Catalytic Carbonylative Functionalization of Multiple Carbon-Carbon Bonds

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Universität Rostock

Abstract

Catalytic Carbonylative Functionalization of Multiple Carbon-Carbon Bonds

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This thesis is mainly concerned with the carbonylative functionalization of unsaturated organic substrates in the presence of homogeneous catalysts. More specifically, alkoxy- and aminocarbonylations, as well as hydroformylation and domino hydroformylation reactions of alkynes, alkenes and 1,3-dienes are presented. The resulting *α,β*-unsaturated aldehydes, saturated esters and amides, *β,γ*-unsaturated esters and amides constitute important intermediates for both organic synthesis and chemical industries. Regarding methodology developments the combination of hydroformylation with Diels-Alder reaction has been investigated as a novel multicomponent reaction for the synthesis of interesting organic building blocks. In addition, the hydroformylation methodology was successfully applied as part of various domino reactions for the highly selective synthesis of *α,β*-unsaturated aldehydes and ketones from easily available olefins. In all the above mentioned areas systematic catalyst optimization studies were performed and the scope and limitations of the respective protocol presented.

Diese Arbeit ist hauptsächlich auf die carbonylierende Funktionalisierung ungesättigter organischer Substrate in Gegenwart homogener Katalysatoren gerichtet. Speziell werden sowohl Alkoxycarbonylierungs- und Amino-carbonylierungsreaktionen als auch Hydroformylierungen von Alkinen, Alkenen und 1,3- Dienen präsentiert. Die resultierenden *α,β*-ungesättigten Aldehyde, gesättigte Ester und Amide, *β,γ*-ungesättigte Ester und Amide sind wichtige Zwischenprodukte für die organische Synthese und für die chemische Industrie. Bezüglich der Entwicklung von neueren Methoden ist die Kombination der Hydroformylierung mit Diels-Alder Reaktionen als neue Multikomponentenreaktion zur Synthese interessanter organischer Bausteine untersucht worden. Weiterhin wurden Hydroformylierungsmethoden erfolgreich als Teil verschiedener Dominoreaktionen zur hochselektiven Synthese von *α,β*-ungesättigten Aldehyden und Ketonen aus leicht verfügbaren Olefinen etabliert. In allen oben genannten Reaktionen wurden systematische Optimierungsstudien durchgeführt und die Möglichkeiten und Grenzen der jeweiligen Protokolle vorgestellt.

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List of Abbreviations

acac	*Acetylacetone*
atm	*atmosphere*
Ar	*Aryl*
BASF	*Badische Anilin- & Soda-Fabrik*
Bn	*Benzyl*
Bu	*Butyl*
^{t}Bu	*Tert-butyl*
Cy	*Cyclohexyl*
Cat.	*Catalyst*
cod	*Cycloocta-1,5-diene*
DEHP	*Bis(2-ethylhexyl) phthalate*
d	*Day*
dba	*trans, trans-Dibenzylideneacetone*
dppp	*1,3-Bis(diphenylphosphino)propane*
dppb	*1,4-Bis(diphenylphosphino)butane*
ee	*Enantiomeric excess*
etc.	*Et cetera*
et al.	*Et alii*
E	*Entgegen (describing the absolute stereochemistry of double bonds)*
EWG	*electron-withdrawing group*
h	*Hour*
iso	Sum of branched products
LDA	*Lithiumdiisopropylamid*
L	*Ligand*
MeOH	*Methanol*
MSA	*Methanesulfonic acid*
n	*Amount of linear product*
N-	*Nitrogen substituted*

NMP	*N-Methylpyrrolidone*
NuH	*Nucleophile*
OAc	*Acetate*
OMe	*Methoxy*
Ph	*Phenyl*
***p*-TsOH**	*para-Toluenesulfonic acid*
Ph	*Phenyl*
PVC	*Polyvinylchloride*
S	*Solvent*
TM	*Transition metal*
TMS	*Trimethylsilyl*
THF	*Tetrahydrofuran*
TFA	*Trifluoroacetic acid*
TPPTS	*3,3',3''-Phosphanetriyltris(benzenesulfonic acid) trisodium salt*
TBS	*tert-Butyldimethylsilyl*
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)*

1 Introduction

Carbon monoxide (CO) was discovered in the 18th century by de Lassone by heating zinc oxide with coke. Soon after, it was first identified by William Cumberland Cruikshank.[1] Nowadays, this gas is used as an inexpensive and easily available C1 source for all kinds of chemical transformations. More specifically, carbonylation reactions provide useful carbonyl containing intermediates, which are readily modified further on. Already one century ago, the first work on transition-metal-catalyzed carbonylations has been performed. Since then, impressive progress has been achieved in this area. Notably, apart from academic developments these reactions are also applied on bulk scale in industry. For example, today the vast majority of acetic acid is produced *via* carbonylation of methanol in the presence of rhodium (Monsanto process) or iridium-based catalysts (Cativa^{TM} process).[2]

The reactivity of multiple carbon-carbon bonds is relatively greater than that of single C-C bonds, which are found in alkanes. In general, π electrons of multiple carbon-carbon bonds are more exposed and less stable. Catalytic carbonylations of unsaturated substrates are known since the pioneering work of Walter Reppe at BASF.[3] Since then, transition-metal-catalyzed carbonylation reactions have gained in importance. More specifically, the palladium-catalyzed addition of carbon monoxide to alkenes and alkynes in the presence of an acidic hydrogen donor has received considerable attention during the last years and has been used to prepare a range of important products. Another special case of the carbonylation of unsaturated substrates is the so-called hydroformylation, which makes use of hydrogen as nucleophile.[4] With respect to scale this process represents the most important homogeneous catalytic reaction.

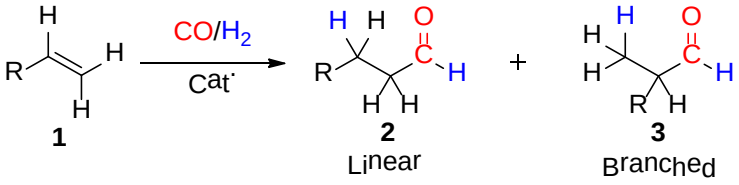
At the beginning of industrial homogeneous catalysis, nickel and cobalt catalysts prevailed in alkoxycarbonylations and hydroformylations. Due to the improved activities and selectivities since the 1970's catalyst developments focused especially on rhodium (for hydroformylations) and palladium (for alkoxycarbonylations) as base metals. More recently, there is an increasing interest to develop less expensive and environmentally benign catalysts for these reactions.

The present dissertation highlights recent achievements in hydroformylation and domino hydroformylation reactions as well as palladium-catalyzed carbonylation reactions of alkenes. It is also presented as a cumulative collection of publications which have been already released in international journals and patent applications.

1.1 Hydroformylation

1.1.1 Hydroformylation of Alkenes

Otto Roelen discovered the hydroformylation reaction in 1938 during an investigation of the origin of oxygenated products occurring in cobalt catalyzed Fischer-Tropsch reactions. Roelen's observation that ethylene, H_2 and CO were converted into propanal, and at higher pressures, diethyl ketone, marked the beginning of hydroformylation catalysis. In the hydroformylation reaction, the elements of formaldehyde (H and CHO) are added across a double bond to give an aldehyde (Scheme 1).[5] Both linear and branched products can be produced. Depending on the catalyst and conditions, the aldehydes can be directly reduced to alcohols during the reaction.



Scheme 1: The hydroformylation reaction.

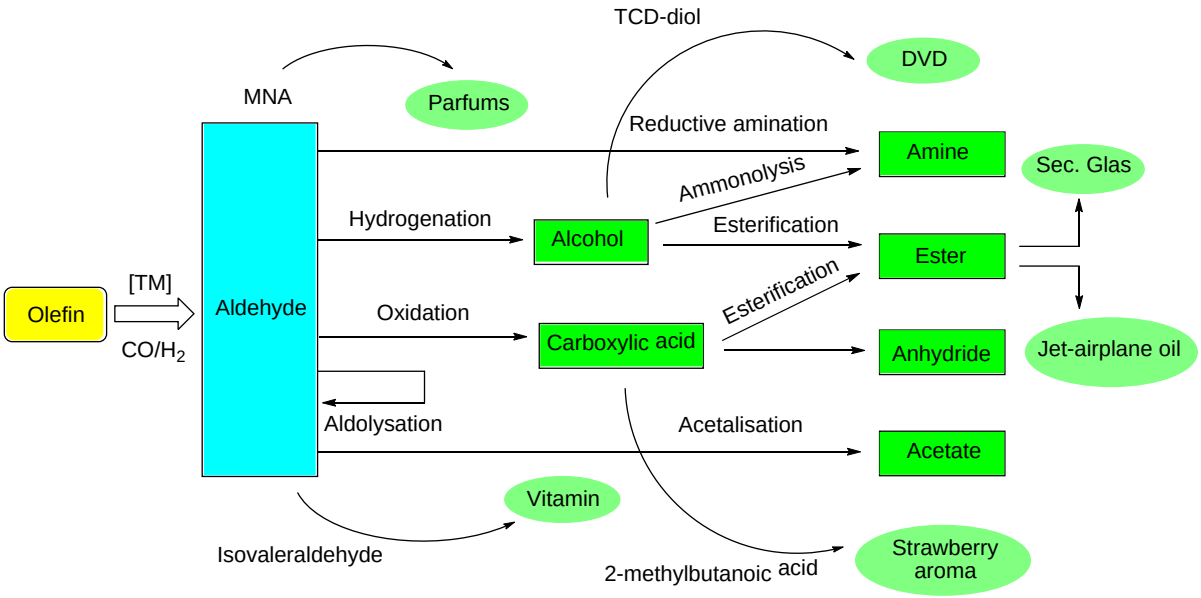
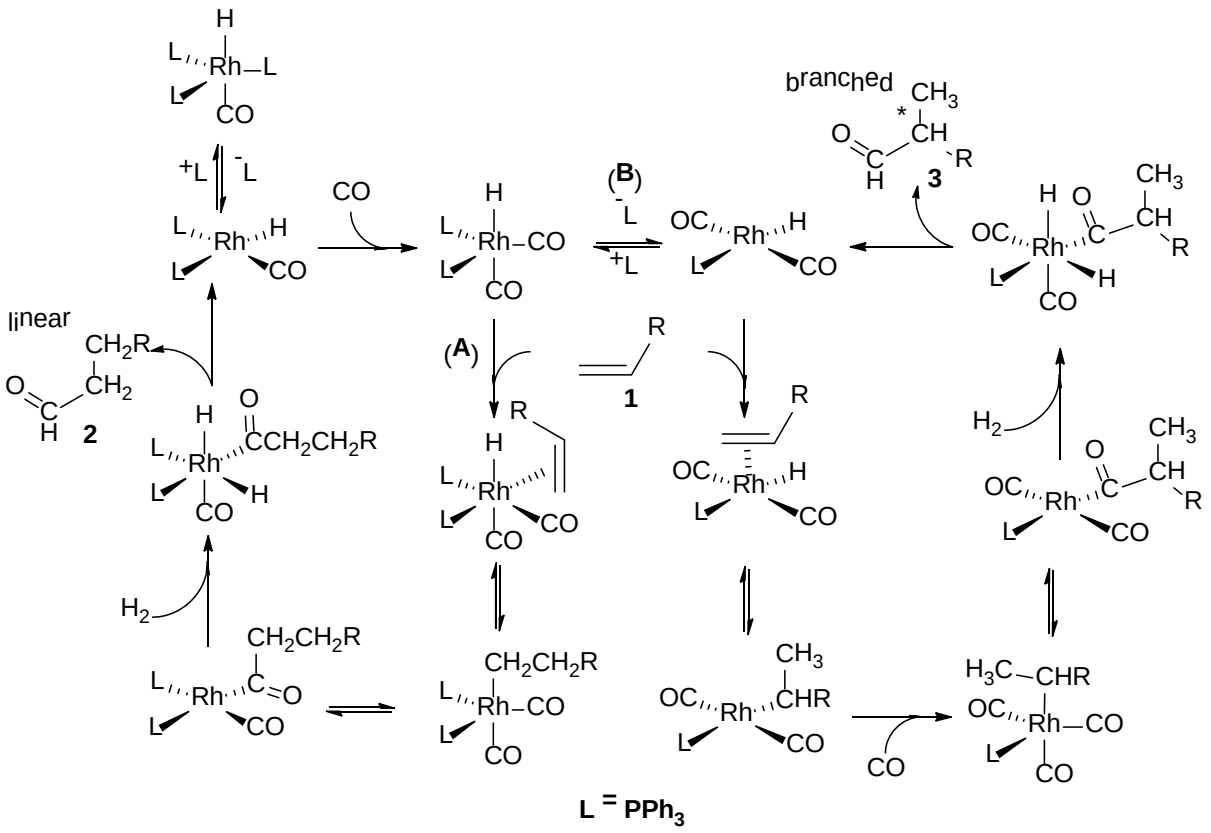


Figure 1: Various products accessible through hydroformylation.

Nowadays, hydroformylation of alkenes constitutes one of the most important homogeneously catalyzed processes in industry, which covers an annual production of almost ten million tons of aliphatic aldehydes,[6] which are key intermediates in the market for bulk and fine chemicals (Figure 1).[7]



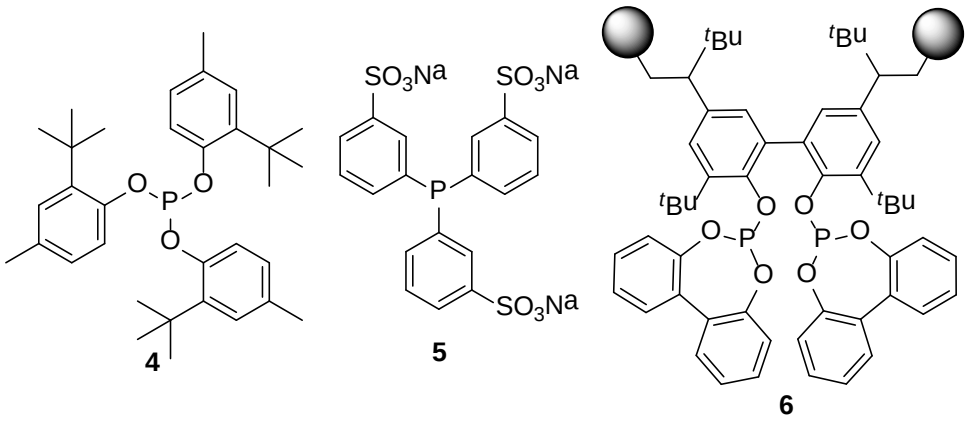
Scheme 2: Mechanism of the rhodium-catalyzed ligand modified hydroformylation.

Despite investigations for more than 40 years some mechanistic issues still remain open. In 1960, Heck and Breslow published their seminal work on the hydroformylation mechanism, which is in principle still valid today.[8] Further fundamental progress was made by Wilkinson and co-workers.[9] He expanded the valid mechanism by two possible pathways: the associative (**A**) and the dissociative (**B**) as shown in Scheme 2.

Because of the easily available raw materials and the need for novel polymer additives (plasticizer alcohols for PVC) the success of the hydroformylation began. Nowadays, commercial hydroformylation plants are run exclusively with catalysts based on either rhodium or cobalt as the central metal. The first generation of hydroformylation processes (BASF, ICI, Ruhrchemie) used cobalt carbonyl as a catalyst because of it was the first metal discovered for this reaction with sufficient activity. Although cobalt catalysts are easily accessible and therefore have a relatively low price, in order to prevent the catalyst from decomposition to metallic cobalt high pressure of 200-350 bar CO is needed. To retain an acceptable rate of activity the temperature had to be adjusted to 150-180 °C. Later, Shell introduced a phosphine-modified cobalt complexes process for the synthesis of detergent alcohols, which is still in use today. With the rapidly increasing commercial production, the research in this area was intensified as well. Since the 1970's rhodium-based catalysts entered the industrial stage, since they are more active and require lower pressure and allow for higher selectivity. Hence, in 1974 Celanese Corporation started the first plant using a

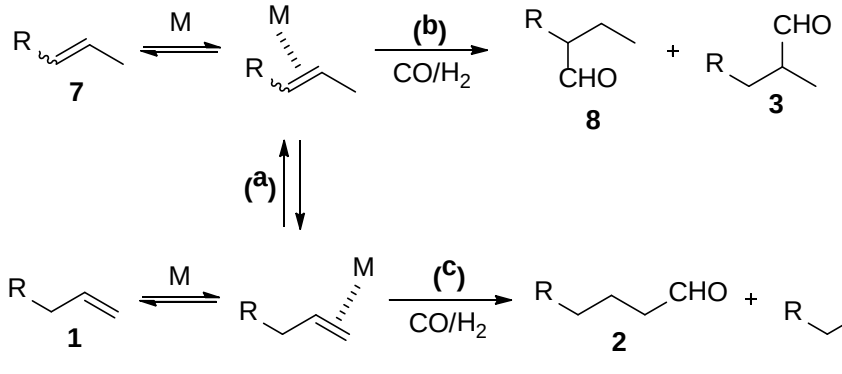
rhodium-phosphine system,[10a] which operates at 10-20 bar and 80-120 °C and slowly replaced most of the cobalt processes for lower olefins.[10b] Later on, the development of phosphite ligands such as **4** allowed for further increased reaction rates.[10c] This class of ligands also allowed to transform sterically hindered substrates, which are usually difficult to hydroformylate.

