos as the ligand, β,γ-unsaturated esters are produced selectively in good yields. In contrast, the corresponding α,β-unsaturated esters are obtained with high regioselectivity in the presence of PPh₂Py as the ligand. Preliminary mechanistic studies revealed that these two catalytic processes proceed by different reaction pathways. In addition, this novel protocol was successfully applied to convert an industrially available bulk chemical, 1,2-butadiene, into dimethyl adipate, which is a valuable feedstock for polymer and plasticizer syntheses, with high yield and TON (turnover number).
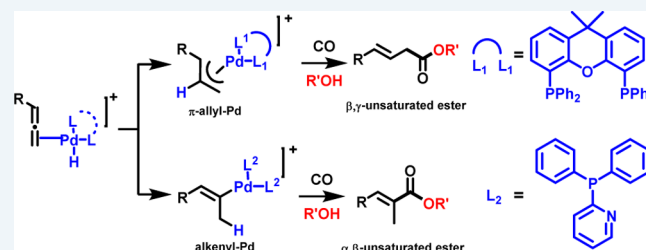
■ INTRODUCTION

Carbonylation reactions are widely used in industrial production of fine and bulk chemicals as well as organic synthesis since it can efficiently introduce the synthetically versatile carbonyl group and easily expand carbon chains.[1] Within this class of reactions, transition metal catalyzed alkoxycarbonylations, also called hydroesterifications, represent a straightforward method for the conversion of widely available unsaturated compounds, CO and alcohols into the corresponding esters.[2] In this respect, catalytic alkoxycarbonylation is also of considerable interests for the synthesis of α,β- and β,γ-unsaturated carboxylic acid derivatives, which represent important intermediates, building blocks and functional molecules in organic synthesis, the chemical industry as well as biological systems.[3] Since the original work of Reppe in the past century,[2a,4] alkoxycarbonylations of π-unsaturated compounds such as alkenes,[2a,5] alkynes,[6] 1,3-dienes[5c,7] and allylic compounds[8] have been extensively studied and improved. Despite all these works, it is still highly desirable to develop catalytic systems for the straightforward, convenient, and regioselective synthesis of α,β- and β,γ-unsaturated carboxylic acid derivatives from other easily accessible start materials. Key requirements for the applicability of such methodologies are high atom-economy, broad substrate scope as well as chemo- and regioselectivity.
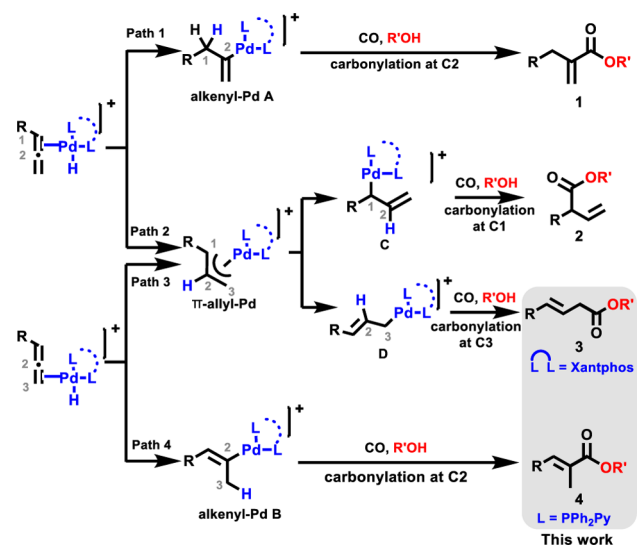
Compared to other available olefins, the functionalization of allenes has been only scarcely investigated over the years. Nevertheless, they have become an important class of synthon in organic synthesis, which can be applied to construct a variety of valuable molecules based on their functionalization.[9] As cumulated unsaturated species, allene is recognized that all the three carbons (C1, C2 and C3 position) on its double bonds can be the potential reaction sites.[10] This allows for various transformations at different positions on allenes. However, it also brings out a challenge to realize regioselective reactions. Although allenes functionalizations including addition reactions,[11] cyclizations,[12] oxidation[13] and reduction[14] reactions are well developed in recent years, the carbonylation of allenes is still challenging and very few examples are known.[15] This is mainly due to the above-mentioned difficult regioselectivity control of allenes, thus resulting in poor selectivity of α,β- and β,γ-unsaturated carbonylation products.[10a,15e] Taking palladium-catalyzed alkoxycarbonylations for instance, which are not known for allenes as the substrates until now,[16] there are four possible pathways for allene insertion into the Pd−H bond (Scheme 1): (1) When palladium coordinates to C1−C2 double bond, it will lead to two different insertions, from which alkenyl-Pd complex **A** and π-allyl-Pd intermediate are formed, respectively. Then, complex **A** further experiences the subsequent alkoxycarbonylation process to give the C2 carbonylation adduct **1** (α,β-unsaturated esters), while π-allyl-Pd intermediate enables an equilibration between σ-allyl-Pd species **C** and **D**, which potentially provides the C1 or C3 carbonylation adduct **2** or **3** (β,γ-unsaturated esters). (2) Alternatively, palladium coordinates to the C2−C3 double bond. Again, two different possibilities for the insertion step result, which provide alkenyl-Pd complex **B** and π-allyl-Pd

Scheme 1. Possible Pathways for Palladium-Catalyzed Allene Alkoxycarbonylation Reactions

Scheme 2. Ligand Effect for the Palladium-Catalyzed Alkoxycarbonylation of Propa-1,2-Dienylbenzene 1a and n-Butanol 2a[a]

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), Pd(OAc)$_2$ (1.0 mol %), monodentate ligand (4.0 mol %), bidentate ligand (2.0 mol %), PTSA·H$_2$O (4.0 mol %), CO (40 bar), toluene (2 mL), 110 °C, 20 h. Yields were determined by GC analysis using isooctane as the internal standard.

intermediate (the same species as above). The later Pd complex will form the C1 or C3 carbonylation adduct **2** or **3** (β,γ-unsaturated esters) again. Differently, C2 carbonylation adduct **4** is generated by the following alkoxycarbonylation of complex **B**.

We thought that the ligand should be able to play a key role in controlling the regioselectivity, thus leading to the generation of the α,β- or β,γ-unsaturated esters in a selective manner. On the basis of our continuing interest in the development of hydroesterification of unsaturated compounds,[7c,8e,17] we herein present the first example of palladium-catalyzed alkoxycarbonylation of allenes to synthesize α,β- and β,γ-unsaturated esters regioselectively promoted by two different ligands.

■ RESULTS AND DISCUSSION

Initially, we investigated the Pd-catalyzed alkoxycarbonylation of conveniently available propa-1,2-dienylbenzene **1a** and n-butanol **2a** as a model reaction. It is noteworthy that three products were detected in this reaction: β,γ-unsaturated esters **3a**, α,β-unsaturated esters **4a** and direct C−O coupling product **5a**. In order to improve the selectivity, we first studied the ligand effect using Pd(OAc)$_2$ as the catalyst precursor and PTSA·H$_2$O (p-toluenesulfonic acid monohydrate) as the acid cocatalyst (Scheme 2). The application of monodentate ligands, such as PPh$_3$, PCy$_3$, P^{t}Bu$_3$ and PAd$_2$^{n}Bu, all gave quite low catalytic activity with less than 10% yield of carbonylative products. Interestingly, when PPh$_2$Py was applied as the ligand, α,β-unsaturated ester **4a** was formed with high selectivity albeit only 18% yield was gained. Then, a serial of bidentate ligands were also tested. Bis[(2-diphenylphosphino)phenyl] ether (DPEphos) and 1,1,-bis(diphenylphosphino)ferrocene (DPPF) exhibited low reactivity for the carbonylation process, which mainly led to the C−O coupling product **5a**. The application of 1,4-bis(diphenylphosphino)butane (DPPB), gave worse result with less than 5% yield of the desired product. To our delight, using α,α′-bis-[di-tert-butylphosphino]-o-xylene (d^{t}bpx) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) as ligands, **5a** was not observed and Xantphos was identified as the most effective ligand to afford **3a** in 90% yield with excellent selectivity.
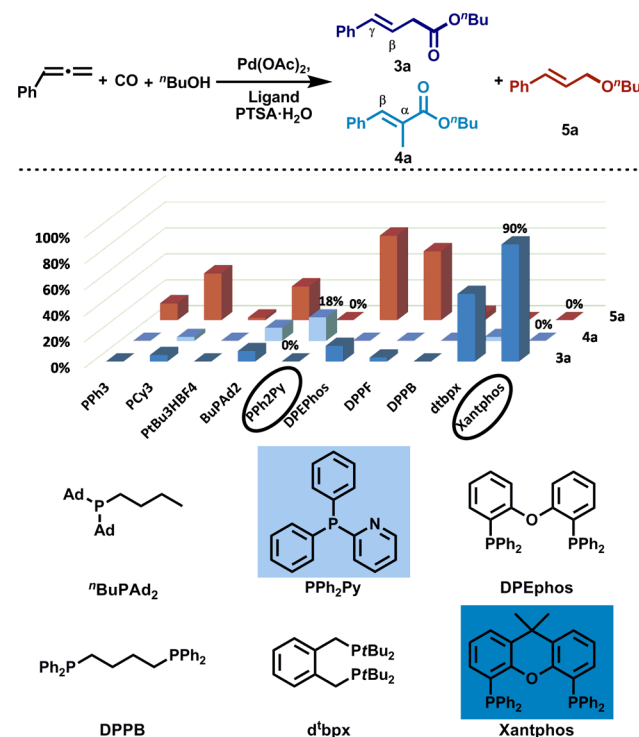
After optimizing the reaction conditions for the synthesis of butyl 4-phenyl-3-butenoate (see Supporting Information, Tables S1−S5), we continued to explore the scope of different allenes (Table 1). To our delight, the catalytic system can be applied in a straightforward manner to a series of aryl-substituted allenes, and good yields were obtained with substrates bearing halogen or alkyl groups at both para (**3b**, **3c**, **3f** and **3g**), meta (**3d**) and ortho positions (**3e**). In all these cases exclusive formation of the E-regioisomers took place. Notably, aliphatic allenes were found to be suitable substrates under similar conditions to afford the corresponding carbonylative products in moderate to good yields. As an example, cyclohexylallene participated in this carbonylation reaction with high reactivity (**3h** and **3i**). Remarkably, 1,2-butadiene, an industrial side-product from oil cracking, also reacted smoothly and gave the β,γ-unsaturated ester (**3j**) in good yield with only 0.1 mol % Pd catalyst! Moreover, electron-deficient allenes, e.g., ethyl 2,3-butadienoate, reacted smoothly and furnished a moderate yield of the desired product (**3k**). Gratifyingly, the reaction of 1,1-disubstituted allene such as 3-methyl-1,2-butadiene also furnished the desired carbonylation product in moderate yield (**3l**).

Furthermore, the reactivity of different alcohols was also investigated (Scheme 3). First, a variety of simple primary aliphatic alcohols were tested under the optimal reaction conditions. The corresponding esters were generated in good yields (**3aa** to **3af**). Moreover, secondary alcohols also underwent this transformation smoothly with excellent

Table 1. Variation of Different Allenes for the Synthesis of β,γ-Unsaturated Esters[a]

Entry	Allene	Product	Yield [%][b]
1	R = H	3a	85
2	R = 4-F	3b	76
3	R = 4-Cl	3c	79
4	R = 3-Cl	3d	70
5	R = 2-Cl	3e	76
6	R = 4-Br	3f	81
7	R = 4-Me	3g	68
8[c]		3h R³ = ⁿBu	66 (91/9)
9[c]		3i R³ = Bn	63 (90/10)
10[d]		3j	76 (76/24)
11[c]		3k	65 (85/15)
12[e]		3l	57

[a]Reaction conditions: 1 (1.0 mmol), 2 (1.2 mmol), Pd(OAc)₂ (1.0 mol %), Xantphos (2.0 mol %), PTSA·H₂O (4.0 mol %), CO (40 bar), toluene (2 mL), 110 °C, 20 h. [b]Isolated yields. E/Z ratio is shown in the parentheses and determined by GC. [c]1 (1.0 mmol), 2 (4.0 mmol), Pd(OAc)₂ (1.0 mol %), Xantphos (2.0 mol %), PTSA·H₂O (4.0 mol %), CO (40 bar), toluene (2 mL), 110 °C, 20 h. [d]1 (25 mmol), 2 (20 mmol), Pd(cod)Cl₂ (0.1 mol %), Xantphos (0.2 mol %), PTSA·H₂O (0.4 mol %), CO (80 bar), toluene (10 mL) in a 25 mL autoclave, 130 °C, 20 h. [e]1 (1.0 mmol), 2 (4.0 mmol), Pd(OAc)₂ (1.0 mol %), Xantphos (2.0 mol %), PTSA·H₂O (4.0 mol %), CO (80 bar), toluene (2 mL), 130 °C, 20 h.