The next era in catalyst development for hydroformylations started in the 1980's and dealt with the recycling of the catalyst because of the high value of the metal.[10d] An interesting industrial development in this area is the Ruhrchemie/Rhône-Poulenc-process. Based on the original idea of Kuntz,[11] an Rh/TPPTS **5** complex was used as the water-soluble catalyst for the hydroformylation of propene, which accounts for the major share of hydroformylation capacity. The economic competitiveness of this process is based on a two phase system, which allows the catalyst to be recycled by simple phase separation.[12] A more recent approach to catalyst recycling is filtration over a membrane, where ligands with a high molar mass such as **6** are used. These molecules do not fit through the pores of the membrane.[13]

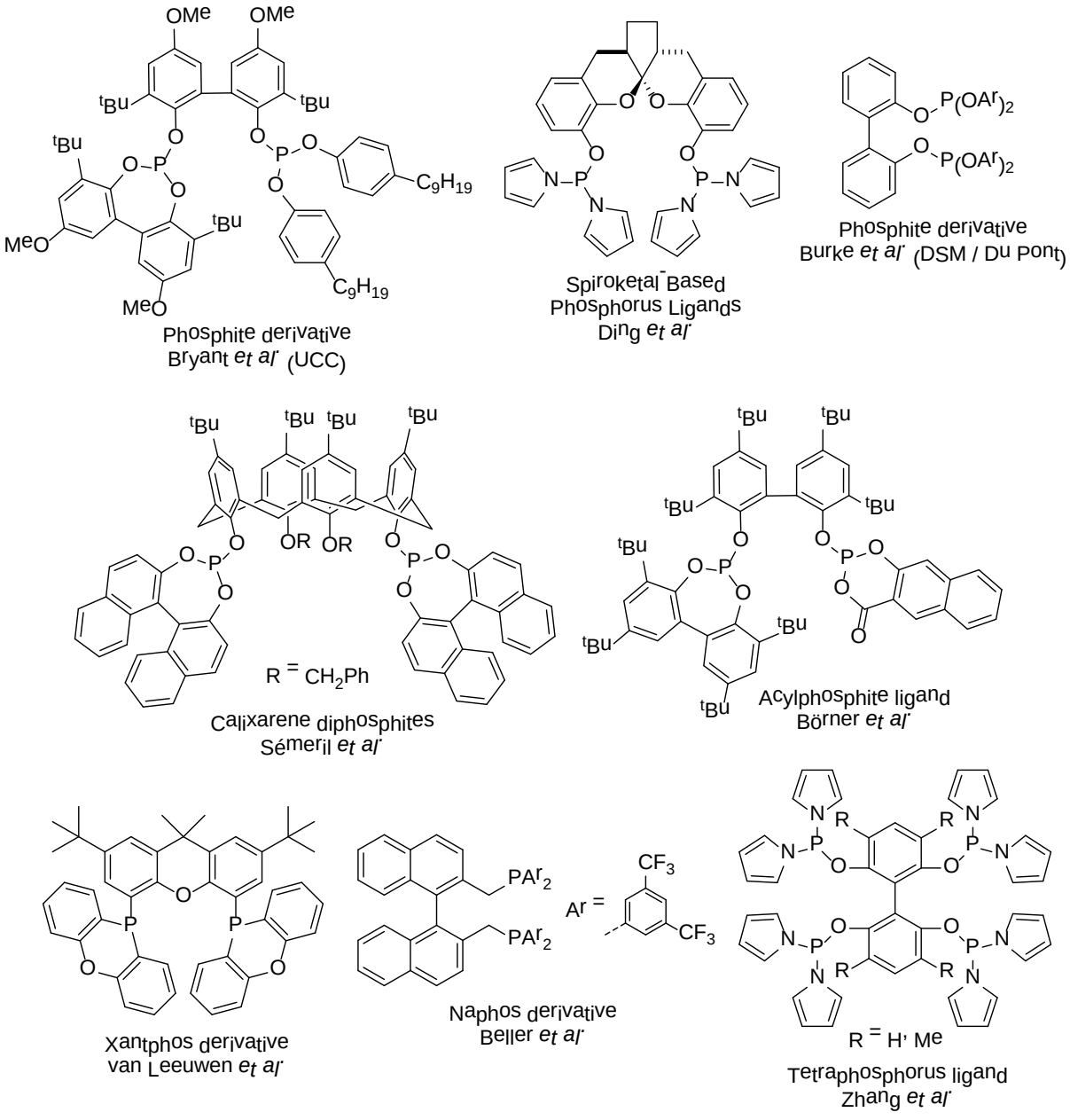


Scheme 3: Ligands for special applications in hydroformylation.

For the bulk chemical industry, a key issue for any larger scale application is the price of starting materials. Hence, it is not surprising that there exists a continuing interest to substitute more expensive terminal olefin feedstock by cheaper mixtures of olefines. Typical examples of this strategy are the use of mixtures of butenes to give valeraldehyde as well as C8-olefins to yield nonanals. A general scheme of the isomerization-hydroformylation sequence is shown in Scheme 4. In order to obtain the mainly desired linear aldehyde from the corresponding internal olefins, isomerization of internal olefins must occur faster than the hydroformylation reaction (Scheme 4, **a**). In addition, there should be a reasonable difference in the rate of hydroformylation of internal (Scheme 4, **b**) and terminal olefins (Scheme 4, **c**) and finally the catalyst should be highly *n*-selective for the hydroformylation step of the terminal olefin.



Scheme 4: Selective hydroformylation of internal olefins to give linear aldehydes: (**a**) isomerzation; (**b**) hydroformylation of internal olefin; (**c**) hydroformylation of terminal olefin.



Scheme 5: Ligands for hydroformylation of internal olefins to linear aldehydes.

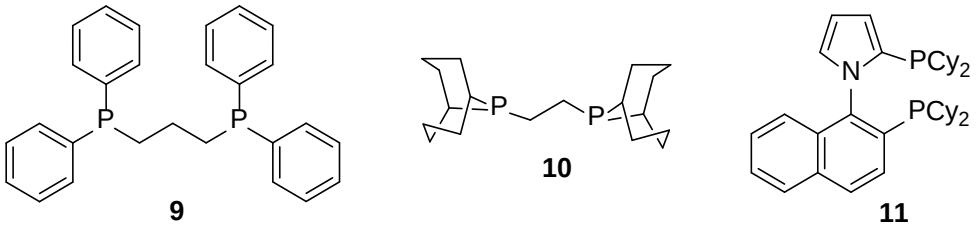
In general cobalt-based homogenous catalyst systems show the same hydroformylation activity for terminal and internal olefins. It is well known that coordinatively unsaturated rhodium species with less electron-rich ligands exhibit significant activity towards isomerization of the substrate. Such active catalysts are formed in the presence of sterically demanding phosphites or phosphines. Our group started working on this topic in the late 1990's. 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 (Scheme 5).[14-21]

1.1.2 Alternative Metals in Hydroformylation

Since the 1970's, both in industry and academic laboratories the majority of the work on catalysts for hydroformylation focused on rhodium- and cobalt-based complexes.[22] The increasing demand and resulting high cost of this precious metal has resulted in alternative non-noble metals catalysts becoming highly desirable. In this regard, especially bio-relevant iron complexes were highly appealing. As mentioned earlier on, other metals have only been scarcely applied in these transformations so far. The main reasons for this were the low activity of the corresponding metal carbonyl complexes (Scheme 6) as well as the tendency to undergo increased side reactions such as hydrogenations. On the other hand, alternative metals might display new reactivity in the presence of suitable ligands and offer also easier patent strategies. Thus, there is room for improvement using other metals. Here, we focus on the recent developments applying palladium complexes for hydroformylations.

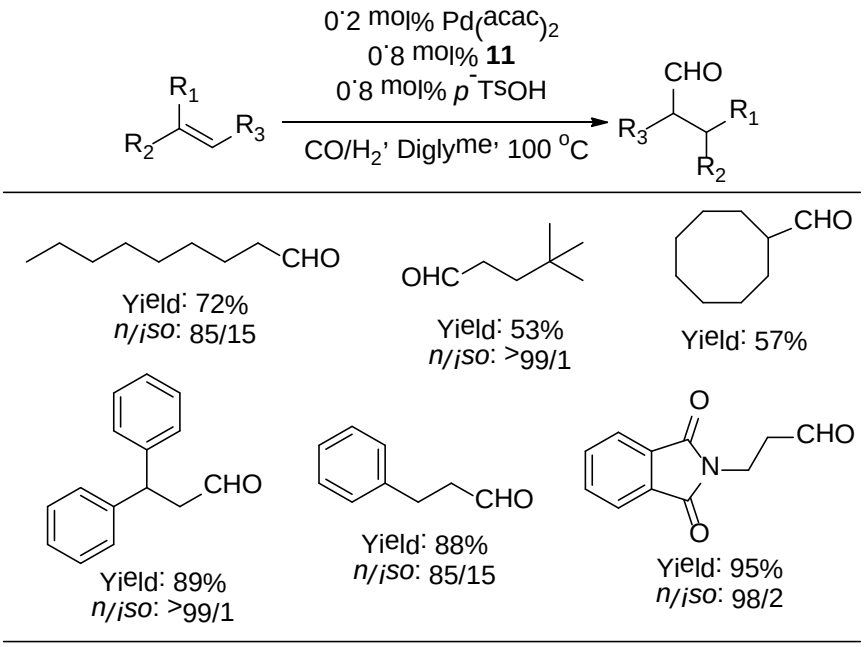
Rh >> Co > Ir, Ru > Os > Pt > Pd > Fe > Ni

Scheme 6: Hydroformylation activity of different metal carbonyls.[23]



9 **10** **11**

Scheme 7: Ligands used for palladium-catalyzed hydroformylation.



Scheme 8: Palladium-catalyzed hydroformylation of alkenes.

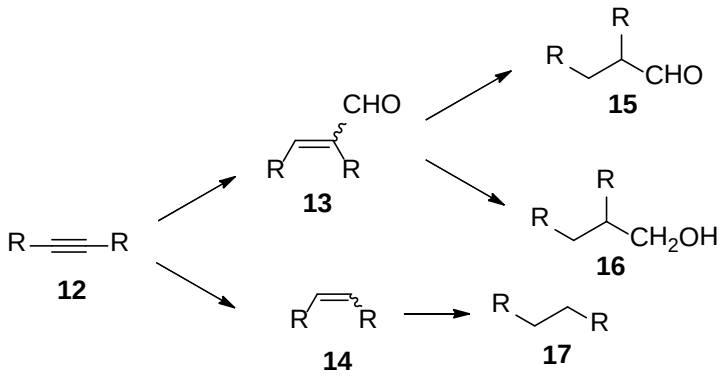
In 2000, Drent and co-workers developed an interesting carbonylation catalyst consisting of palladium, the bidentate phosphorous ligand dppp (Scheme 7, **9**) and a non-coordinating acid for the hydroformylation of olefins.[24] In the presence of trifluoroacetic acid they were able to get 98% yield of nonanal from 1-octene with only 1 mol% palladium. This gave new impetus for the development of palladium catalysts for hydroformylations. Further advances were made again by Drent in 2006, when he introduced the BCOPE (Scheme 7, **10**) ligand which together with halide promoter yielded 95% nonanol from 1-octene.[25] Unfortunately, the substrate scope with these catalysts was not demonstrated. Therefore we investigated these systems further on. More specifically, we used less aggressive acids such as *p*-toluolsulfonic acid in the presence of 0.2 mol% of palladium and ligand **11**.[26] Under optimized conditions of temperature, pressure and acid, the system was successfully applied to various substrates providing good to excellent selectivity (Scheme 8).

1.1.3 Hydroformylation of Alkynes

Compared to the well-known hydroformylation of olefins using Rh or Co catalysts, the corresponding reaction of alkynes has been much less investigated. This is because of the lack of general catalytic systems for this transformation and the low selectivity of this process, which leads to the formation of undesired products. However, acetylenes easily available and the resulting unsaturated products are versatile intermediates in organic synthesis.

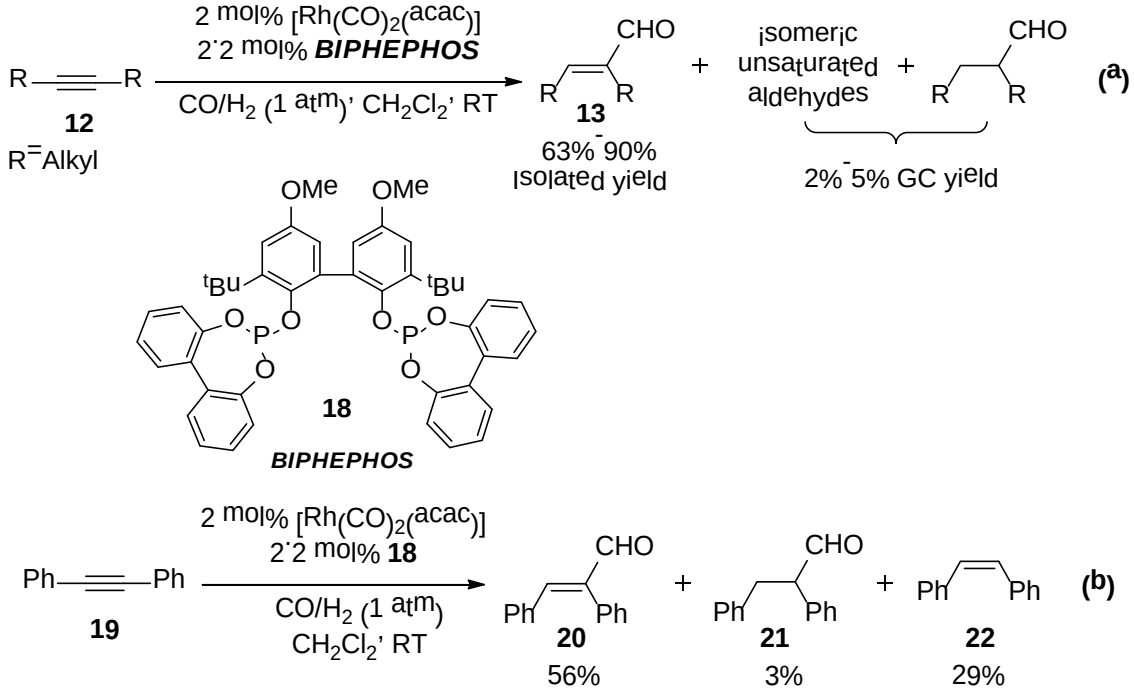
In early studies, it was found that the hydroformylation of alkynes usually suffers from low chemoselectivity and/or low yield of the desired *α,β*-unsaturated aldehyde (**13**), primarily

because the formation of the corresponding saturated aldehydes (**15**) and alkenes (**14**) is hardly suppressed (Scheme 9).[27]



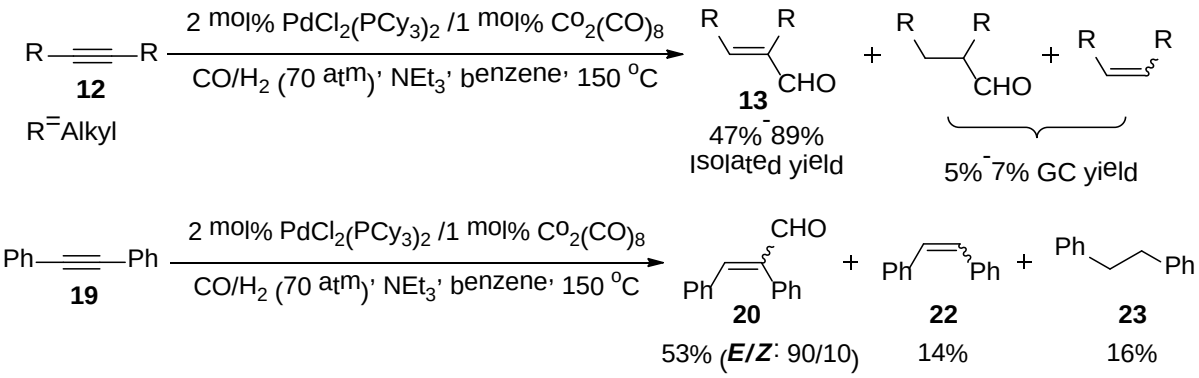
Scheme 9: Hydroformylation and competing hydrogenation of alkynes

First investigations were carried out with conjugated dialkynes, which, in the presence of Rh catalysts, produced formylbutadienes with low yields.[28] Buchwald and co-workers reacted several monoalkynes with Rh/BIPHEPHOS (**18**) at 1 atm syngas pressure and room temperature to give good yields of *α,β*-unsaturated aldehydes (Scheme 10, **a**).[29] However, especially with aryl alkynes, hydrogenation of the triple bond becomes a serious competitive reaction. Thus, besides the unsaturated aldehyde, diphenylacetylene **19** also produced *cis*-stilbene **22** (Scheme 10, **b**). Noteworthy, unsymmetrically substituted alkynes exhibited low regioselectivity.



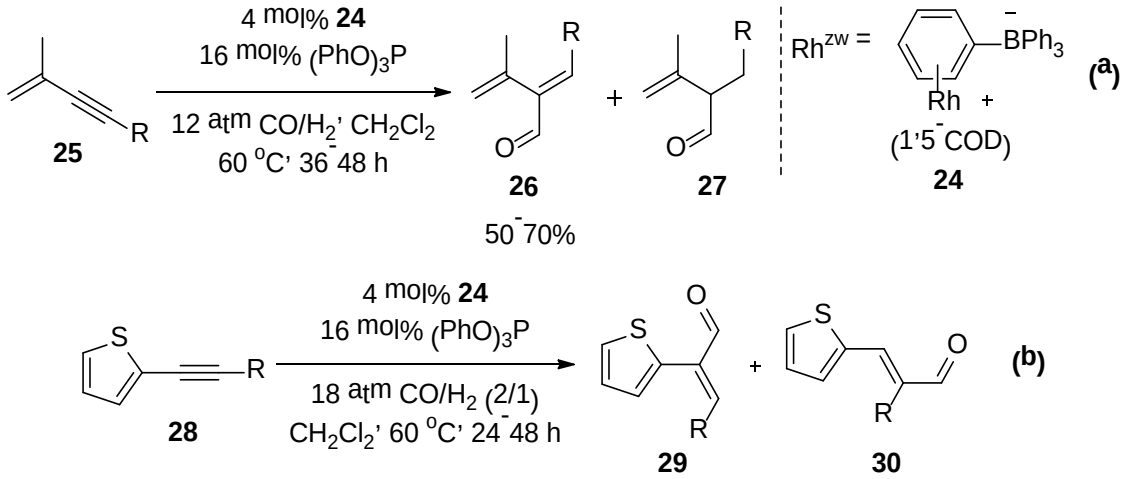
Scheme 10: Rh/BIPHEPHOS (**7**) catalyst system for hydroformylation of alkynes.

The use of bimetallic catalyst systems such as $[PdCl_2(PCy_3)_2]/[Co_2(CO)_8]$, led to good yields of the corresponding *α,β*-unsaturated aldehydes in the hydroformylation of symmetric internal alkynes as reported by Hidai (Scheme 11).[30]

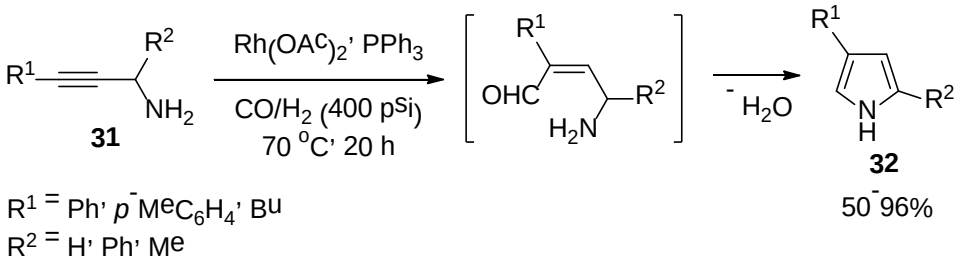


Scheme 11: Bimetallic catalyst system for hydroformylation of alkynes.

Interestingly, the hydroformylation of compounds which have a triple bond conjugated with a double bond (1,3-enynes **25**) takes place contrary to what might be expected to give mainly formyl dienes **26**. While the catalytic system $[RhH(PPh_3)_3]$ provides a mixture of diene and cyclopentanone. Alper developed zwitterionic rhodium complex **24**/$P(OPh)_3$ for regioselective hydroformylation of 1,3-enynes **25** to provide formyl dienes **26** in moderate to good yields along with the nonconjugated unsaturated aldehyde **27** as by-product (Scheme 12, **a**).[31] Later, the same catalyst system was also applied for the regioselective hydroformylation of acetylenic thiophenes **28** and good to complete regioselectivity was observed in these reactions (Scheme 12, **b**).[32] Noteworthy, these studies have demonstrated the significant influence of double bonds and the sulfur atom on the regioselectivity of the hydroformylation of alkynes.