regioselectivity (3ag to 3ai). It is noteworthy that by tuning the amount of allenes, the mono- and dicarbonylation products of diols can be selectively formed, respectively (3aj and 3ak). Interestingly, bioactive alcohols such as amino acid derivatives (3al) and carbohydrates (3am) can be used in this transformation and synthetically useful yields were obtained. Last but not the least, some natural and functionalized alcohols showed good reactivity as well. For instance, (−)-nopol (3an),

Scheme 3. Variation of Different Alcohols for the Synthesis of β,γ-Unsaturated Esters[a]
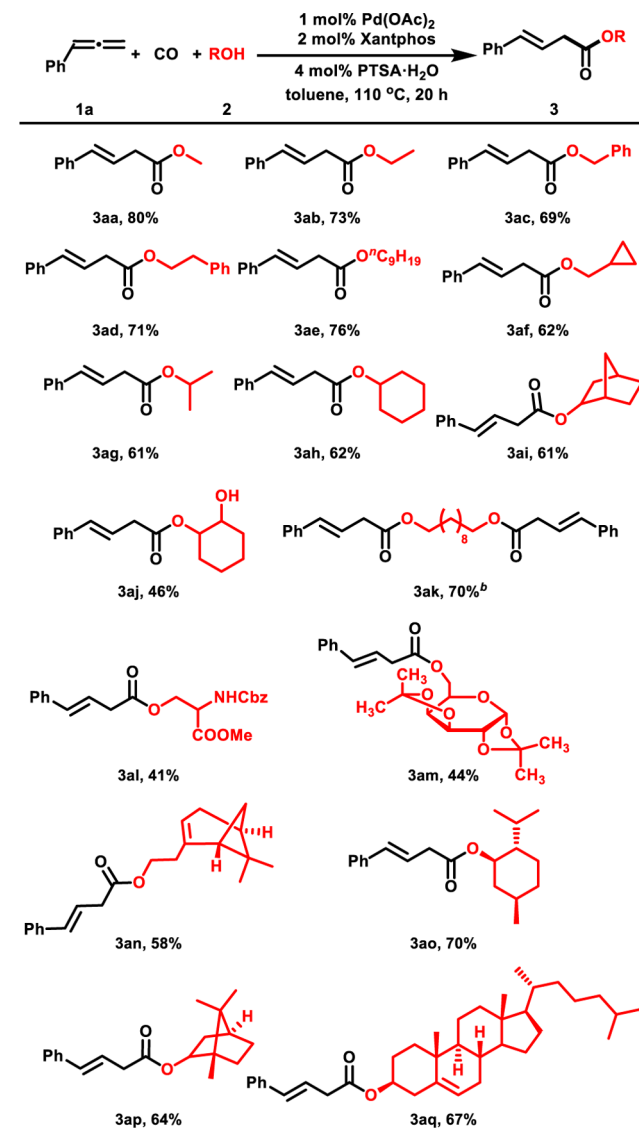
[a]Reaction conditions: 1a (1.0 mmol), 2 (1.2 mmol), Pd(OAc)₂ (1.0 mol %), Xantphos (2.0 mol %), PTSA·H₂O (4.0 mol %), CO (40 bar), toluene (2 mL), 110 °C, 20 h. Isolated yield. [b]1a (1.5 mmol), 2 (0.5 mmol), Pd(OAc)₂ (1.0 mol %), Xantphos (2.0 mol %), PTSA·H₂O (4.0 mol %), CO (40 bar), toluene (2 mL), 110 °C, 20 h. Isolated yield.

bearing a C=C bond, proved to be suitable. Notably, secondary natural alcohols, such as menthol (3ao), (−)-borneol (3ap), and cholesterol (3aq) participated in this transformation efficiently highlighting the broad substrate scope of this protocol and its potential utility in organic synthesis.

In order to gain some mechanistic insights into this reaction, a deuterium labeling experiment was carried out. When methanol-d_4 was applied in this transformation, 68% of the ester product was D-labeled only at the β-position along with 32% nonlabeled product (eq 1). The proton at the β-position in nonlabeled product might be introduced from acid cocatalyst and trace amount of water in the solvent. Therefore, deuterated acid TsOD·D₂O was employed as well, and 8% of deuterated ester product at C2 position was obtained (eq 2) which indicates a partial scrambling process. Nevertheless, these

$$\text{Eq.1} \qquad \text{yield 76\%} \qquad \text{D:H = 68:32}$$

$$\text{Eq.2} \qquad \text{yield 71\%} \qquad \text{D:H = 8:92}$$
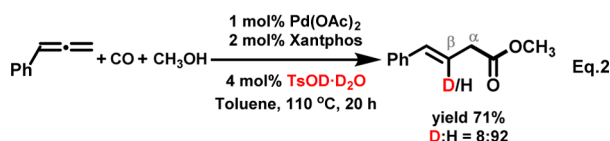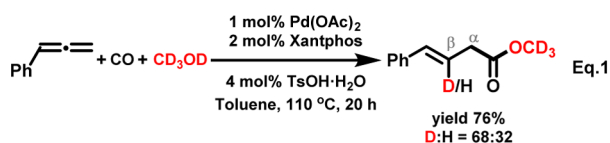
results demonstrate a selective insertion of the double bond between C2 and C3 positions of allene into the Pd−D or Pd−H bond and the β,γ-unsaturated ester products were not generated via isomerization of preformed α,β-unsaturated isomers as mentioned in Scheme 1.

Next, the kinetic progress of the reaction between propa-1,2-dienylbenzene **1a** and *n*-butanol **2a** was examined under the optimal conditions (Figure 1). It is shown that **1a** is initially
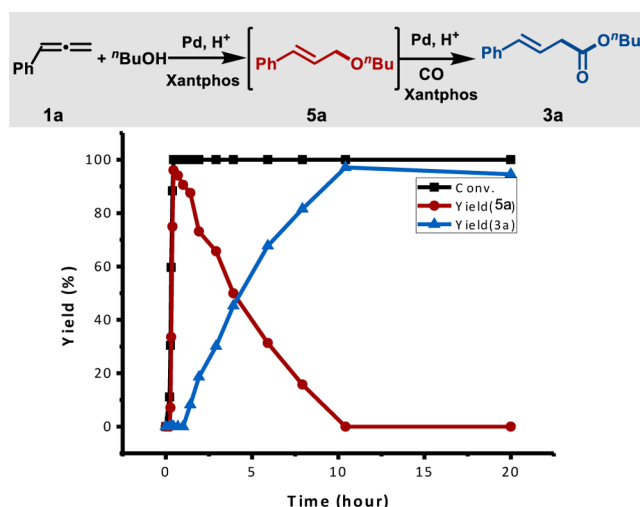

Figure 1. Kinetic profile for the carbonylation reaction of **1a** and **2a** for the synthesis of β,γ-unsaturated esters.

converted into the C−O coupling product **5a**. Then, the β,γ-unsaturated ester **3a** is generated at a lower reaction rate along with the consumption of the reaction intermediate **5a**. This observation is well in accordance with our previous study for the alkoxycarbonylation of allylic alcohols.[8e] It illustrates that a common reaction intermediate, π-allyl-Pd species, is involved in these two reactions, which is more prone to undergo nucleophilic addition with aliphatic alcohols compared to the slow CO insertion step.