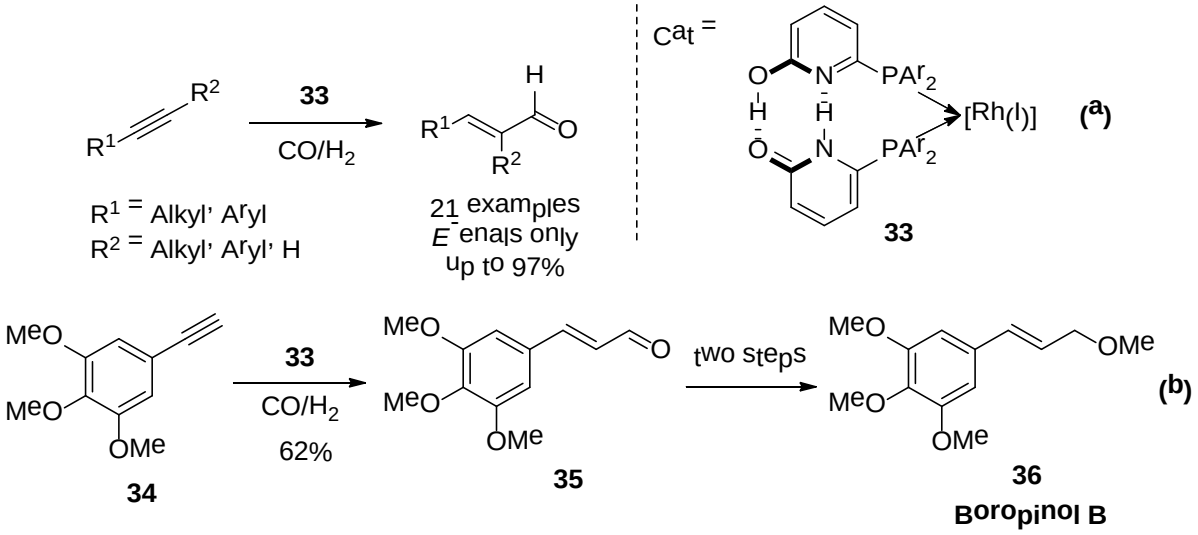
Scheme 12: Zwitterionic rhodium complex catalyst system for hydroformylation of alkynes.



Scheme 13: Hydroformylation of functionalized alkynes to form pyrrole derivatives.

Reactions of functionalized alkynes often give carbocyclic or heterocyclic compounds.[28a, 28b, 33] For example, Scampi *et al.* reacted propargylamines **31** with syngas in presence of a Rh/phosphine catalyst system and obtained pyrrole derivatives **32** in good yields (Scheme 13).[33a, 34] The reaction is believed to proceed *via* an unsaturated aldehyde and usually accompanied by lactone by-products arising from deamination, as well as hydrogenated by-products.

A recent improvement was reported by Breit and co-workers who used a rhodium-based catalyst system employing a self-assembling ligand for the selective hydroformylation of alkynes (Scheme 14, **a**).[35] Noteworthy, challenging substrates such as terminal alkynes provided the corresponding *α,β*-unsaturated aldehydes in fair to good yields using this special catalyst. Notably, the bioactive compound Boropinol B **36** was successfully synthesized by this protocol (Scheme 14, **b**).



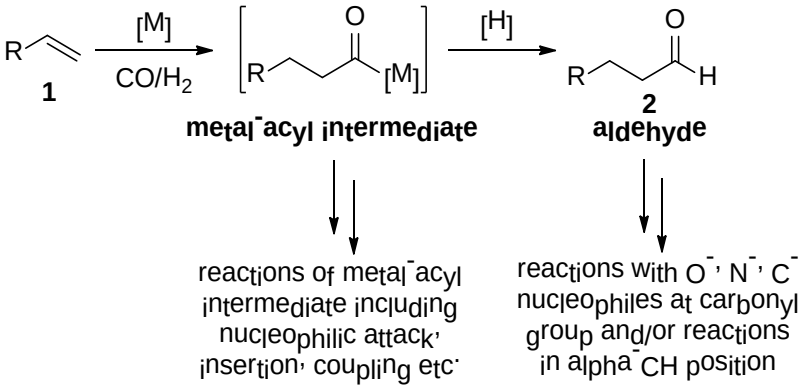
Scheme 14: Rhodium-catalyzed hydroformylation of alkynes employing a self-assembling ligand system.

Within the framework of this dissertation, most recently, we demonstrated the palladium-catalyzed hydroformylation of alkynes, too.[36] Notably, competing hydrogenation side reactions were almost completely suppressed. Various alkynes were smoothly transformed

to the corresponding *α*,*β*-unsaturated aldehydes in good to excellent yields with good stereoselectivities. The whole scope of this protocol is shown in chapter 4.1.

1.2 Domino Hydroformylation Reactions

Domino reactions that involve two or more bond-forming reactions in one process have potential for the efficient synthesis of natural products and pharmaceuticals, in the chemical industry, *etc*.[37] In general, they reduce the need for additional reagents, solvents, energy supplies and waste, thereby decreasing the environmental impact as well as production costs. In recent decades, a significant efforts have been invested into the development of catalytic domino reactions, which make use of transition-metal catalysis[37a-d] or organocatalysis[37a, e-g]. With the increasing importance of transition-metal catalysis and the rapid advancement of organocatalysis, also combination of both areas for domino reactions has emerged. Applying this principle, a number of new domino reactions were recently disclosed.[38]



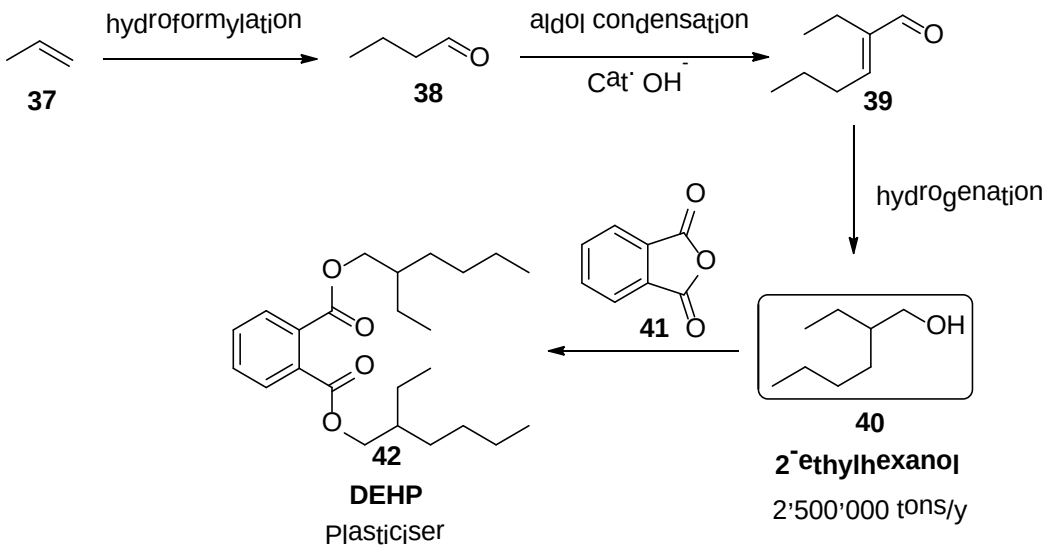
Scheme 15: Selected examples of domino and tandem reactions including hydroformylation reactions.

Hydroformylation is established as an important industrial tool for the production of aldehydes and the products derived from them *in-situ*.[4] Due to the versatile chemistry of the aldehyde group,[39] the resulting products are easily further converted to give alcohols, amines, carboxylic acid derivatives, aldol condensation products and many others *via* nucleophilic attack at the carbonyl group, electrophilic attack on the acidic *α*-position, reduction, or oxidation (Scheme 15).[40] However, the additional reagents, products or variations of reaction conditions optimized for the subsequent functionalization step, may suppress or hinder the initial hydroformylation step. Here, we focus on the developments on hydroformylation/aldol reaction sequence and hydroformylation/Diels-Alder sequence because these reactions were investigated within this thesis.

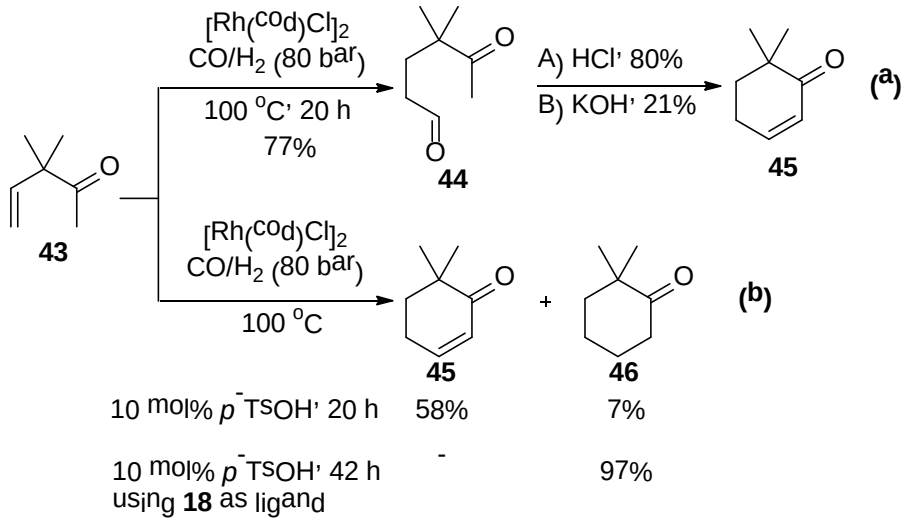
1.2.1 Hydroformylation/Aldol Condensation Sequence

Aldol addition of aldehydes represent one of the most important reactions in synthetic organic chemistry.[41] Often, homo-condensation of oxo aldehydes is observed as an

unwanted side reaction under hydroformylation conditions.[42] On the other hand, self-condensation of aldehydes is one of the most important transformations, leading to new functionalized skeletons like, *β*-hydroxy aldehydes, *α,β*-unsaturated aldehydes, or hydrogenation products.[40a] Some of these homo-condensation products constitute important industrial compounds such as 2-ethyl-hexanol **40**, obtained *via* propene **37** hydroformylation followed by aldol addition and dehydration followed by reduction (Scheme 16).



Scheme 16: Industrial synthesis of 2-ethyl-hexanol.

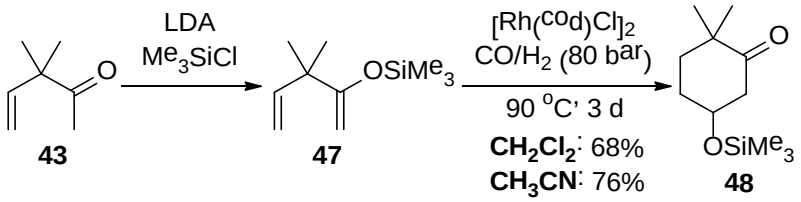


Scheme 17: Hydroformylation/aldol reaction.

So far, synthetic applications of tandem hydroformylation/aldol reactions are limited due to regioselectivity problems. However, various examples of intramolecular tandem hydroformylation-aldol reactions have been described by Eilbracht and co-workers. For example, the tandem hydroformylation/aldol condensation of ketoolefins, such as *β,γ*-

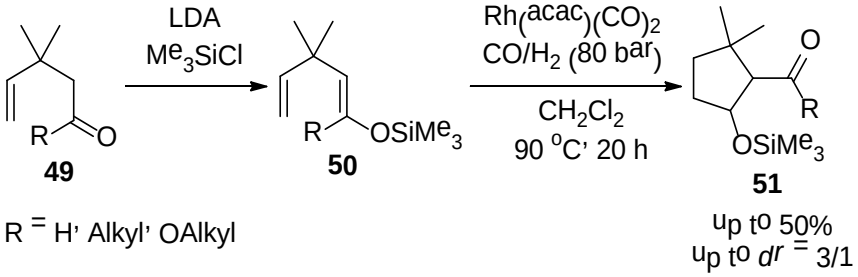
unsaturated ketones **43**, gives a single cyclization product under acid catalysis (Scheme 17, **a**). Similar to the stepwise reaction, the *in-situ* generated aldehyde preferentially acts as the electrophilic carbonyl component, while the ketone acts as the nucleophilic enol to form the five-membered ring product **45**. Subsequent dehydration and hydrogenation of the resulting enone readily occurs under the reductive reaction conditions used (Scheme 17, **b**).[43]

Although the saturated ketone can be obtained in nearly quantitative yields, the loss of a synthetically valuable olefinic group is unfavorable and can be overcome by a modification of the tandem sequence. Hence, the use of the corresponding unsaturated silyl enol ether **47** in a tandem hydroformylation/Mukaiyama aldol reaction gives the desired aldol adduct **48** with complete transfer of the silyl group to aldol hydroxyl group (Scheme 18).[43, 44] Obviously, the less substituted double bond is hydroformylated selectively resulting in a regioselective tandem reaction.



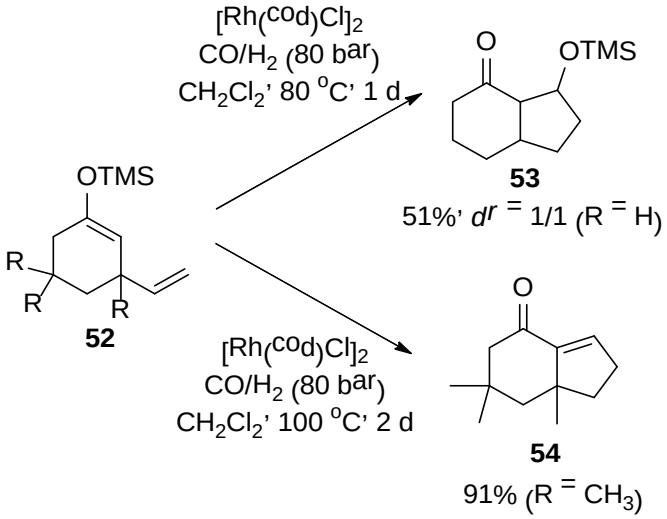
Scheme 18: Hydroformylation/Mukaiyama aldol reaction.

This method can also be applied to silyl enol ethers of homologous unsaturated ketones as well as of unsaturated aldehydes or esters.[44-46] While unmodified unsaturated esters give only the corresponding aldehydes without cyclization under tandem hydroformylation/aldol reaction conditions, the corresponding silylated ester enolates smoothly cyclize in a tandem hydroformylation/Mukaiyama aldol reaction (Scheme 19).[44-46]



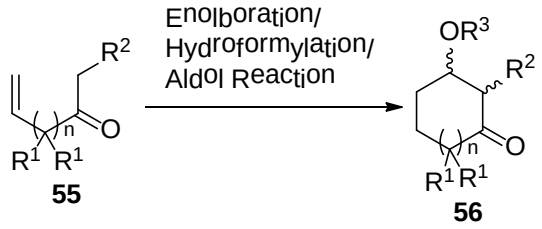
Scheme 19: Unsaturated aldehydes, ketones and esters in the hydroformylation/Mukaiyama aldol reaction.

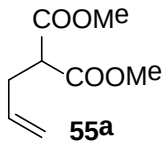
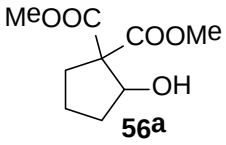
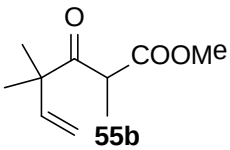
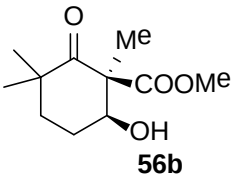
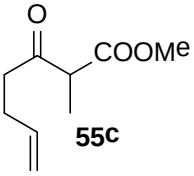
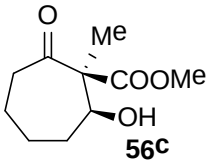
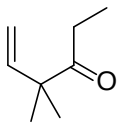
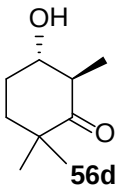
Similarly, tandem hydroformylation/aldol sequences can be applied to the formation of bicyclic and spirocyclic compounds. Thus, silyl enol ethers of 3-vinyl and 3-allyl cycloalkanones **52** give ring annulated products (Scheme 20).[45, 46]



Scheme 20: Bicyclic aldols and enones *via* hydroformylation/aldol reaction.

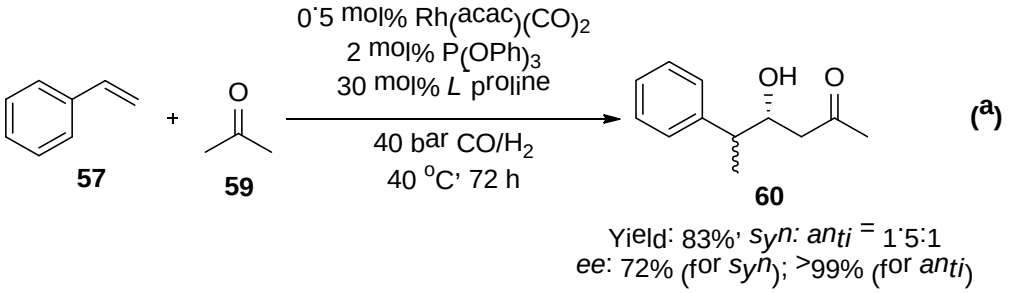
Table 1: Enolboration/hydroformylation/aldol reaction: diastereoselective access to cyclic aldols.

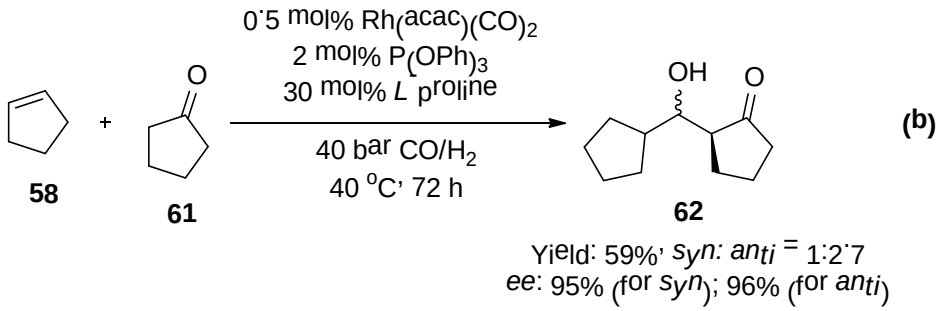


Entry	Olefin	Product	Yield	*dr*
1	 **55a**	 **56a**	51%	–
2	 **55b**	 **56b**	51%	2.5:1
3	 **55c**	 **56c**	51%	6:1
4	 **55d**	 **56d**	51%	20:1

A tandem sequence consisting of enolboration/hydroformylation/aldol reaction has also been described by Eilbracht and co-workers.[47] Here, the configuration of the enol boronate is transferred to the aldol product, allowing good to excellent diastereoselectivities in the hydroformylation/aldol reaction. With this method, 5-7-membered rings products **56** are obtained in excellent yields (Table 1).