In order to confirm whether **5a** is an intermediate in this carbonylation reaction, it was applied to the standard conditions and the corresponding β,γ-unsaturated ester **3a** was obtained with 76% yield (eq 3). This result revealed that **5a** should be a reaction intermediate in this carbonylation process.
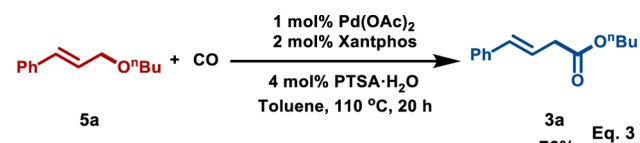
$$\text{Eq. 3} \qquad 76\%$$

To further verify that the direct C−O coupling process is catalyzed by palladium and acid cocatalyst, three control experiments were carried out. As shown in Table 2, under the

Table 2. Control Experiments for the Formation of the Allylic Ether 5a

entry	variation from "standard condition"	conv. [%]	yield [%]
1	none	79	77
2	without [Pd] and Xantphos	0	–
3	without PTSA·H$_2$O	0	–

standard conditions, the direct C−O coupling product **5a** is obtained in 77% yield after 15 min. However, in the absence of either Pd catalyst or PTSA·H$_2$O, there was no conversion of starting material **1a** at all.

On the basis of all these experimental findings, the following mechanism is proposed for the synthesis of β,γ-unsaturated esters (Scheme 4). Initially, Pd(II) catalyst precursor is in situ

Scheme 4. Proposed Mechanism for the Synthesis of β,γ-Unsaturated Esters (L,L = Xantphos)
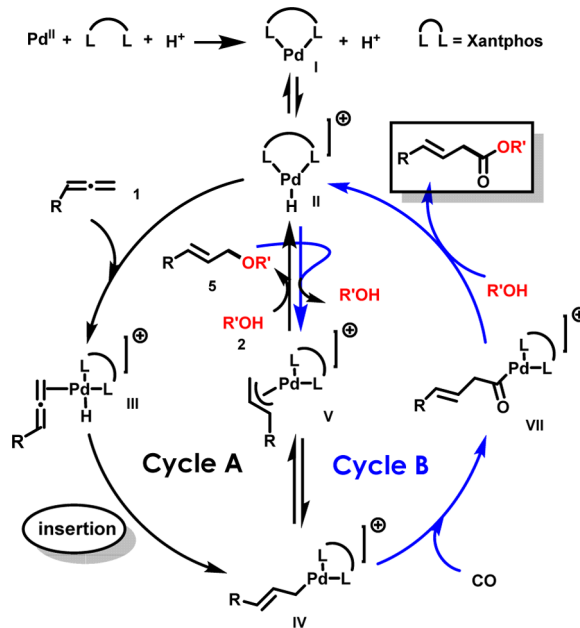
reduced to Pd(0) species **I** in the presence of excess amount of phosphine ligands.[18] In the presence of acid, this complex is in an equilibrium with the corresponding Pd(II) hydride complex **II**, which are both key catalytically active species to initiate the following domino catalytic cycles.[8e,17d] The allene substrate **1** coordinates to Pd−H species to form the Pd complex **III**, and consequent insertion of C2−C3 double bond will give σ- and π-allyl-Pd intermediates **IV** and **V**. These intermediates undergo a fast nucleophilic substitution by the aliphatic alcohol **2** at the less sterically hindered terminal position to afford the C−O coupling product **5** and regenerate Pd hydride species **II** to finish cycle A. Subsequently, in the presence of acid, **5** is activated and reacts with Pd(0) species **I** via oxidative addition to form reaction intermediates **V** and **IV** again. Then, complex

IV experiences a CO insertion process to afford acyl Pd species **VII**. Finally, the alcoholysis of intermediate **VII** provides the desired carbonylation product β,γ-unsaturated esters **3** and regenerates Pd hydride species **II**. Although we could not exclude the reaction path 2 (Scheme 1), which can also lead to the same product in this reaction, we prefer the shown mechanistic proposal. Considering the steric effect at C1 position of the different allenes, it is more likely that the less steric hindered double bond coordinates to the Pd center bearing the bulky ligand Xantphos and delivers the thermodynamically more stable reaction intermediate **III**.

Furthermore, we were interested in demonstrating the utility of this method for the synthesis of an industrially important building block. 1,2-Butadiene is a minor product from oil cracking which is available from industry on multitons-scale. To the best of our knowledge no catalytic applications have been described of this feedstock in the open literature. Indeed, we succeeded to convert 1,2-butadiene into dimethyl adipate **6m**, which is a valuable start material for polymer and plasticizer synthesis, in two steps (Scheme 5). The first alkoxycarbony-

Scheme 5. Synthetic Application by Using 1,2-Butadiene as the Substrate
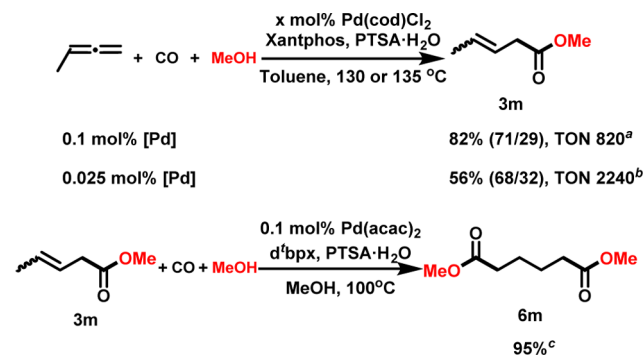
^{a}Reaction conditions: 1,2-butadiene (20−25 mmol), methanol (20 mmol), Pd(cod)Cl$_2$ (0.1 mol %), Xantphos (0.2 mol %), PTSA·H$_2$O (0.4 mol %), CO (80 bar), toluene (10 mL), 130 °C, 20 h. GC yield. E/Z ratio is shown in the parentheses and determined by GC. ^{b}Reaction conditions: 1,2-butadiene (20−25 mmol), methanol (20 mmol), Pd(cod)Cl$_2$ (0.025 mol %), Xantphos (0.05 mol %), PTSA·H$_2$O (0.1 mol %), CO (80 bar), toluene (10 mL), 135 °C, 72 h. GC yield. E/Z ratio is shown in the parentheses and determined by GC. ^{c}Reaction conditions: **3m** (10 mmol), methanol (10 mL), Pd(acac)$_2$ (0.1 mol %), d^{t}bpx (0.4 mol %), PTSA·H$_2$O (0.8 mol %), CO (40 bar), 100 °C, 20 h. GC yield.