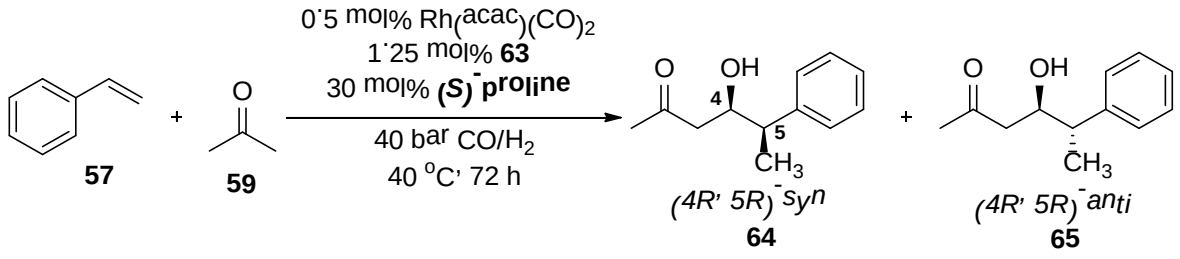
In 2007, Eilbracht and co-workers successfully combined a rhodium(I) phosphite complex and *L*-proline as an efficient catalyst system for domino hydroformylation/enantioselective aldol reactions. Notably, organocatalysis of aldol reactions even under hydroformylation conditions occurs with high enantioselectivities, although the usually observed diastereoselectivities have still to be optimized. It should be mentioned that only styrene **57** (Scheme 21, **a**) and cyclic alkenes **58** (Scheme 21, **b**) were selected as model substrates in order to avoid the regioselectivity problems of the hydroformylation step.[48]





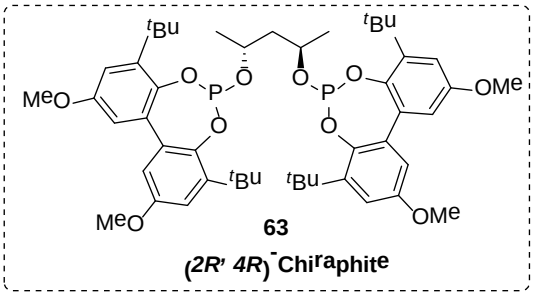
Scheme 21: Domino hydroformylation/enantioselective aldol reaction of styrene and cyclopentene.

Later, Eilbracht and co-workers developed the combination of rhodium/chiraphite (**63**) and (*S*)-proline as an efficient catalyst system for domino enantioselective hydroformylation/enantioselective aldol reactions (Scheme 22).[49] Interestingly, the diastereoselectivity of the reaction between styrene, syngas and acetone can be considerably increased by using a *matched* pair of catalysts [Rh/(*2S,4S*)-chiraphite]/(*S*)-organocatalyst.



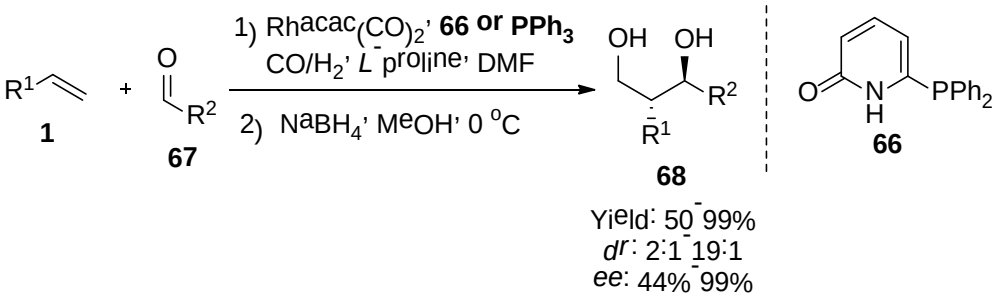
mismatched: *(2R,4R)*-**Chiraphite** Yield: 64% *syn: anti* = 1.3:1 *ee*: 76% (for *syn*); 98% (for *anti*)

matched: *(2S,4S)*-**Chiraphite** Yield: 65% *syn: anti* = 3:1 *ee*: 84% (for *syn*); 80% (for *anti*)



Scheme 22: Domino enantioselective hydroformylation/enantioselective aldol reaction of styrene.

In 2007, Breit and co-workers reported a domino hydroformylation/enantioselective cross-aldol reaction sequence. In general, the difficult task in this reaction is to avoid the formation of the homo-aldol product. Key to success is the inherently low concentration of the aldehyde formed in the hydroformylation step. 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 23).[50]



Yield: 50-99%
dr: 2:1-19:1
ee: 44%-99%

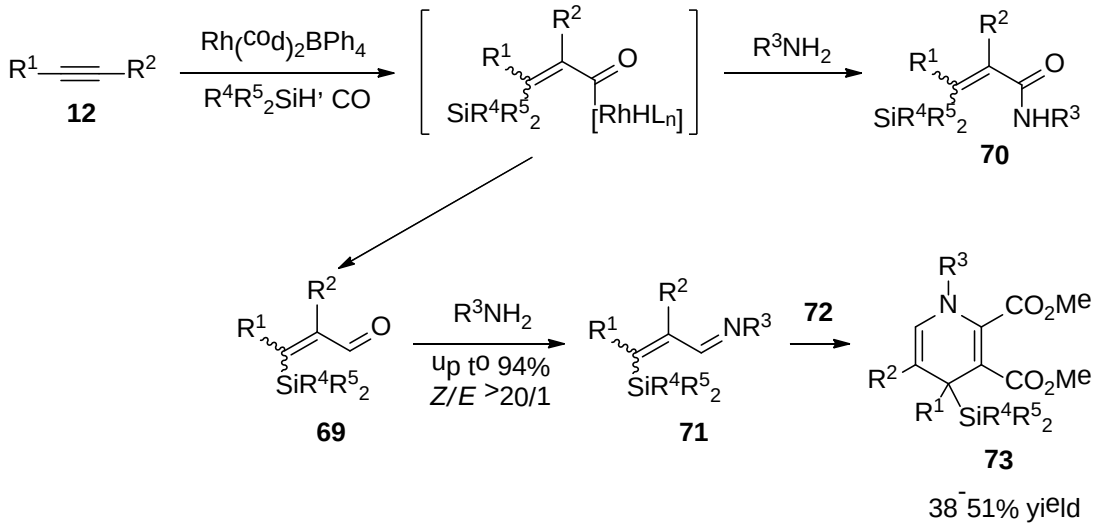
Scheme 23: Domino hydroformylation/enantioselective cross-aldol reaction sequence.

Within the framework of this dissertation, we published two patents and two manuscripts in international journals, which show our new developments in this area. We developed a novel cooperative catalyst system consisting of a specific rhodium(I) phosphine complex and pyrrolidinium benzoate, which catalyzes selectively the domino hydroformylation/aldol condensation[51] and hydroformylation/aldol condensation/hydrogenation[52] of alkene. Various olefins underwent efficient transformation to afford the corresponding *α*,*β*-unsaturated

aldehydes and ketones in good to excellent yields with high selectivities. We were able to show that our catalyst system can be applied to a broad scope of substrates. The detailed results are shown in chapters 4.7 and 4.8.

1.2.2 Hydroformylation/Diels-Alder Sequence

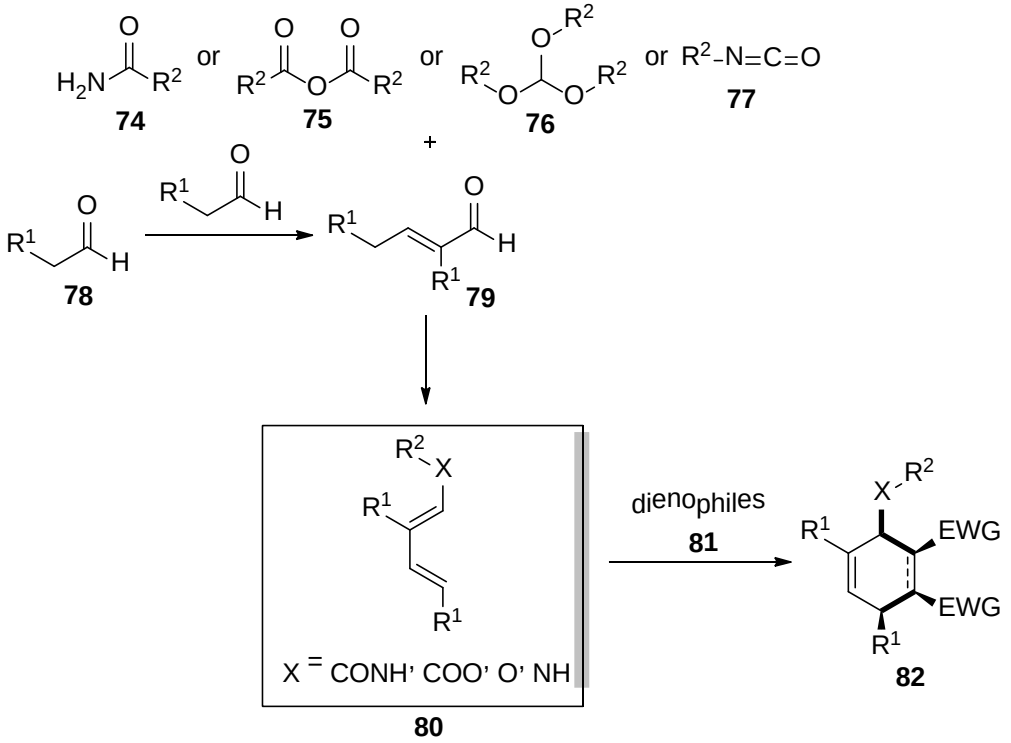
Alkynes can also undergo consecutive processes under silylformylation conditions. Thus, rhodium catalyzed silylformylation of alkynes in the presence of primary or secondary amines leads directly to the azadiene **71** by silylformylation and enamine formation. These azadienes undergo Diels-Alder reaction with dimethyl acetylendicarboxilate (**72**) to give dihydropyridines **73** (Scheme 24).[53]



Scheme 24: Silylformylation/Diels-Alder reaction sequence.

Multicomponent reactions (MCRs)[54] which directly yield the target products by domino or cascade reaction sequences offer significant advantages over conventional linear-step syntheses. The resulting reduced number of synthetic and purification steps for a given molecule increases the attractiveness and practicability of the process. In this context, our group developed multicomponent reactions, in which amides **74** (AAD-reaction: **A**mides-**A**ldehydes-**D**ienophiles), or anhydrides **75** (ANAD-reaction: **An**hydrides-**A**ldehydes-**D**ienophiles), orthoesters **76** (OAD-reaction: **O**rthoesters-**A**ldehydes-**D**ienophiles) and even to isocyanates **77** (IAD-reaction: **I**socyanates-**A**ldehydes-**D**ienophiles) react with aldehydes **78** and dienophiles **81**, respectively to afford a variety of multi-substituted cyclohexene and cyclohexadiene derivatives **82**.[55] As shown in Scheme 25, these transformations take advantage of an initial condensation reaction of amides and aldehydes to give amido-substituted 1,3-butadienes (**80**, Scheme 25) as key intermediates, which are subsequently converted with electron-deficient dienophiles to the corresponding MCR products. The versatility of functionalized 1,3-butadienes for Diels-Alder chemistry[56] has also been

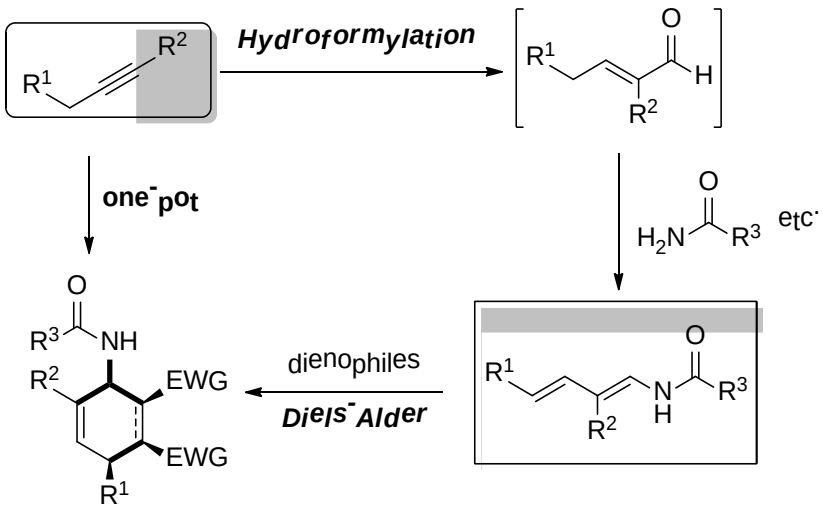
demonstrated in the preparation of important natural products such as pumiliotoxin,[57] gephyrotoxin,[58] dendrobine,[59] and tabersonine[60]. Furthermore, we have demonstrated the synthetic applicability of MCRs in the preparation of highly substituted anilines,[61] bicyclo[2.2.2]-oct-2-enes,[62] enantiomerically pure cyclohexenols,[63] and cyclohexenylamines,[64] phthalic acids,[65] luminol,[66] phenanthridones[67] as well as lactam derivatives[68].



Scheme 25: Schematic representation of the AAD-, ANAD-, OAD-, IAD-reaction protocols.

As shown in chapter 3.1, we demonstrated that palladium complexes with heterocyclic phosphine ligands are efficient catalysts for the hydroformylation of alkynes to give selectively *α,β*-unsaturated aldehydes.[36] On the basis of this work, we utilized this protocol for the synthesis of more complex organic molecules. Advantageously, both the palladium-catalyzed hydroformylation and the AAD-type reactions require acid as co-catalyst. From this point of view, it should be possible to combine them as it is postulated in Scheme 26.

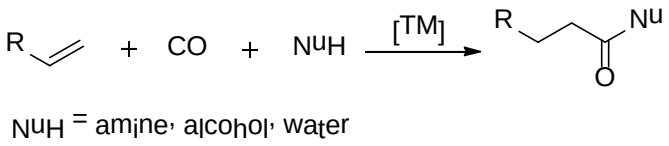
Indeed, we successfully developed a two-step, one-pot synthesis of diverse multi-substituted cyclohexenes and cyclohexadienes by combining hydroformylation and Diels-Alder reactions.[69] Notably, this methodology provides an interesting option to synthesize new organic products as the corresponding *α,β*-unsaturated aldehydes are traditionally difficult to synthesize and only few examples are commercially available. We were able to show that our novel protocol can be applied to a broad scope of substrates. The detailed results are shown in chapter 4.6.



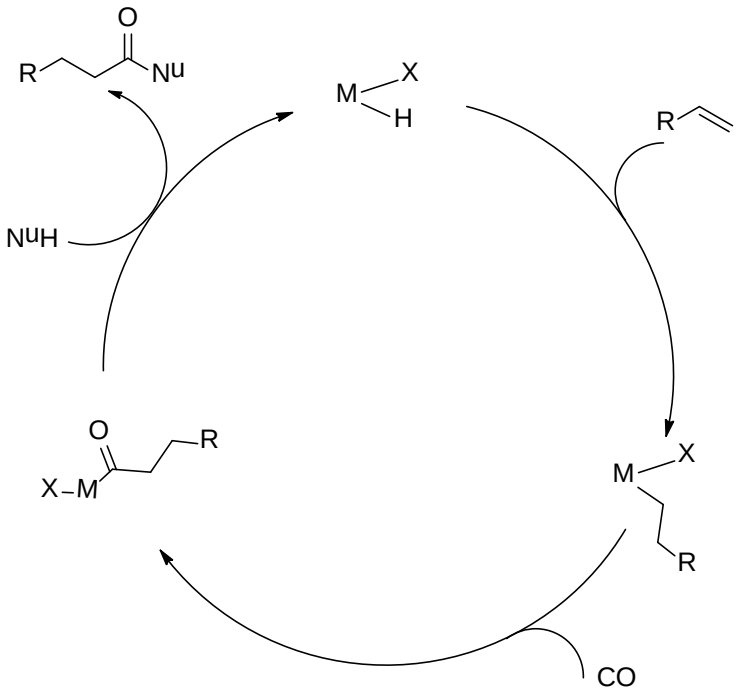
Scheme 26: Sequential hydroformylation/AAD-reactions.

1.3 Carbonylation of Alkenes

The transition-metal-catalyzed carbonylation of olefins with nucleophiles (e.g. water, alcohol, and amine) constitute an important route for the preparation of a variety of valuable carboxylic acids, esters and amides (Scheme 27).[70]



Scheme 27: Carbonylation of olefins.

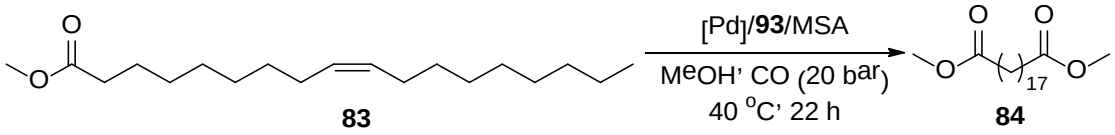


Scheme 28: General reaction mechanism for carbonylation of alkenes.

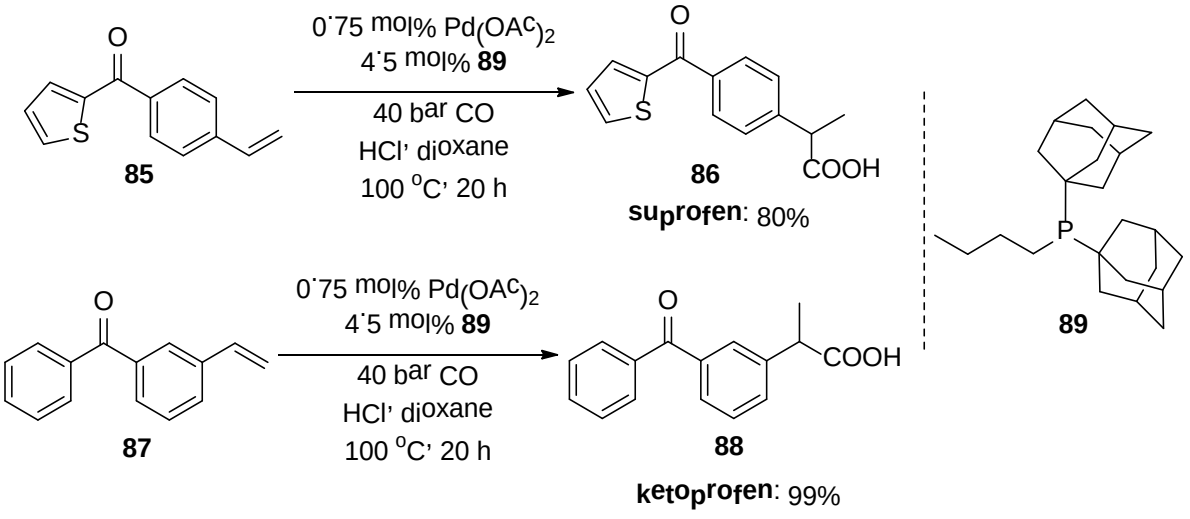
From the point view of reaction mechanism, despite the differences in catalysts, substrates, and nucleophiles, the general accepted reaction mechanism is shown in Scheme 28.[71] It is proposed that the reaction starts with the corresponding metal-hydride species, which is primarily formed by the reaction of the pre-catalyst with acid additives (TsOH, HBF_4, etc.) or from the reaction of a suitable acylmetal complex with nucleophiles during the catalytic cycle. Subsequent coordination, insertion of the olefin, 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.

1.3.1 Palladium-catalyzed Alkoxycarbonylation of Alkenes

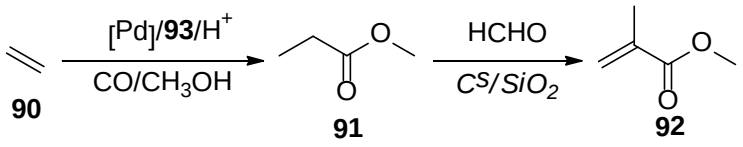
Initial reports of Reppe made use of [Ni(CO)$_4$] as catalyst under drastic conditions.[3] Since then, transition-metal-catalyzed alkoxycarbonylation reactions have been dramatically improved.[70] More specifically, the palladium-catalyzed addition of carbon monoxide to alkenes in the presence of an acidic hydrogen donor has received considerable attention during the last years and has been used to prepare a range of important products. For example, industrially valuable carboxylic acids such as linear fatty acids (Scheme 29)[72] and branched 2-arylpropionic acids (Scheme 30)[73] are directly accessible *via* hydroxycarbonylation or hydroesterification followed by hydrolysis. The latter compounds belong to the most important class of non-steroidal anti-inflammatory agents (e.g. suprofen **86** and ketoprofen **88**). An important example of an industrial application it the methoxycarbonylation of ethylene for the production of methyl methacrylate **92** (Lucite alpha process), a large-scale chemical intermediate for the synthesis of homopolymers and co-polymers (Scheme 31).[74]



Scheme 29: Palladium-catalyzed methoxycarbonylation of methyl oleate.

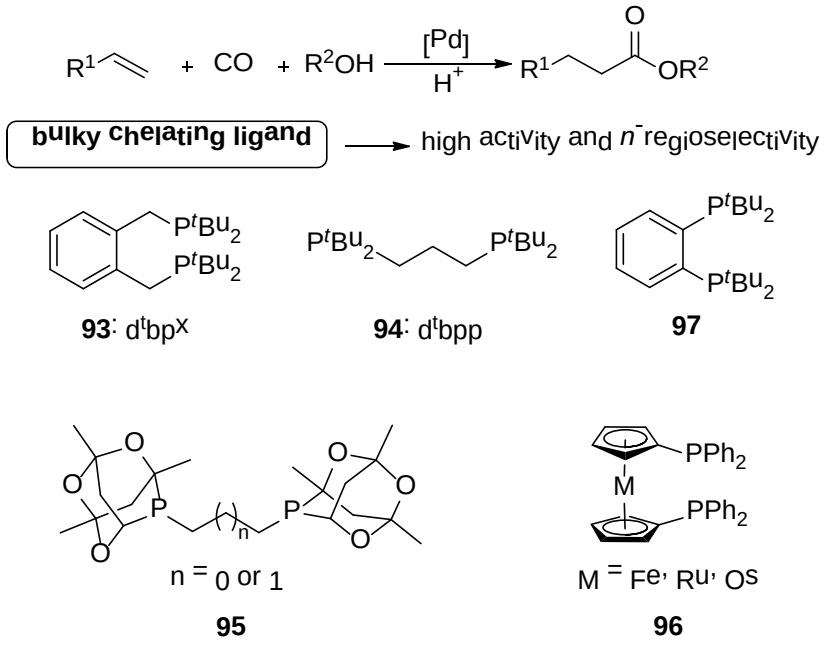


Scheme 30: Synthesis of suprofen and ketoprofen by Pd-catalyzed hydroxycarbonylation of vinyl arenes.



Scheme 31: Lucite alpha process

Generally, the use of Pd(0) or Pd(II) precursors in combination with bulky chelating ligands such as d^{t}bpx **93**,[75] d^{t}bpp **94**,[76] bis(phosphaadamantyl)diphosphines **95**,[77] 1,1′-bis(diphenylphosphino)metallocenes **96**[78] or other bidentate phosphines **97**[79] resulted in a greatly improved regioselectivity towards linear esters (Scheme 32).

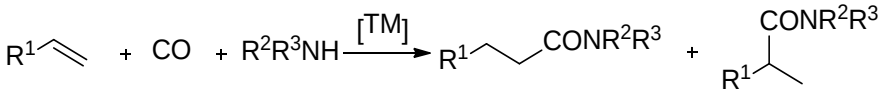


Scheme 32: Ligands for alkoxycarbonylation of internal olefins to linear esters.

Within the framework of this dissertation, very recently, we synthesized various carbocyclic and *N*-heterocyclic analogues of the industrially applied ligand bis(di-tert-butylphosphinomethyl)benzene (**93**).[80] Furthermore, the benchmark reaction, the palladium-catalyzed methoxycarbonylation of 1-octene using these types of ligands was also tested. The detailed results are shown in chapter 4.2.

1.3.2 Palladium-catalyzed Aminocarbonylation of Alkenes

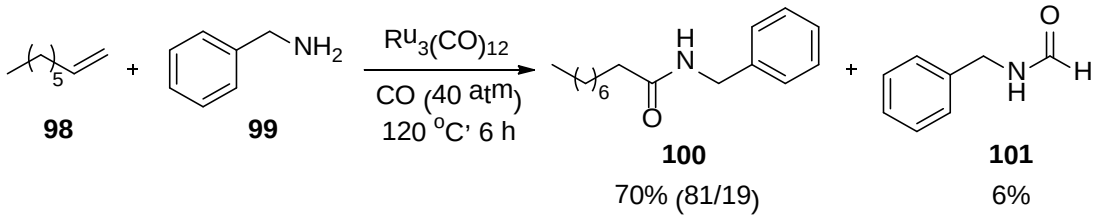
The palladium-catalyzed carbonylation of alkenes with CO and amines (aminocarbonylation) constitutes a straightforward and atom-efficient route to saturated carboxylic amides (Scheme 33). Compared with the reaction of alkenes, carbon monoxide and alcohols (hydroesterification) or water (hydrocarboxylation), related aminocarbonylations leading to amides have found much less attention.[70]



Scheme 33: Transition-metal-catalyzed aminocarbonylation of alkenes.

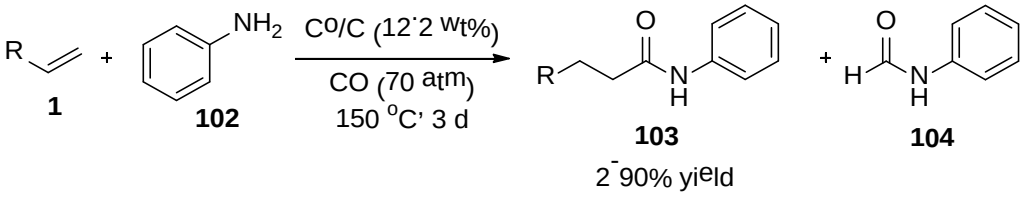
In early studies of aminocarbonylation of alkenes, cobalt carbonyl complexes[81] or nickel cyanide[82] were mainly used as catalysts. Iron carbonyl[83] and ruthenium chloride[84] also showed some catalytic activity. However, all these reactions were carried out under severe conditions (>200 °C; >150 atm).

In the presence of olefins, $Ru_3(CO)_{12}$ is an effective catalyst for the carbonylation of amines to *N*-substituted alkanamides (Scheme 34).[85] Notably, *N*-substituted formamides were always formed as by-products, the chemoselectivities to *N*-substituted alkanamides and formamides were greatly affected by the molar ratio of the olefin to the amine. *N*-Substituted alkanamides were obtained in high selectivities only at a high molar ratio of the olefin to the amine. Other aliphatic primary amines were also carbonylated in the presence of 1-octene, but the chemoselectivities to *N*-substituted C9-amides were somewhat low compared with benzylamine. Aniline was not carbonylated at all under the present conditions.



Scheme 34: Ruthenium-catalyzed aminocarbonylation of alkenes.

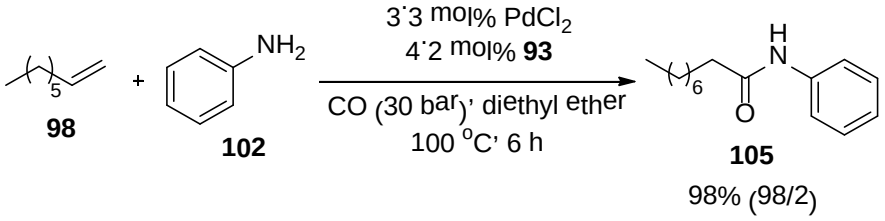
In 2002, Chung and co-workers reported cobalt on charcoal-catalyzed aminocarbonylation of alkene and aniline to produces *N*-phenyl alkyl amides in reasonable to high yields (Scheme 35).[86] This is the first heterogeneous catalytic formation of *N*-phenyl alkyl amides. Notably, the formation of the corresponding formamide by-products was hardly suppressed under these conditions.



Scheme 35: Cobalt/C-catalyzed aminocarbonylation of alkenes.

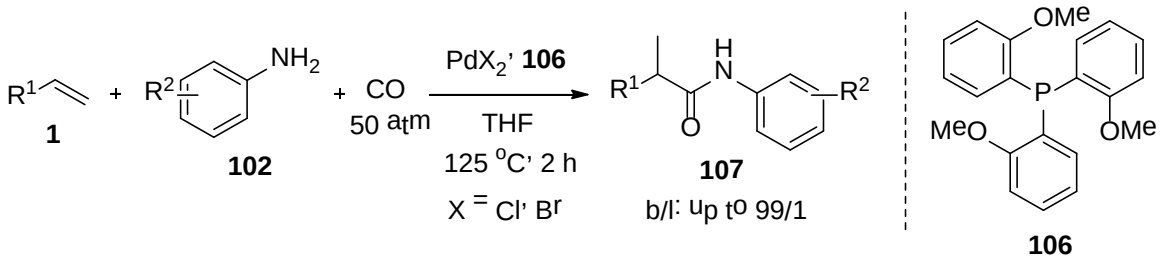
Most recently, Cole-Hamilton and co-workers reported that the catalyst system involving palladium complexes of 1,2-*bis*(di*tert*butylphosphinomethyl)benzene (**93**) for

aminocarbonylation of long chain alkenes with aniline to produce the corresponding amides with high linear selectivity (Scheme 36).[87] Notably, the reaction proceeds with much higher rates and the catalyst stability is improved if 2-naphthol and sodium or potassium iodide are added.

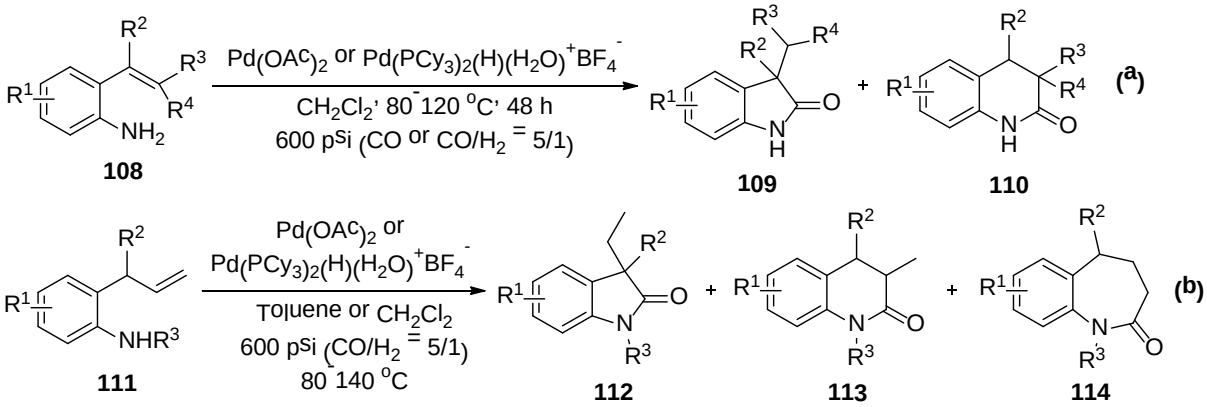


Scheme 36: Palladium-catalyzed aminocarbonylation of alkenes.

Most recently, Liu and co-workers described an efficient method for the synthesis of *N*-aryl monosubstituted carboxamides *via* the palladium-catalyzed aminocarbonylation of alkenes with CO and anilines (Scheme 37).[88] Notably, the catalyst does not require acid, base or any other promoters and employs a commercially available bulky monophosphine ligand to give the branched isomer regioselectively.



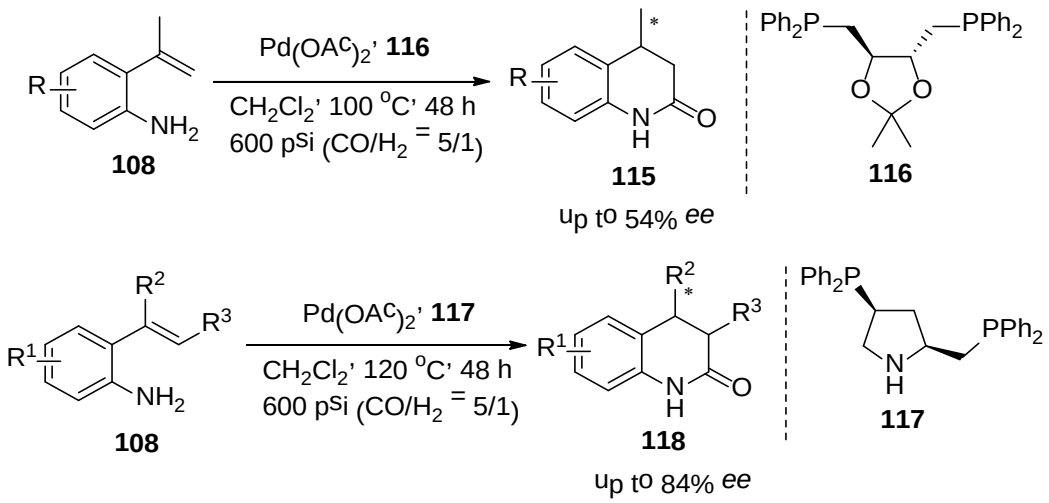
Scheme 37: Acid-free branched regioselective aminocarbonylation of alkenes.



Scheme 38: Palladium-catalyzed intramolecular aminocarbonylation of 2-aminostyrenes and 2-allylanilines.

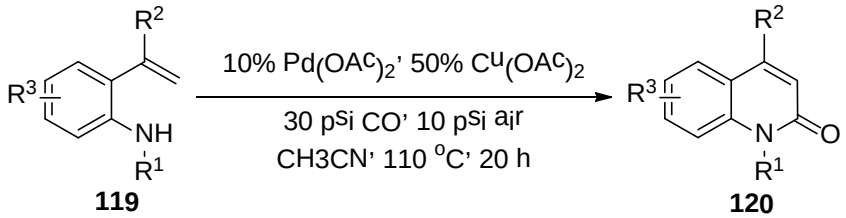
The palladium-catalyzed intramolecular aminocarbonylation of 2-aminostyrenes **108** (Scheme 38, **a**) and 2-allylanilines **111** (Scheme 38, **b**) has been applied to synthesize cyclic amides (lactams) of different ring size in high yields.[89] The optimum conditions for the preparation of bicyclic lactams are five-membered rings from **108** with $Pd(OAc)_2$ and PCy_3, six-membered rings from **111** with $Pd(OAc)_2$ and PPh_3, and seven-membered rings from **111** with $Pd(OAc)_2$ and dppb.

Notably, good enantioselectivity was achieved in asymmetric aminocarbonylation reactions. For example, the asymmetric aminocarbonylation of 2-(1-methylvinyl)anilines proceeded by means of $Pd(OAc)_2$ in the presence of (-)-DIOP **116**[90] and (*S,S*)-DDPP **117**[91] to give 4-methyl-3,4-dihydroquinolin-2-one derivatives in up to 54% and 84% *ee*, respectively (Scheme 39).



Scheme 39: Asymmetric intramolecular aminocarbonylation of 2-aminostyrene derivatives.

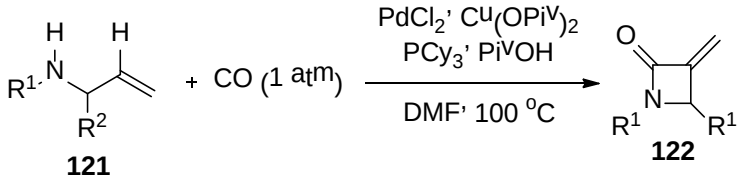
In 2013, Alper and co-workers developed an efficient palladium-catalyzed oxidative aminocarbonylation of *N*-monosubstituted-2-vinylanilines **119** to prepare 2(*1H*) quinolinones **120** in high yields (Scheme 40).[92]



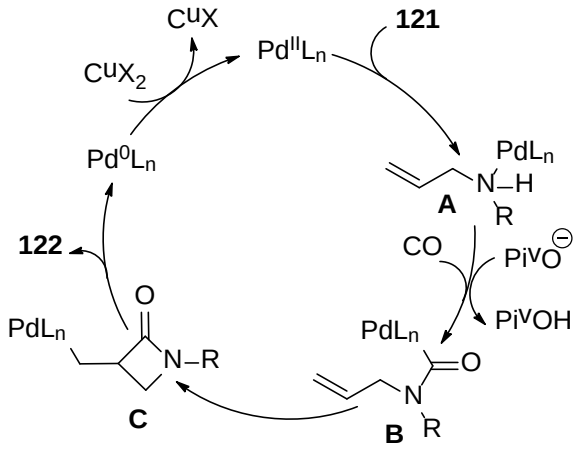
Scheme 40: Palladium-catalyzed oxidative aminocarbonylation of *N*-monosubstituted-2-vinylanilines.

Very recently, Lei and co-workers reported a novel palladium-catalyzed intramolecular oxidative aminocarbonylation of *N*-allylamines **121** to form *α*-methylene-*β*-lactams **122** (Scheme 41).[93] A possible mechanism for this reaction has been outlined in Scheme 42.

The intermediate **A** is formed by the chelation of **121** to palladium, and subsequent migratory insertion of the coordinated CO into the nitrogen-palladium bond forms **B**. Next, olefin insertion into the acyl-palladium bond generates the intermediate **C**. *β*-H elimination of **C** affords the final product **122** and releases a palladium hydride species which is oxidized by the copper catalyst to regenerate Pd(II) and complete the catalytic cycle.



Scheme 41: Palladium-catalyzed intramolecular aminocarbonylation of *N*-allylamines.



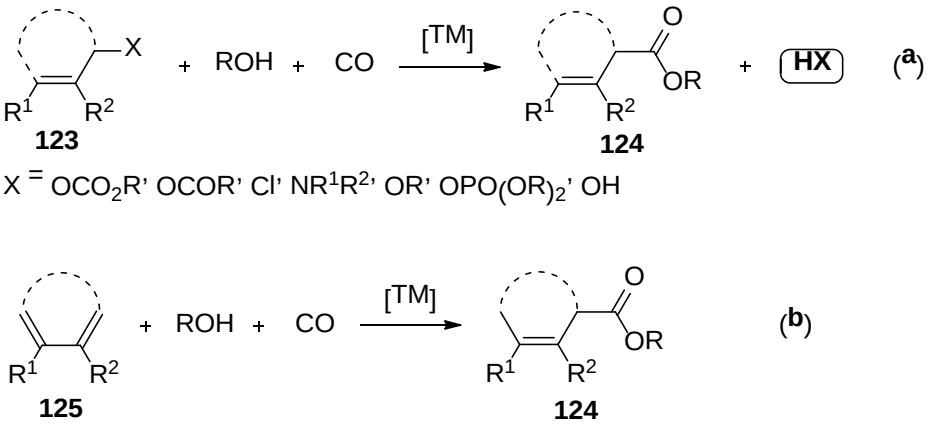
Scheme 42: Proposed catalytic cycle for aminocarbonylation of *N*-allylamines.