lation reaction takes place with only 0.1 mol % Pd catalyst loading to give the β,γ-unsaturated esters **3m** with a turnover number (TON) of 820. Further decrease of the Pd catalyst loading led to a TON of even 2240. Subsequent transformation of **3m** gave selectively dimethyl adipate **6m** in high yield via the second alkoxycarbonylation step based on a known isomerization carbonylation catalyst system.[7c]

As we discussed above (Scheme 2), it is interesting to note that in the presence of PPh$_2$Py as ligand a good selectivity for the synthesis of the other regioisomer **4a** is observed, albeit in a low yield. This result intrigued us to vary the reaction conditions to improve the yield of this transformation. As shown in Table 3 the performance of the catalyst is influenced by the different acid cocatalysts. TFA (trifluoroacetic acid) showed superior reaction activity compared to other tested acid cocatalysts including PTSA·H$_2$O, CH$_3$SO$_3$H and CF$_3$SO$_3$H

Table 3. Effect of Acid Cocatalyst and Ligand for the Synthesis of 4a^a

entry	acid	X:Y	yield **4a** [%]	yield **3a** [%]
1	PTSA·H$_2$O	4:4	18	trace
2	CH$_3$SO$_3$H	4:4	20	trace
3	CF$_3$SO$_3$H	4:4	4	trace
4	TFA	4:4	44	4
5	TFA	4:5	43	5
6	TFA	4:6	49	5
7	TFA	6:6	56	7
8	**TFA**	**6:8**	**75**	**7**
9	TFA	6:10	66	11

^{a}Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), Pd(OAc)$_2$ (1.0 mol %), PPh$_2$Py (X mol %), Acid (Y mol %), CO (40 bar), toluene (2.0 mL), 110 °C, 20 h. GC yield.

(Table 3, entries 1−4). Then, the effects of ligand and cocatalyst concentrations were investigated as well. Actually, both the concentrations of the acid cocatalyst TFA and the ligand have a profound influence on the yield of **4a** (Table 3, entries 5−9). To our delight, under optimized conditions the desired product **4a** is obtained in 75% yield (entry 8) along with 7% of **3a** as byproduct. However, a higher loading of the acid cocatalyst compressed the reaction efficiency (entry 9).

With the optimal conditions established, various alcohols **2** were employed to react with allenes **1** to produce the corresponding α,β-unsaturated esters **4** (Scheme 6). All tested primary aliphatic alcohols gave the desired carbonylation product in good yields (**4a** to **4e**). Interestingly, some bioactive secondary alcohols were also compatible in this transformation and moderate yields were obtained (**4f** and **4g**). Then, different allenes were investigated in this transformation as well: 4-methyl phenyl substituted allene worked well under the standard conditions (**4h**); remarkably, aliphatic allenes including cyclohexylallene (**4i**), and 1,2-butadiene (**4k**) gave the corresponding ester product in moderate to good yields. Finally, it is worth noting that a functionalized substrate, ethyl 2,3-butadienoate (**4j**), underwent this transformation smoothly as well.

Regarding the mechanism a similar deuterium labeling experiment was carried out. When methanol-d_4 was applied to this reaction, 76% of the ester product was deuterated only at C3 position along with 24% nonlabeled product (eq 4).
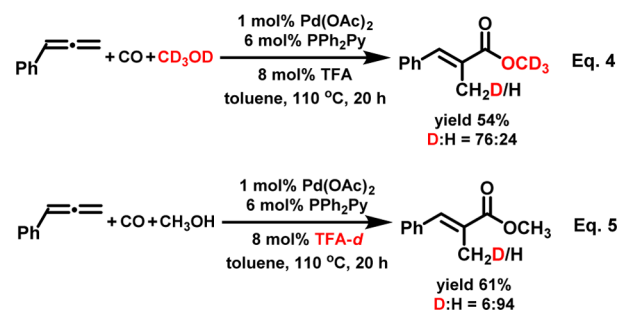
Additionally, using TFA-d instead of TFA gave 6% of deuterated ester product at C3 position (eq 5). These results indicate that the double bond between C2 and C3 positions

Scheme 6. Scope of Different Allenes 1 and Alcohols 2 for the Synthesis of α,β-Unsaturated Esters 4[a]
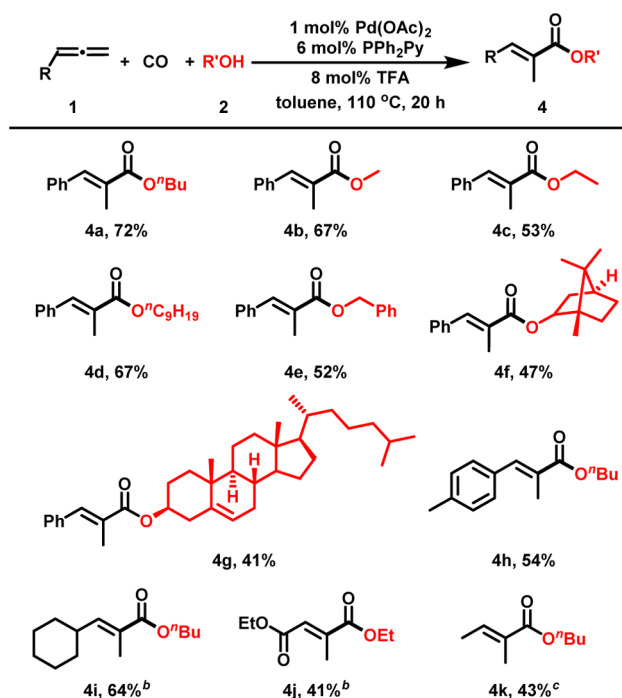
[a]Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), Pd(OAc)$_2$ (1.0 mol %), PPh$_2$Py (6.0 mol %), TFA (8.0 mol %), CO (40 bar), toluene (2 mL), 110 °C, 20 h. Isolated yields. [b]**1** (1.0 mmol), **2** (4.0 mmol), Pd(OAc)$_2$ (1.0 mol %), PPh$_2$Py (6.0 mol %), TFA (8.0 mol %), CO (40 bar), toluene (2 mL), 110 °C, 20 h. Isolated yields. [c]**1** (18 mmol), **2** (20 mmol), Pd(cod)Cl$_2$ (0.2 mol %), PPh$_2$Py (1.2 mol %), TFA (1.6 mol %), CO (80 bar), toluene (10 mL) in a 25 mL autoclave, 130 °C, 20 h. Isolated yields.

inserts into the Pd−D or Pd−H bond in a reverse manner compared to the synthesis of β,γ-unsaturated esters, and the carbonylation products are not generated via the isomerization of other isomers as well.