Within the framework of this dissertation, we showed that palladium complexes with heterocyclic phosphines represent fast and selective catalysts for aminocarbonylation of olefins with (hetero)aromatic amines to alkanamides.[94] Notably, a wide range of olefins are efficiently transformed to the corresponding *N*-(hetero)aryl amides in good yields with often high regioselectivity. Furthermore, we reported the first catalytic aminocarbonylations of olefins utilizing easily accessible nitroarenes. We were able to show that our catalyst system can be applied to a broad scope of substrates. The detailed results are shown in chapter 4.3.

1.4 Carbonylation of 1,3-Dienes

1.4.1 Alkoxycarbonylation of 1,3-Dienes

The transition-metal-catalyzed carbonylation of allylic compounds **123** is of considerable interest for the synthesis of versatile *β,γ*-unsaturated esters **124**.[95] In the past, effective carbonylation methods for reactions of allylic carbonates,[96] acetates,[97] chlorides,[98] amines,[99] ethers,[100] phosphates,[97b, e, 101] and alcohols[95e, 98b, 102] have been developed (Scheme 43, **a**). Obviously, a general drawback of all these reactions is the stoichiometric generation of by-products. Alternatively, *β,γ*-unsaturated esters **124** can be synthesized by carbonylation of 1,3-dienes **125** (Scheme 43, **b**). Despite the advantage of this more atom-efficient route, the carbonylation of 1,3-dienes has scarcely been explored in academic laboratories. However, the selective alkoxycarbonylation of 1,3-butadiene **126** is of major industrial interest. This substrate (produced in about 12 × 10^6 metric tons annually) offers the possibility to produce bulk chemicals like adipic acid and *ε*-caprolactam *via* 3-pentenoic acid esters **127**.[103]

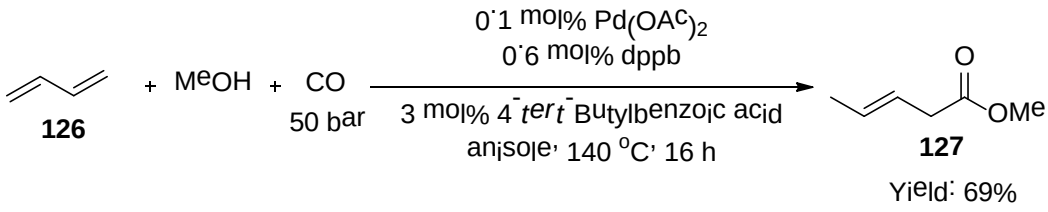


Scheme 43: Synthesis of *β,γ*-unsaturated esters *via* alkoxycarbonylation reactions.

Up to now, catalysts based on Co (mainly studied before 1990),[103b, c, 104] Pd (more important since 1990),[103a, 105] Rh, and Ir have been used for this reaction. The carbonylation of butadiene was first reported by Reppe in the early 1940's, who obtained carbonylated vinylcyclohexene derivatives in the presence of $Co_2(CO)_8$ as catalyst.[104c] Later on, Du Pont reported the methoxycarbonylation of 1,3-butadiene to methyl pentenoate by using a Co/Cu/Th catalyst at very high pressure (810 bar).[106] In the late 1960's, Tsuji[107] described this reaction in the presence of a catalytic amount of palladium chloride to give ethyl 3-pentenoate. While no product yield was given in the original paper, later on Tsuji et al.[107b] reported an optimized yield of approximately 30% of ethyl 3-pentenoate. Matsuda and co-workers demonstrated also the use of cobalt catalysts in the presence of pyridines for this reaction.[108] However, only low catalyst turnover numbers (25-80) were achieved and high

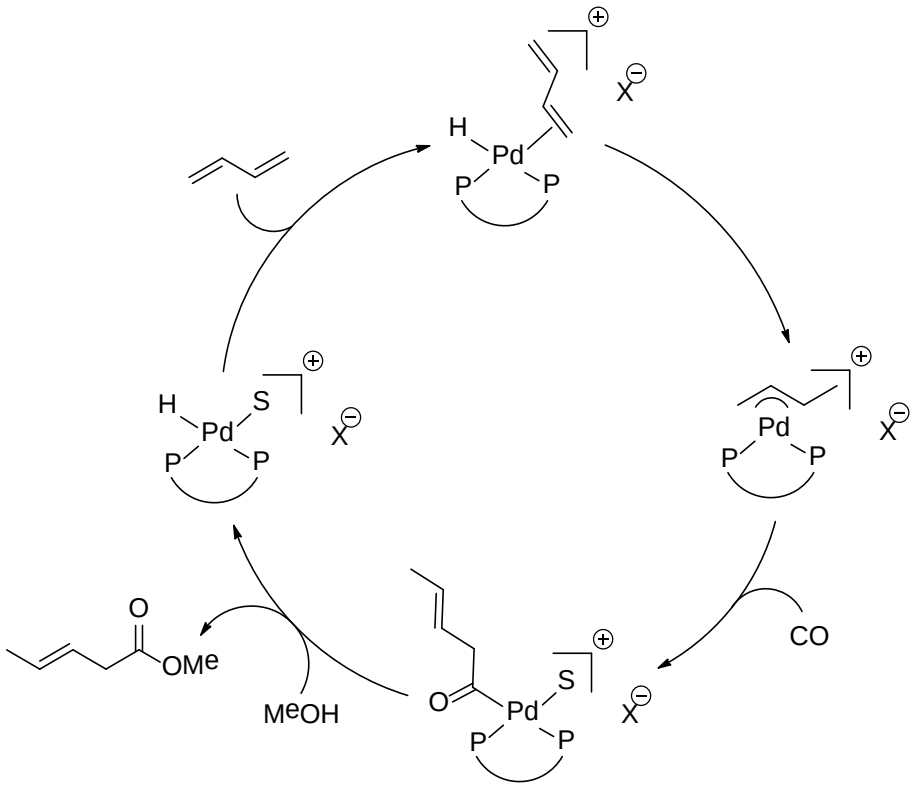
CO pressure was needed. A systematic investigation of the palladium-catalyzed carbonylation of 1,3-dienes was done by Knifton.[109] Despite variation of different ligands and solvents, mainly 3,8-nonadienoate esters (telomerization products) were obtained. A survey of the patent literature reveals significant work on the palladium-catalyzed methoxycarbonylation of 1,3-dienes by Shell,[105, 110] Du Pont, and DSM.[103a,111] The latter companies and also Rhone Poulenc[112] disclosed a positive influence of added acids or quaternary onium salts on selectivity, conversion, and stability of the palladium catalyst. In addition, a Shell patent reported that by controlling the polarity of the reaction medium higher reaction rates can be achieved.[113]

In line with our interest in industrially relevant carbonylation reactions, we performed a systematic study on the methoxycarbonylation of 1,3-butadiene.[114] Examination of the influence of different reaction parameters on product yield and selectivity demonstrated the importance of chelating phosphine ligands and benzoic acids as additive in order to get good results. After considerable screening of ligands and reaction conditions, **127** was obtained in 69% yield and high selectivity in the presence of 0.1 mol % of palladium catalyst containing dppb as ligand (Scheme 44).



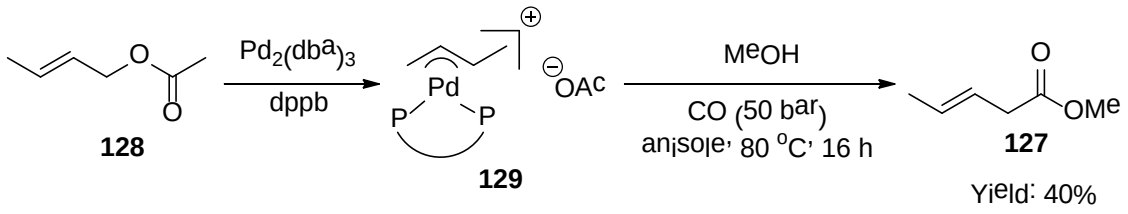
Scheme 44: Palladium-catalyzed methoxycarbonylation of 1,3-butadiene.

Scheme 45 shows the generally accepted mechanism for the alkoxycarbonylation of 1,3-butadiene.The first step of the reaction is the coordination of the 1,3-diene to a palladium hydride complex formed by oxidative addition of an acid to Pd(0). After generation of the crotylpalladium complex, CO insertion leads to the corresponding acylpalladium complex. Subsequent attack by the alcohol forms the product and the palladium hydride complex is regenerated.



Scheme 45: Proposed catalytic cycle for methoxycarbonylation of 1,3-butadiene.

In order to examine the mechanism of the methoxycarbonylation more closely defined intermediates of the catalytic cycle were prepared and the elementary steps of the reaction were separately investigated. First, cationic crotylpalladium complexes were synthesized. Under standard reaction conditions, the cationic crotylpalladium acetate complex **129**, which resembles the actual intermediate of the catalytic cycle, gave the best yield (40%) of the desired ester **127** at 80 °C (Scheme 46).



Scheme 46: Synthesis cationic crotylpalladium complex **129**.

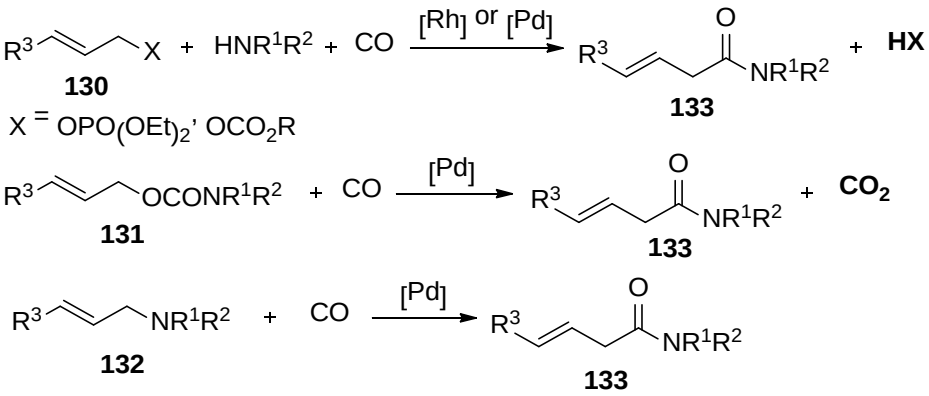
Mechanistic studies revealed that the first half of the catalytic cycle appears to be occurring without difficulty, although there is a negative influence of the CO pressure on the yield of the crotylpalladium complex. Furthermore, carbonylation experiments of different crotylpalladium complexes showed that the yield of **127** depends on the counterion and on the ligand. In all reactions, an acylpalladium complex could neither be observed nor be isolated. The formation of these complexes might be the most difficult step under our reaction conditions.

In summary, until today, basically all of the published catalyst systems for carbonylation of 1,3-dienes suffer from drawbacks such as the need of harsh reaction conditions and/or additives (e.g. acids), narrow substrate scope, relatively low product yield and limited selectivity. In this regard, the development of improved and acid-free catalyst systems for this reaction is of high importance and constitutes a challenging and relevant topic for academic and industrial research.

Within the framework of this dissertation, we developed an improved palladium-based catalyst system for the selective alkoxycarbonylation of 1,3-dienes under relatively mild conditions.[115] Notably, the various *β,γ*-unsaturated esters were obtained in high yield with good selectivity under acid-free conditions. We were able to show that our catalyst system can be applied to a broad scope of substrates. The detailed results are shown in chapter 4.4.

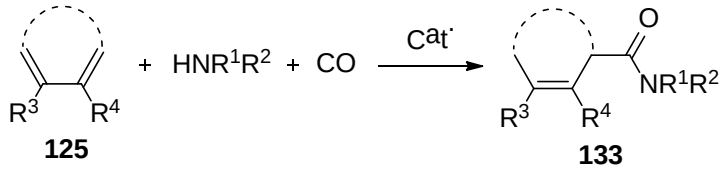
1.4.2 Aminocarbonylation of 1,3-Dienes

Comparing to the well-studied carbonylation reaction of allyl derivatives to form *β,γ*-unsaturated esters, there are few examples known that allow the synthesis of related *β,γ*-unsaturated amides **133** *via* carbonylation of allyl-X compounds (Scheme 47).[96a, 99, 116]



Scheme 47: Synthesis of *β,γ*-unsaturated amides *via* carbonylation of allyl-X compounds.

A major problem for any aminocarbonylation methodology is the competing direct amination of the substrate. In fact, such aminations of allyl-X compounds should proceed faster than carbonylations. Moreover, a general drawback of these reactions is the stoichiometric generation of by-products (e.g. salts). Alternatively, *β,γ*-unsaturated amides **133** might also be synthesized by carbonylation of 1,3-dienes **125**. Despite the inherent advantage of this atom-economic green route (100% atom-efficient route), the carbonylation of 1,3-dienes has scarcely been explored in academic laboratories. Comparing to the well-studied alkoxycarbonylation of 1,3-dienes,[103-114] to the best of our knowledge comparable aminocarbonylation reactions to *β,γ*-unsaturated amides have not yet been reported (Scheme 48).



Scheme 48: Synthesis of *β,γ*-unsaturated amides *via* aminocarbonylation of 1,3-dienes.

Within the framework of this dissertation, we developed the first general palladium-based catalyst system for the aminocarbonylation of 1,3-dienes.[117] Applying a variety of aromatic amines leads to *β,γ*-unsaturated amides in good yields and selectivities under neutral conditions. More detailed results are shown in chapter 4.5.

1.5 References

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2. Objectives of this work

As described in the introduction, the carbonylation of easily available feedstocks such as olefins, 1,3-butadiene and alkynes with carbon monoxide as a carbonyl source has become an important and convenient method for the selective preparation of important fine and bulk chemicals (Figure 2). Although much research has been accomplished in this field, there still exists significant academic and industrial interest to increase the efficiency and selectivity of the processes through the development of new catalyst systems.

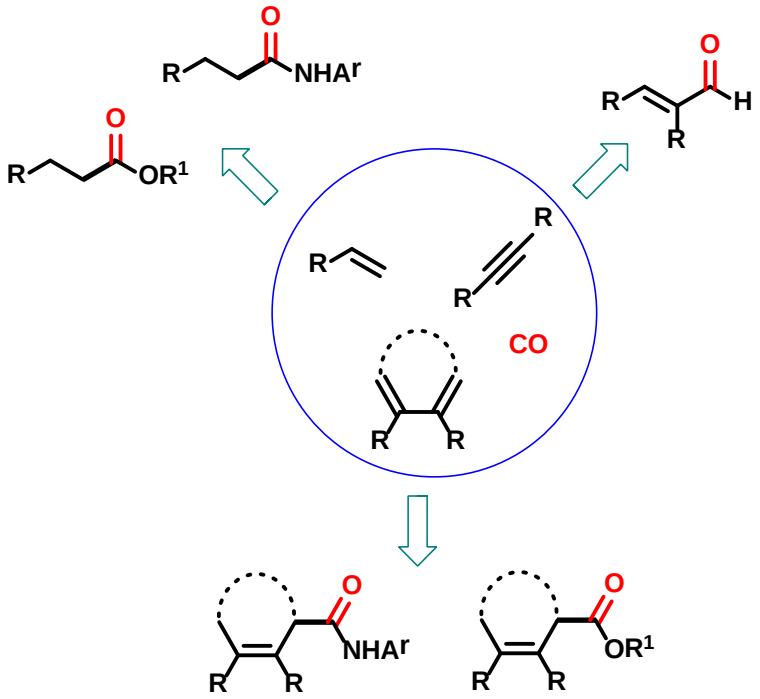


Figure 2: Carbonylation of alkenes, alkynes and 1,3-dienes.

Additionally, hydroformylation is established as an important industrial tool for the production of aldehydes, which are easily further converted to variety of useful products by domino processes or multicomponent reactions (Figure 3). These processes are of particular interest in terms of atom-efficiency, selectivity and applicability.

Therefore, the major aim of this work was the development of novel catalysts system for carbonylation of multiple C-C bonds to useful bulk and fine chemicals. In addition, exploitation of novel domino and one-pot processes to fine or bulk chemicals as well as biologically active compounds from alkenes or alkynes is also a main goal of this thesis.

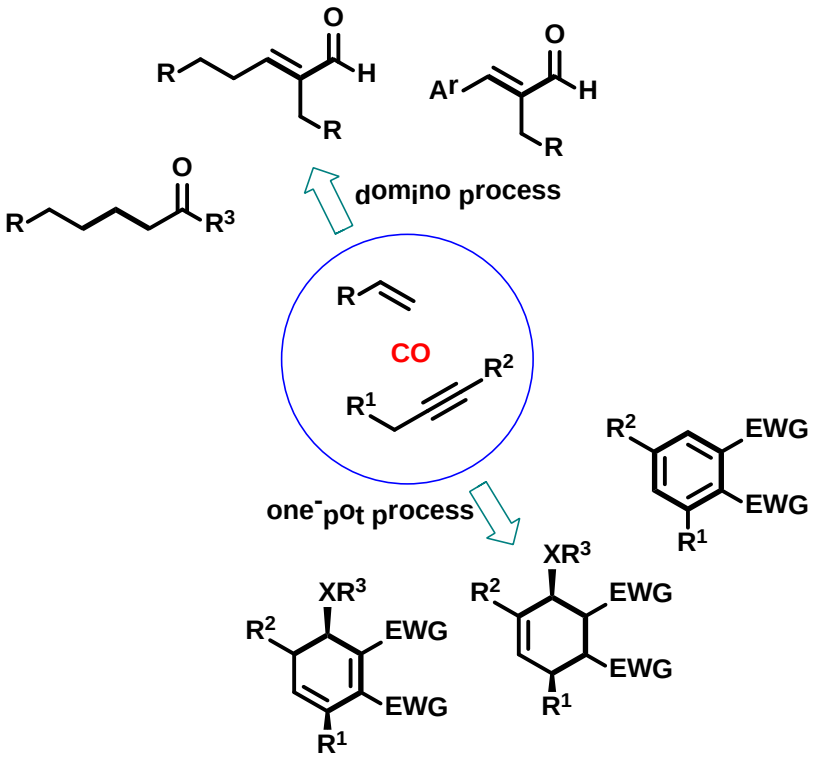
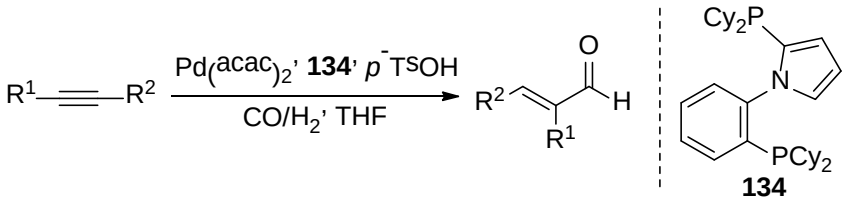


Figure 3: Domino and one-pot processes involving hydroformylation reactions.