In order to confirm whether the C−O coupling reaction intermediate is involved in this transformation, the kinetic progress was also examined under the optimal conditions. As is shown in Figure 2, the corresponding C−O coupling product was not observed during the whole reaction process. The carbonylation product **4a** was accumulated from the very beginning along with the gradual consumption of the allene substrate **1a**.[19] This result proves that this reaction undergoes a mechanistically different reaction pathway compared to the synthesis of the β,γ-unsaturated esters.

On the basis of this experimental observation, a possible reaction pathway is proposed for the synthesis of α,β-unsaturated esters. As shown in Scheme 7, the catalyst precursor leads to an equilibrium of the active Pd(0) species **I** with the Pd(II) hydride complex **II**.[18] Then, allene **1** coordinates to Pd to form the complex **III**, and subsequent double bond insertion in a reverse manner affords the alkenyl-Pd intermediate **VIII** instead of π-allyl-Pd intermediate formed in the previous example.[20] Therefore, in contrast to the reaction pathway for the formation of β,γ-unsaturated esters, the direct C−O coupling product was not observed in this case as the reaction intermediate (the reaction process shown in gray color in Scheme 7). It is due to the difficult C−O bond reductive elimination between alkenyl and alkoxyl groups.[21] Then, Pd
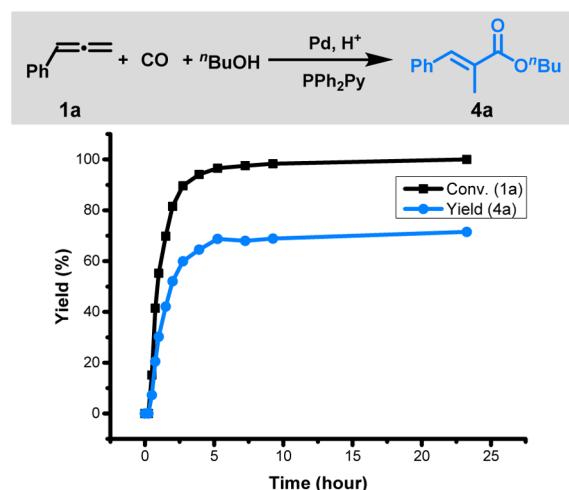
Figure 2. Kinetic profile for the carbonylation reaction of **1a** and **2a** for the synthesis of α,β-unsaturated esters.

Scheme 7. Proposed Mechanism for the Synthesis of α,β-Unsaturated Esters
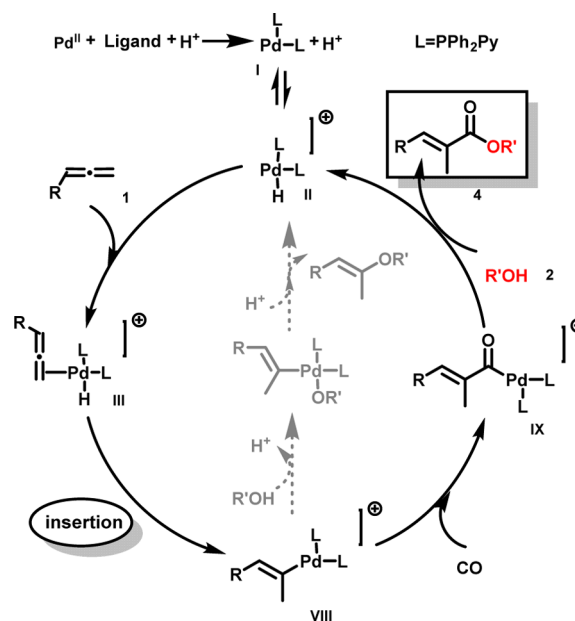
complex **VIII** directly undergoes a facile CO insertion process to give the corresponding acyl Pd species **IX**. Finally, alcoholysis of intermediate **IX** generates the desired product α,β-unsaturated esters **4** and closes the catalytic cycle.

■ CONCLUSIONS

In summary, we have developed the first general carbonylation reaction of allenes with aliphatic alcohols to produce a variety of synthetically useful unsaturated esters. Depending on the ligand present, α,β- and β,γ-unsaturated esters are selectively formed. Interestingly, these two catalytic reactions proceeded via different reaction pathways supported by mechanistic studies. Moreover, the first catalytic reactions of the industrially available 1,2-butadiene are described. The valuable building block dimethyl adipate was obtained in high yield at low catalyst loadings. These procedures are expected to complement the current methods for carbonylation reactions in organic synthesis.

ASSOCIATED CONTENT

S Supporting Information

Additional experimental results and procedures and characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04052.

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REFERENCES

(1) (a) Catalytic Carbonylation Reactions. In *Catalytic Carbonylation Reactions*; Beller, M., Ed.; Springer: Berlin, 2006. (b) *Modern Carbonylation Methods*; Wiley-VCH Verlag GmbH: Weinheim, 2008. (c) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114−4133. (d) Liu, Q.; Zhang, H.; Lei, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 10788−10799. (e) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986−5009. (f) Wu, X.-F.; Fang, X.; Wu, L.; Jackstell, R.; Neumann, H.; Beller, M. *Acc. Chem. Res.* **2014**, *47*, 1041−1053.

(2) (a) Kiss, G. *Chem. Rev.* **2001**, *101*, 3435−3456. (b) Brennführer, A.; Neumann, H.; Beller, M. *ChemCatChem* **2009**, *1*, 28−41. (c) Wu, L.; Liu, Q.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 6310−6320.

(3) (a) Satoh, T.; Ikeda, M.; Kushino, Y.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997**, *62*, 2662−2664. (b) Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals. In *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*; Beller, M., Bolm, C., Eds.; Wiley-VCH Verlag GmbH: Weinheim, 2008. (c) Wu, L.; Fang, X.; Liu, Q.; Jackstell, R.; Beller, M.; Wu, X.-F. *ACS Catal.* **2014**, *4*, 2977−2989.

(4) Reppe, W.; Kröper, H. *Justus Liebigs Ann. Chem.* **1953**, *582*, 38−71.

(5) (a) del Río, I.; Ruiz, N.; Claver, C.; van der Veen, L. A.; van Leeuwen, P. W. N. M. *J. Mol. Catal. A: Chem.* **2000**, *161*, 39−48. (b) del Río, I.; Claver, C.; van Leeuwen, Piet W. N. M. *Eur. J. Inorg. Chem.* **2001**, *2001*, 2719−2738. (c) Kégl, T. Carbonylation of Alkenes and Dienes. In *Modern Carbonylation Methods*; Wiley-VCH Verlag GmbH: Weinheim, 2008; pp 161−198. (d) Chen, H.; Cai, C.; Liu, X.; Li, X.; Jiang, H. *Chem. Commun.* **2011**, *47*, 12224−12226. (e) Eastham, G. R.; Waugh, M.; Pringle, P.; Turner, T. P. W. WO2011083305. 2011. (f) Blanco, C.; Godard, C.; Zangrando, E.; Ruiz, A.; Claver, C. *Dalton Trans.* **2012**, *41*, 6980−6991. (g) Malkov, A. V.; Derrien, N.; Barlóg, M.; Kočovský, P. *Chem.—Eur. J.* **2014**, *20*, 4542−4547. (h) Wang, L.; Wang, Y.; Liu, C.; Lei, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 5657−5661.

(6) (a) Reppe, W. *Justus Liebigs Ann. Chem.* **1953**, *582*, 1−37. (b) Drent, E.; Arnoldy, P.; Budzelaar, P. H. M. *J. Organomet. Chem.* **1993**, *455*, 247−253. (c) Drent, E.; Arnoldy, P.; Budzelaar, P. H. M. *J. Organomet. Chem.* **1994**, *475*, 57−63. (d) Doherty, S.; Knight, J. G.; Smyth, C. H. Recent Developments in Alkyne Carbonylation. In *Modern Carbonylation Methods*; Wiley-VCH Verlag GmbH: Weinheim, 2008; pp 251−290. (e) Nunez Magro, A. A.; Robb, L.-M.; Pogorzelec, P. J.; Slawin, A. M. Z.; Eastham, G. R.; Cole-Hamilton, D. J. *Chem. Sci.*

2010, *1*, 723−730. (f) Suleiman, R.; Tijani, J.; El Ali, B. *Appl. Organomet. Chem.* **2010**, *24*, 38−46.

(7) (a) Tsuji, J.; Kiji, J.; Hosaka, S. *Tetrahedron Lett.* **1964**, *5*, 605−608. (b) Knifton, J. F. *J. Catal.* **1979**, *60*, 27−40. (c) Fang, X.; Li, H.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 9030−9034.

(8) (a) Murahashi, S.; Imada, Y.; Taniguchi, Y.; Higashiura, S. *J. Org. Chem.* **1993**, *58*, 1538−1545. (b) Mitsudo, T.-a.; Suzuki, N.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, *59*, 7759−7765. (c) Takeuchi, R.; Akiyama, Y. *J. Organomet. Chem.* **2002**, *651*, 137−145. (d) Tommasi, S.; Perrone, S.; Rosato, F.; Salomone, A.; Troisi, L. *Synthesis* **2012**, *44*, 423−430. (e) Liu, Q.; Wu, L.; Jiao, H.; Fang, X.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 8064−8068.

(9) (a) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805−2827. (b) Schuster, H. E.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley: New York, 1984. (c) *Modern Allene Chemistry*; Wiley-VCH Verlag GmbH: Weinheim, 2008. (d) Yu, S.; Ma, S. *Chem. Commun.* **2011**, *47*, 5384−5418. (e) Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074−3112.

(10) (a) Bai, T.; Ma, S.; Jia, G. *Coord. Chem. Rev.* **2009**, *253*, 423−448. (b) Sam, B.; Breit, B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 3267−3274.

(11) (a) Ma, S.; Ren, H.; Wei, Q. *J. Am. Chem. Soc.* **2003**, *125*, 4817−4830. (b) Lu, Z.; Chai, G.; Ma, S. *J. Am. Chem. Soc.* **2007**, *129*, 14546−14547. (c) Hartung, J.; Kopf, T. Fundamentals and Application of Free Radical Addition to Allenes. In *Modern Allene Chemistry*; Wiley-VCH Verlag GmbH: Weinheim, 2008; pp 701−726. (d) Jeganmohan, M.; Cheng, C.-H. *Chem. Commun.* **2008**, 3101−3117. (e) Inagaki, F.; Kitagaki, S.; Mukai, C. *Synlett* **2011**, *2011*, 594−614. (f) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994−2009. (g) Zeng, R.; Fu, C.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3888−3891. (h) Li, C.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 862−865. (i) Li, C.; Kähny, M.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 13780−13784. (j) Xu, K.; Thieme, N.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 7268−7271. (k) Pritzius, A. B.; Breit, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 3121−3125.

(12) (a) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12−21. (b) Tius, M. A. Cyclizations of Allenes. In *Modern Allene Chemistry*; Wiley-VCH Verlag GmbH: Weinheim, 2008; pp 817−845.

(13) (a) Lotesta, S. D.; Kiren, S.; Sauers, R. R.; Williams, L. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7108−7111. (b) Horváth, A.; Bäckvall, J.-E. Oxidation of Allenes. In *Modern Allene Chemistry*; Wiley-VCH Verlag GmbH: Weinheim, 2008; pp 973−994. (c) Spencer, W. T.; Levin, M. D.; Frontier, A. J. *Org. Lett.* **2011**, *13*, 414−417.

(14) (a) Jeganmohan, M.; Cheng, C.-H. *Chem.—Eur. J.* **2008**, *14*, 10876−10886. (b) Moran, J.; Preetz, A.; Mesch, R. A.; Krische, M. J. *Nat. Chem.* **2011**, *3*, 287−290. (c) Sam, B.; Montgomery, T. P.; Krische, M. J. *Org. Lett.* **2013**, *15*, 3790−3793. (d) Sam, B.; Luong, T.; Krische, M. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 5465−5469.

(15) (a) Xiao, W.-J.; Vasapollo, G.; Alper, H. *J. Org. Chem.* **1998**, *63*, 2609−2612. (b) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2004**, *2004*, 3377−3383. (c) Kodama, S.; Nishinaka, E.; Nomoto, A.; Sonoda, M.; Ogawa, A. *Tetrahedron Lett.* **2007**, *48*, 6312−6317. (d) Guo, H.; Ma, S. *Adv. Synth. Catal.* **2008**, *350*, 1213−1217. (e) Nomoto, A.; Ogawa, A. Carbonylation of Allenes. In *Modern Carbonylation Methods*; Wiley-VCH Verlag GmbH: Weinheim, 2008; pp 291−300. (f) Breit, B.; Diab, L. 4.18 Hydroformylation and Related Carbonylation Reactions of Alkenes, Alkynes, and Allenes. In *Comprehensive Organic Synthesis II*, 2nd ed.; Knochel, P., Ed.; Elsevier: Amsterdam, 2014; pp 995−1053. (g) Köpfer, A.; Breit, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 6913−6917.