3. Summary

3.1 Palladium-Catalyzed Hydroformylation of Alkynes

In the context of our ongoing research in the field of hydroformylation, recently we were attracted to study less common hydroformylation catalysts. We demonstrated that other metals beyond rhodium and cobalt can be successfully applied in the hydroformylation of olefins. More specifically, we showed that palladium complexes with heterocyclic phosphines represent fast and selective catalysts for low pressure hydroformylations of aromatic and aliphatic olefins. Therefore, we presumed that these complexes might be also suitable for the hydroformylation of alkynes to give selectively *α,β*-unsaturated aldehydes. Herein, we present an efficient and selective palladium-based catalyst system for a general hydroformylation of alkynes that proceeds under mild conditions (Scheme 49). Notably, high enal product yields from demanding substrates such as aryl alkynes were obtained by effectively suppressing the unwanted hydrogenation side reactions.



Scheme 49: Palladium complexes with heterocyclic phosphines **134** for hydroformylation of alkynes.

Applying optimized conditions good to excellent yields and selectivities towards the *α,β*-unsaturated aldehydes can be obtained from various aromatic and aliphatic alkynes as shown in Figure 4. Substrates having different functional groups (i.e. -Br, -COMe, -NPhth, and -CO_2Et) were well tolerated (**136** and **141**-**143**). Moreover, heterocyclic substituent-containing substrate proved also to be efficient coupling partner to generate the corresponding *α*,*β*-unsaturated aldehyde (**137**) in good yield. From a synthetic point of view, it is important that reactions using unsymmetrical aryl alkynes mainly occurred at the benzylic position. Thus, a good regioselectivity is observed, which is attributed to the formation of the kinetically favored vinyl-palladium species stabilized by aryl groups (**138**-**143**). Aliphatic alkynes, which is a class of less reactive substrates compared to aryl alkynes. By increasing the catalyst loading to 1 mol% of $Pd(acac)_2$ and the reaction temperature to 100 ^oC, all the reactions proceeded smoothly and afforded the desired products in reasonable to excellent yields (eg. **144**). The hydroformylation of the unsymmetrical alkyl alkyne 4, 4′-dimethylpent-2-yne gave the product **145** exclusively in 65% yield. Here, the specific regioselectivity is attributed again to the steric effect.

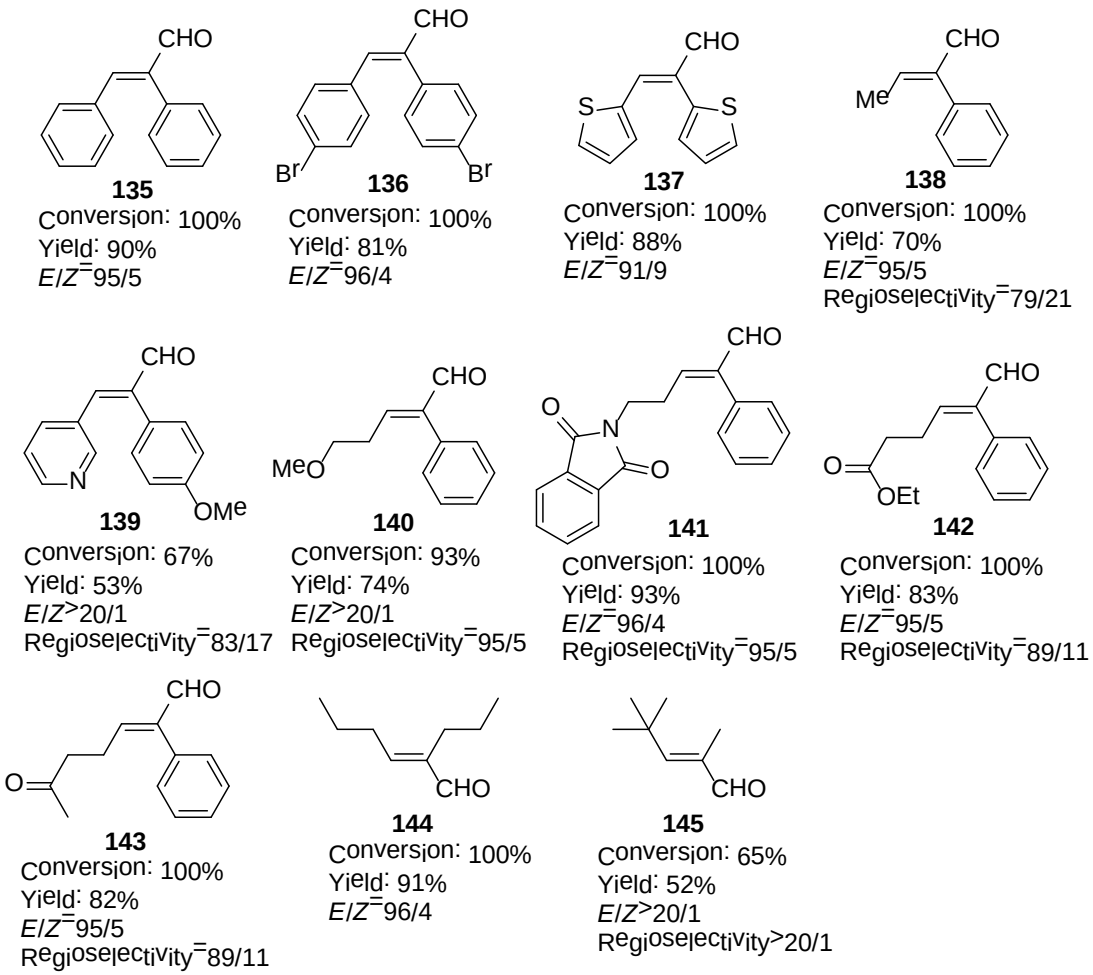


Figure 4: Substrate scope of the palladium-catalyzed hydroformylation of alkynes.

In conclusion, we have developed the first efficient palladium-based catalyst system for selective hydroformylation of alkynes to *α*,*β*-unsaturated aldehydes. Notably, competing hydrogenation side reactions can be almost suppressed. Compared to previously known catalyst systems a wider range of internal alkynes can be efficiently hydroformylated to *α*,*β*-unsaturated aldehydes in good yields with often high regio- and stereoselectivity. For details, see Publication 4.1.

3.2 Synthesis of New Diphosphine Ligands for Palladium-Catalyzed Methoxycarbonylation of Olefins

Recently, diphosphine ligands derived from the industrially applied ligand bis(di-*tert*-butylphosphinomethyl)benzene (**93**) showed their high activity and *n*-regioselectivity in palladium-catalyzed alkoxycarbonylation reactions. Inspired by these achievements, carbocyclic and *N*-heterocyclic analogues have been synthesized in moderate to very good yields. The new ligands are based on benzene, tetralin, lutidine, pyrazine and quinoxaline backbones. Electronic and steric variations of the phosphorous donor sites were performed (Figure 5).

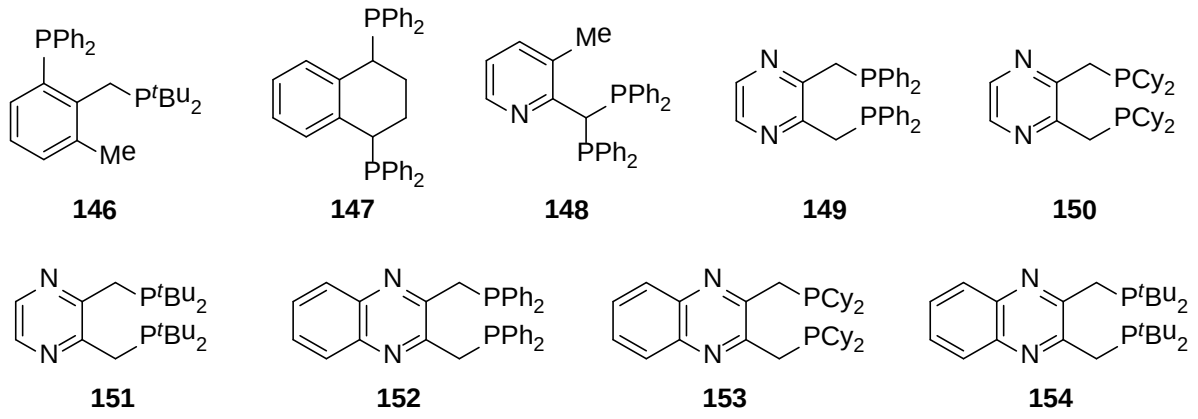
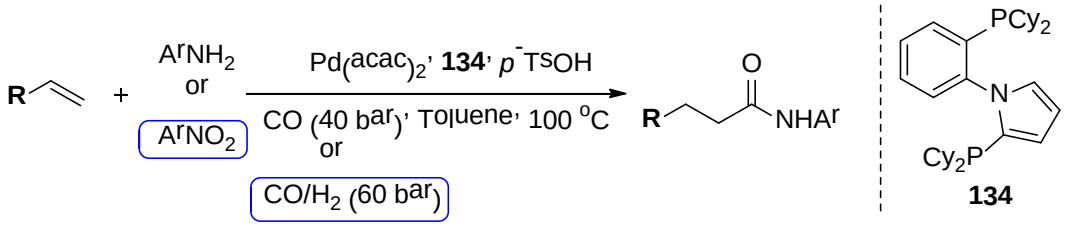


Figure 5: Synthesis of carbocyclic and *N*-heterocyclic analogues of **93**.

As a benchmark reaction the methoxycarbonylation of 1-octene was carried out using 0.04 mol% $Pd(acac)_2$ and 0.16 mol% of the new ligands in the presence of 0.6 mol% methane sulfonic acid in methanol under 40 bar of CO pressure. As expected, the ligand structure has a significant influence on the conversion and regioselectivity. Gratifyingly, better σ-donor di-*tert*-butylphosphino ligands **151** and **154** led to improved results and total ester yields up to 64% and linear regioselectivites up to 92% were reached. For details, see Publication 4.2.

3.3 Palladium-Catalyzed Aminocarbonylation of Olefins

As descried in the introduction part, the reaction of olefins, carbon monoxide and amines (aminocarbonylation) leading to amides has found much less attention compared to related alkoxycarbonylations. This is somewhat surprising as the aminocarbonylation of olefins provides a 100% atom-efficient route for producing carboxamides, which represent versatile building blocks and intermediates for the chemical, pharmaceutical and agrochemical industries. Herein, we developed an efficient homogeneous palladium-based catalyst system for the aminocarbonylation of olefins with a variety of (hetero)aromatic amines or nitro compounds under relatively mild conditions (Scheme 50). Notably, the corresponding products were obtained in high yield with good regioselectivity and unwanted formamides are not observed.



Scheme 50: Palladium complexes with heterocyclic phosphines **134** for aminocarbonylation of olefins.

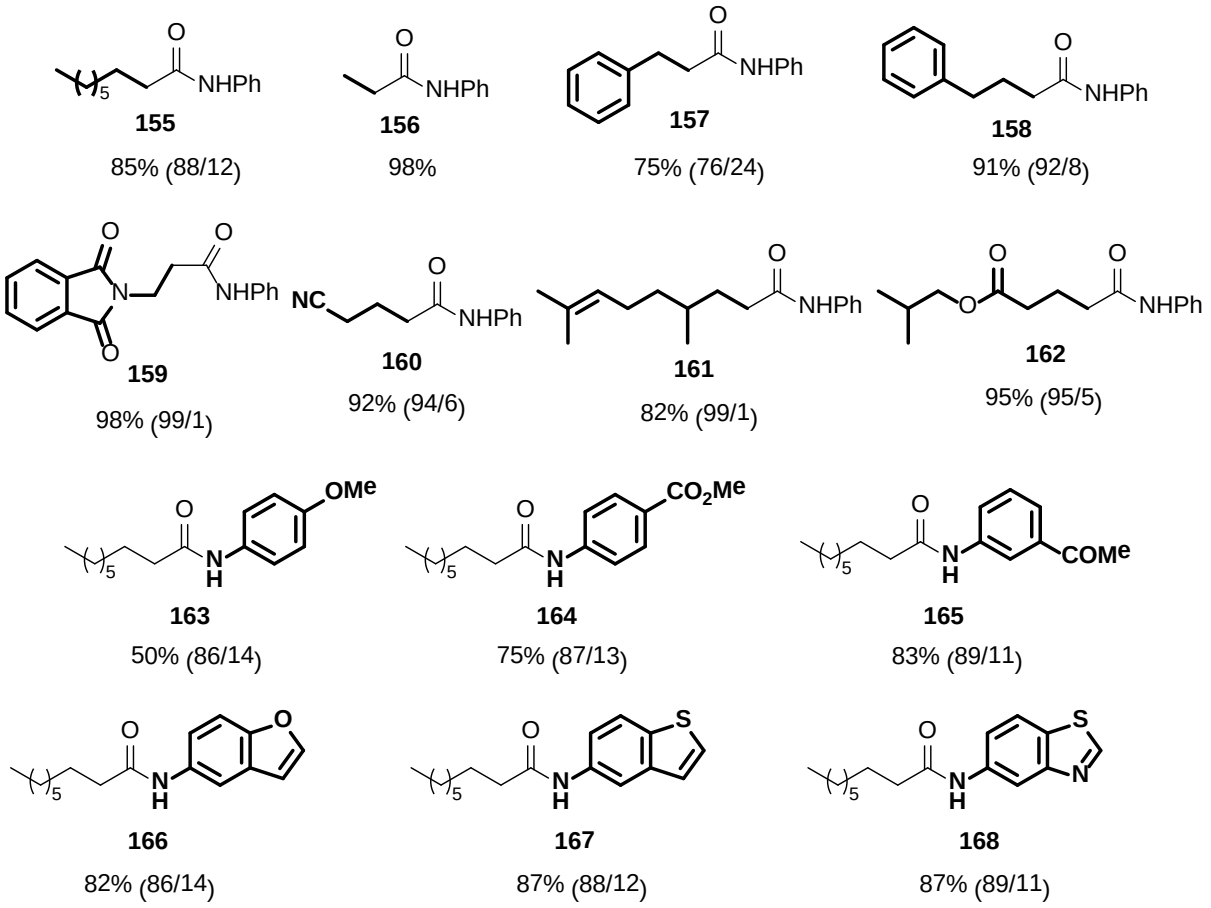
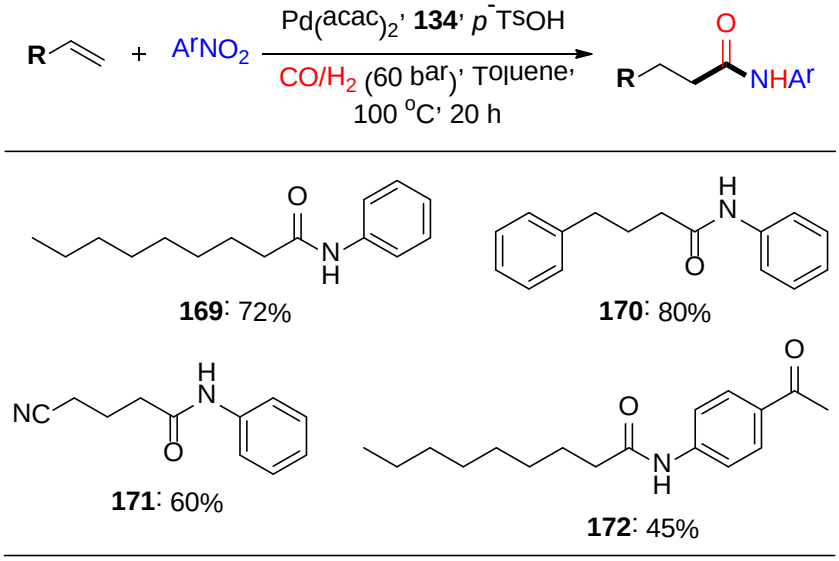


Figure 6: Substrate scope of the palladium-catalyzed aminocarbonylation of olefins with aromatic amines.

In Figure 6, the substrate scope of the aminocarbonylation reaction of olefins with aromatic amines is shown. Most notably, substrates having different functional groups such as phthalimide, nitrile, tri-substituted olefin, and ester were well tolerated, and smoothly transformed to the corresponding functionalized amides in good yields with high linear selectivities (**159**-**162**). Noteworthy, the corresponding formamides were not formed in all these cases. With respect to various amines, general, the aminocarbonylation reaction was sensitive to steric and electronic effects of substituent(s) on the aniline. However, when the catalyst loading was increased to 1.0 mol%, all the reactions of electron-rich and electron-deficient substituted anilines proceeded smoothly and afforded the desired products in moderate to good yields with good regioselectivities (**163**-**165**). Probably based on steric effects, higher linear regioselectivity is observed when *ortho*-substituted anilines were employed as substrates. Moreover, heteroaromatic amines proved to be efficient coupling partners and gave the corresponding products in good yields with good regioselectivities (**166**-**168**). When using aliphatic amines such as butyl- or cyclohexylamine no conversion is

observed. Apparently, the active Pd-H species is not formed in the presence of the more basic aliphatic amines as indicated by the absence of any isomerization side-reaction.



Scheme 51: Palladium-catalyzed aminocarbonylation of olefins with nitroarenes.

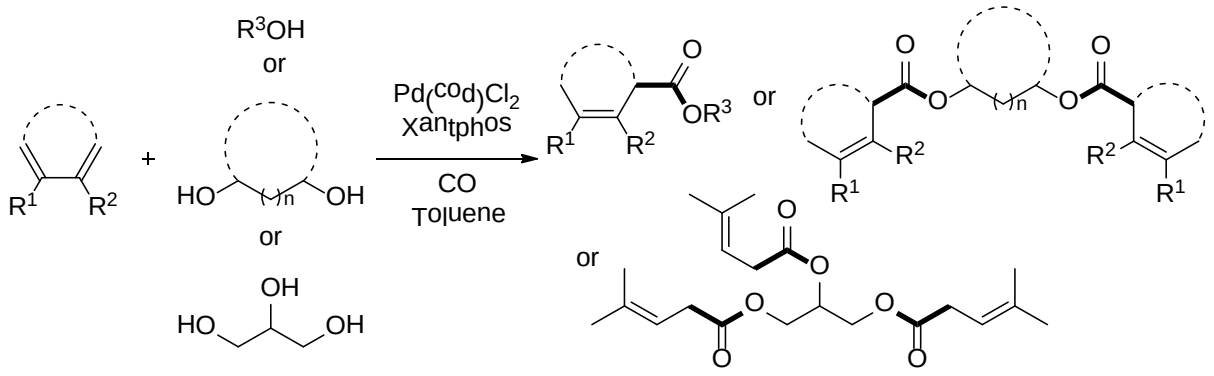
Considering that most of the anilines are prepared from the corresponding nitroarenes, the aminocarbonylation using nitroarenes would allow the elimination of at least one process step and makes use of less expensive starting materials. When using molecular hydrogen as reducing agent, gratifyingly, all the individual reaction steps proceeded smoothly and afforded the desired product in acceptable to good yields (Scheme 51). Substrates having functional groups such as nitrile and even ketone (Scheme 51, **171** and **172**) were well tolerated under these reducing conditions. In general, this latter protocol provides a useful and benign alternative for the synthesis of *N*-aryl carboxamides. To the best of our knowledge such aminocarbonylations of olefin with nitroarenes has never been explored before.

In conclusion, we described a palladium-based catalyst system for a general and selective aminocarbonylation of olefins with (hetero)aromatic amines to alkanamides. Notably, a wide range of olefins are efficiently transformed to the corresponding *N*-(hetero)aryl amides in good yields with often high regioselectivity. Furthermore, we reported the first catalytic aminocarbonylations of olefins utilizing easily accessible nitroarenes. For more details, see Publication 4.3.