(16) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067−3126.

(17) (a) Fleischer, I.; Jennerjahn, R.; Cozzula, D.; Jackstell, R.; Franke, R.; Beller, M. *ChemSusChem* **2013**, *6*, 417−420. (b) Li, H.; Neumann, H.; Beller, M.; Wu, X.-F. *Angew. Chem., Int. Ed.* **2014**, *53*, 3183−3186. (c) Profir, I.; Beller, M.; Fleischer, I. *Org. Biomol. Chem.* **2014**, *12*, 6972−6976. (d) Liu, Q.; Yuan, K.; Arockiam, P.-B.; Franke, R.; Doucet, H.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 4493−4497.

(18) (a) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009−3013. (b) Amatore, C.; Carre, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818−1826.

(19) Although the conversion of **1a** is nearly 100%, the yield of product was only 70%. Apart from the corresponding isomer **3a** (7% yield, detected by GC), the other by-product was not observed from GC. We think allene is polymerized or decomposed under the reaction conditions. For the related polymerization of allenes, see: Osakada, K.; Takeuchi, D. Coordination Polymerization of Dienes, Allenes, and Methylenecycloalkanes. In *Polymer Synthesis*; Springer: Berlin, 2004; Vol. *171*, pp 137−194.

(20) The ligands and counterions effect for the regioselectivity control of allene insertion into Pd−H bond cannot be completely clarified in the current work. For the research on the effect of counterions and monodentate and bidentate ligands on alkene insertion regioselectivity, see: Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2−7. We thank one of the referees for pointing it out.

(21) (a) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860. (b) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 10718−10719. (c) Mann, G.; Shelby, Q.; Roy, A. H.; Hartwig, J. F. *Organometallics* **2003**, *22*, 2775−2789.

■ NOTE ADDED AFTER ASAP PUBLICATION

Scheme 2 was corrected on July 8, 2015.
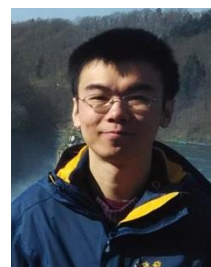
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● <u>Publications:</u>

Journals:

1. **<u>Jie Liu</u>**, Haoquan Li, Anke Spannenberg, Robert Franke, Ralf Jackstell, and Matthias Beller*. *Angew. Chem. Int. Ed.* **2016**, 55, 13544-13548

2. **<u>Jie Liu</u>**, Christoph Kubis, Robert Franke, Ralf Jackstell, and Matthias Beller*. *ACS Catal.*, **2016**, 6, 907–912

3. **<u>Jie Liu</u>**, Qiang Liu*, Robert Franke, Ralf Jackstell, and Matthias Beller*. *J. Am. Chem. Soc.* **2015**, 137, 8556-8563

4. **<u>Jie Liu</u>**, Heng Zhang, Hong Yi, Chao Liu*, and Aiwen Lei*. *Sci. China. Chem.* **2015**, 58, 1323-1328

5. Zhixiong Liao, Hong Yi, Zheng Li, Chao Fan, Xu Zhang, **<u>Jie Liu</u>**, Zixin Deng* and Aiwen Lei*. *Chem. Asian J.* **2015**, 10, 96-99

6. **<u>Jie Liu</u>**, Qiang Liu, Hong Yi, Chu Qin, Ruopeng Bai, Xiaotian Qi, Yu Lan* and Aiwen Lei*. *Angew. Chem. Int. Ed.* **2014**, 53, 502-506

7. **<u>Jie Liu</u>**, Chao Fan, Hongyu Yin, Chu Qin, Guoting Zhang, Xu Zhang, Hong Yi and Aiwen Lei*. *Chem. Commun.* **2014**, 50, 2145-2147

8. Hong Yi, Xu Zhang, Chu Qin, Zhixiong Liao, **<u>Jie Liu</u>** and Aiwen Lei*. *Adv. Synth. Catal.* **2014**, 356, 2873-2877

9. Xu Zhang, Hong Yi, Zhixiong Liao, Guoting Zhang, Chao Fan, Chu Qin, **<u>Jie Liu</u>** and Aiwen Lei*. *Org. Biomol. Chem.*, **2014**, 12, 6790-6793

10. Qiang Liu, Hong Yi, **<u>Jie Liu</u>**, Yuhong Yang, Xu Zhang, Ziqi Zeng and Aiwen Lei*. *Chem. Eur. J.* **2013**, 19, 5120-5126

11. Hong Yi, Qiang Liu, **<u>Jie Liu</u>**, Ziqi Zeng, Yuhong Yang, and Aiwen Lei*. *ChemSusChem* **2012**, 5, 2143-2146

12. Qiang Liu, Pan Wu, Yuhong Yang, Ziqi Zeng, **<u>Jie Liu</u>**, Hong Yi, and Aiwen Lei*. *Angew. Chem. Int. Ed.* **2012**, 51, 4666 –4670

13. Qiang Liu, Qing Yong Zhao, **<u>Jie Liu</u>**, Pan Wu, Hong Yi and Aiwen Lei*. *Chem. Commun.,* **2012**, 48, 3239–3241

14. Qiang Liu, Gang Li, Hong Yi, Pan Wu, **<u>Jie Liu</u>** and Aiwen Lei*. *Chem. Eur. J.* **2011**, 17, 2353-235

Patents:

1. Ralf Jackstell, Haoquan Li, **<u>Jie Liu</u>**, Matthias Beller, Robert Franke, Katrin Marie Dyballa. Doppelcarbonylierung von Allylalkoholen, EP 15200490

2. Matthias Beller, Ralf Jackstell, Haoquan Li, **<u>Jie Liu</u>**, Robert Franke, Katrin Marie Dyballa. Doppelcarbonylierung von Allylethern, EP 15200511

Selbstständigkeitserklärung

Doktorandinnen/Doktoranden-Erklärung gemäß § 4 Absatz 1 Buchstaben g und h der Promotionsordnung der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock

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....
(Straße, PLZ, Wohnort)

Ich habe eine Dissertation zum Thema

Development of selective and efficient catalysts for carbonylation of alkenes
....

....

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

Prof. Dr. Matthias Beller
....
betreut.

Ich gebe folgende Erklärung ab:

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