3.4 Palladium-Catalyzed Alkoxycarbonylation of 1,3-Dienes

In line with our interest in industrially relevant carbonylation reactions, we performed a systematic study on the methoxycarbonylation of 1,3-butadiene earlier on. Examination of the influence of different reaction parameters on product yield and selectivity demonstrated the importance of chelating phosphine ligands and benzoic acids as additive in order to get

good results. However, until today, basically all of the published catalyst systems for carbonylation of 1,3-dienes suffer from drawbacks such as the need of harsh reaction conditions and/or additives, e.g. acids, narrow substrate scope, relatively low product yield and limited selectivity. In this regard, the development of improved and acid-free catalyst systems for this reaction is of high importance and constitutes a challenging and relevant topic for academic and industrial research. Herein, we present an acid-free palladium-based catalyst system for the selective alkoxycarbonylation of 1,3-dienes under relatively mild conditions (Scheme 52).



Scheme 52: Palladium-catalyzed alkoxycarbonylation of 1,3-dienes.

Applying optimized conditions good to excellent yields and selectivities towards the *β,γ*-unsaturated esters can be obtained from various aliphatic alcohols and 1,3-dienes as shown in Figure 7. Interestingly, menthol and heterocyclic alcohols proved to be efficient coupling partners and gave the corresponding esters in excellent yields with good selectivities (**175** and **177**-**179**). Moreover, a broad range of functional groups is tolerated, including reactive alkene (**180**), alkyne (**181**), and benzyl (**173**) groups, which provide useful handles for further synthetic transformations. Noteworthy, we demonstrated the utility of our carbonylation protocol in the reaction of the allylic alcohol geraniol, an ingredient commonly used in perfumes and flavors (**182**). From an industrial point of view it is importantly that 1,3-butadiene (**183**) furnished the corresponding product in good yield. Furthermore, sterically crowded 1,3-dienes and cyclic 1,3-diene were smoothly transformed to the corresponding *β,γ*-unsaturated esters in good yields and with excellent selectivities (**184** and **185**). Notably, the use of the renewable diene myrcene led to the desired functionalized *β,γ*-unsaturated ester in excellent yield though low selectivity (**187**).

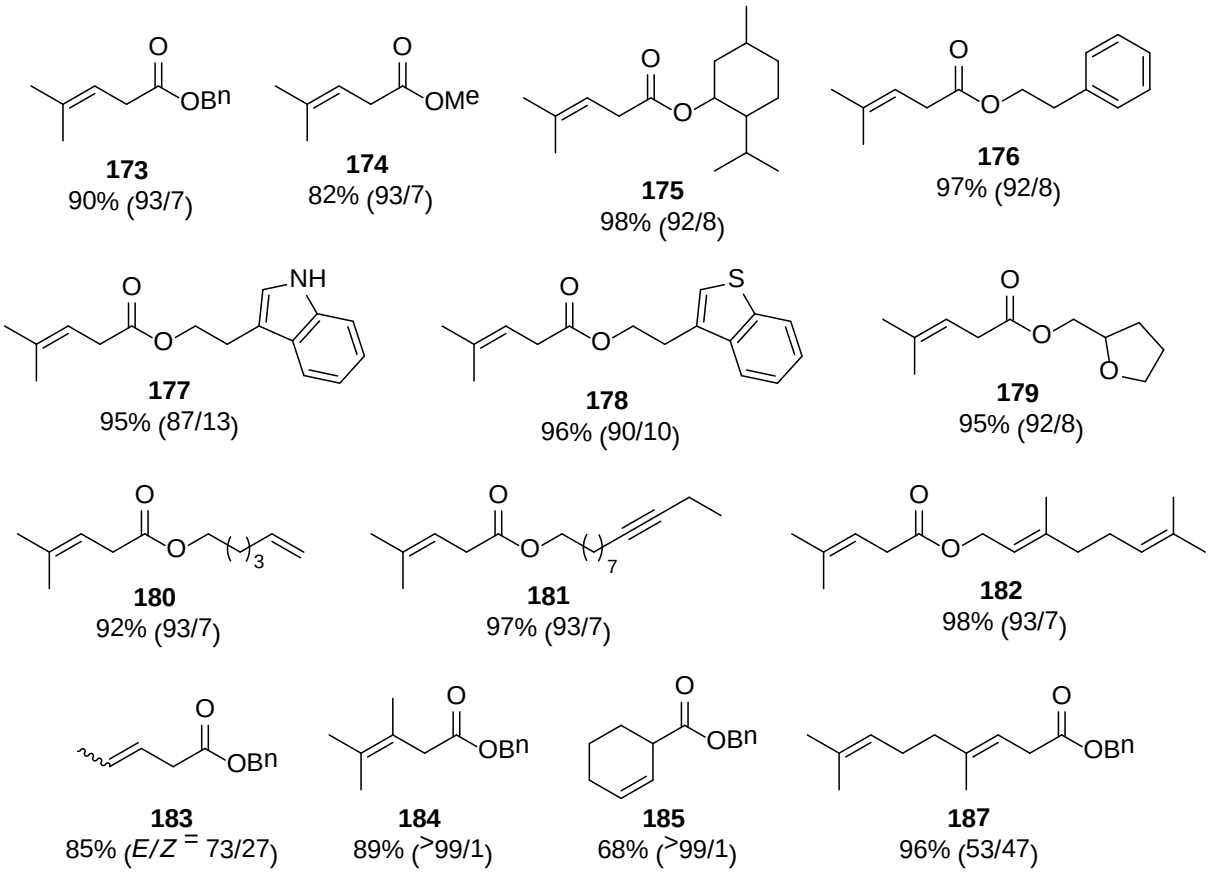
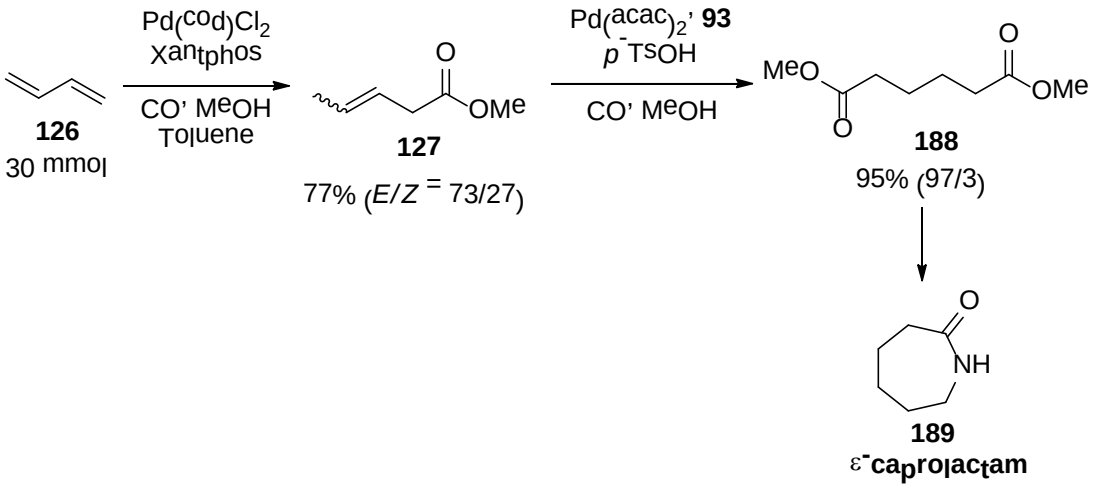


Figure 7: Substrate scope of the palladium-catalyzed alkoxycarbonylation of 1,3-dienes with aliphatic alcohols under acid-free conditions.



Scheme 53: Straightforward synthesis of dimethyl adipate and *ε*-caprolactam from 1,3-butadiene.

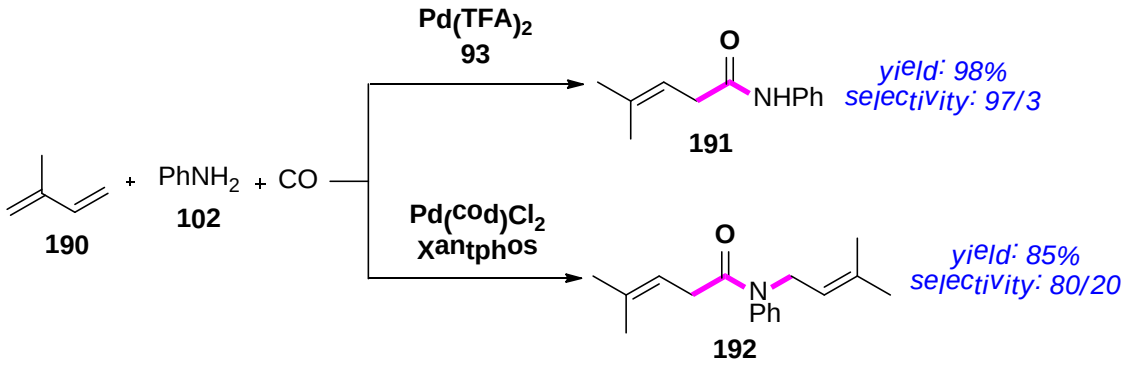
Next, we were interested in demonstrating the usefulness of our procedure for the synthesis of adipic acid esters and *ε*-caprolactam. Hence, the synthesis of **127** was scaled up to 30 mmol of 1,3-butadiene **126**. Indeed, 77% yield of the corresponding *β,γ*-unsaturated

ester was obtained. Subsequent transformation of **127** gave dimethyl adipate **188** in high yield with excellent regioselectivity (Scheme 53). It should be noted that this sequence also allows for a straightforward preparation of *ε*-caprolactam **189**, which is primarily used in the production of nylon 6 fibers and resins.

In conclusion, we developed a novel protocol for the palladium-catalyzed alkoxycarbonylation of conjugated 1,3-dienes to produce a variety of synthetically useful *β,γ*-unsaturated esters in good yields with often high selectivity. Compared to previously known procedures the substrate scope is enhanced and no additives such as acids, which might cause corrosion problems are needed. Furthermore, combining the presented procedure with established carbonylation reactions allows for an efficient preparation of adipates and *ε*-caprolactam. For more details, see Publication 4.4.

3.5 Palladium-Catalyzed Aminocarbonylation of 1,3-Dienes

Comparing to the well-studied alkoxycarbonylation of 1,3-dienes, related aminocarbonylation reactions to *β,γ*-unsaturated amides have not yet been reported. Hence, herein we describe the first general catalyst system for the direct aminocarbonylation of 1,3-dienes. Applying a variety of aromatic amines leads to *β,γ*-unsaturated amides in good yields and selectivities under neutral conditions (Scheme 54).



Scheme 54: Palladium-catalyzed aminocarbonylation of isoprene.

In the presence of different palladium phosphine complexes carbonylation (1:1 adduct, **191**) or a selective hydroamination-carbonylation sequence (2:1 adduct, **192**) was observed, respectively (Scheme 54).

Applying palladium catalysts with bisphosphine ligand **93** good to excellent yields and selectivities towards the *β,γ*-unsaturated amides can be obtained from various aromatic amines and 1,3-dienes as shown in Figure 8. A variety of aromatic amines with electron-neutral, electron-deficient and electron-rich substituents led to the corresponding carbonylative products in good yields and selectivities. Functional groups including reactive halide (**193**), nitrile (**196**), ketone (**197**) and ester (**198**) groups, which provide useful handles for further synthetic transformations, are well tolerated. Interestingly, heteroaromatic amines

(**199** and **200**) proved to be efficient coupling partners and gave the corresponding amides in decent yields with good selectivities. Even secondary aromatic amines underwent this transformation and afforded the desired products in moderate to good yields (**201** and **202**). Considering the importance of diamides which are widely applied for agrochemicals and used in the polymer industry, we tested the dicarbonylation of phenylenediamines. As shown in Figure 8, the reactions of isoprene **190** with *m*-phenylenediamine gave the desired diamide again in good yield and selectivities (**203**). With respect to 1,3-dienes, sterically crowded 1,3-diene was smoothly transformed to the corresponding *β,γ*-unsaturated amide with excellent selectivity (**204**). The cyclic 1,3-diene was also efficiently transformed to the desired *β,γ*-unsaturated amide (**205**). From a synthetic point of view, the synthesis of functionalized *β,γ*-unsaturated amides from functionalized 1,3-dienes is important which is reflected in products **206** and **207**, which are obtained in a straightforward manner using our protocol.

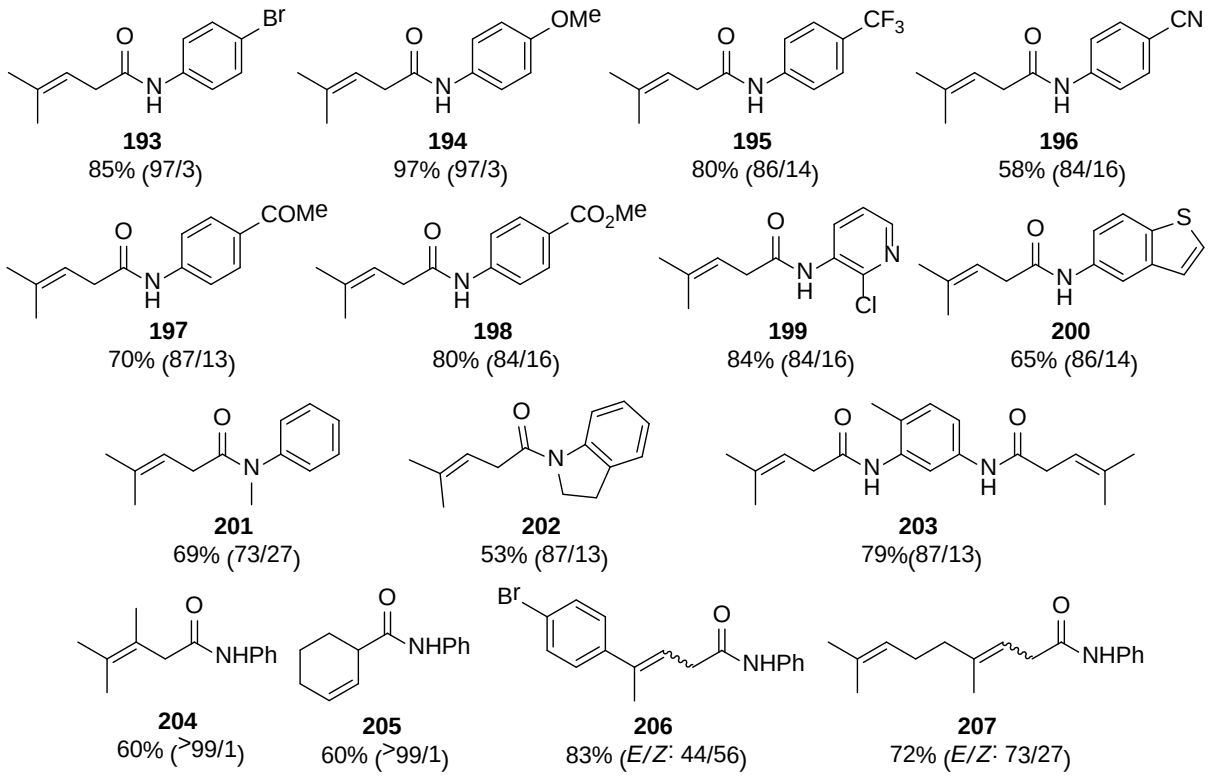
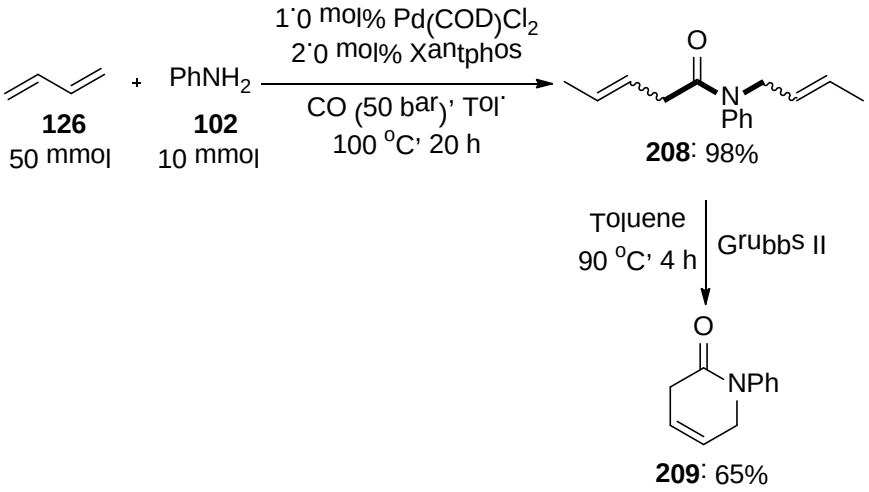


Figure 8: Substrate scope of the palladium-catalyzed aminocarbonylation of 1,3-dienes.

From an industrial point of view it is interesting that 1,3-butadiene (**126**) furnished the corresponding product **208** in excellent yield at low catalyst loading (Scheme 55). Considering the 1,7-diene structural motif, product **208** provides the possibility of further transformations. Indeed, ring-closing metathesis of the **208** occurred smoothly using Grubbs II catalyst to give the 1-phenyl-1,6-dihydropyridin-2(*3H*)-one **209** in 65% yield (Scheme 55).

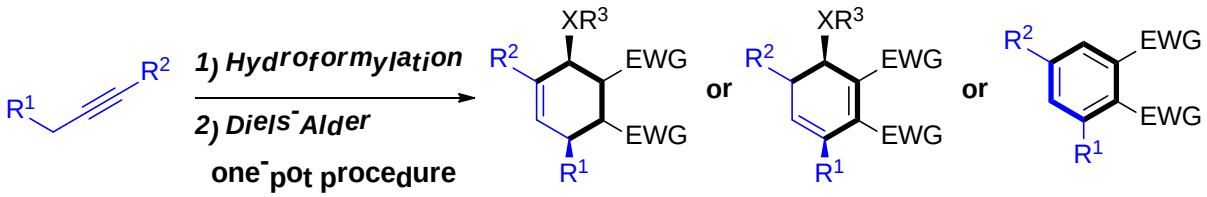


Scheme 55: Straightforward synthesis of 1-phenyl-1,6-dihydropyridin-2(*3H*)-one from 1,3-butadiene.

In conclusion, we developed the first general aminocarbonylation reactions of 1,3-dienes. Using different aromatic amines a variety of synthetically useful *β,γ*-unsaturated amides are produced in good to excellent yields. The high atom economy, the additive-free reaction conditions make this protocol attractive for synthetic applications. For details, see Publication 4.5.

3.6 Sequential Hydroformylation/Diels-Alder Processes

As shown in chapter 3.1, we developed palladium complexes with heterocyclic phosphine ligands as efficient catalysts for the hydroformylation of alkynes to give selectively *α,β*-unsaturated aldehydes. On the basis of this work, we utilized this protocol for the synthesis of more complex organic molecules. Advantageously, both the palladium-catalyzed hydroformylation and the AAD-type reactions (Chapter 1.1.2) require acid as co-catalyst. From this point of view, it was possible to combine them. Hence a two-step, one-pot synthesis of diverse multi-substituted cyclohexenes and cyclohexadienes as well as phthalates by hydroformylation and Diels-Alder reactions was developed (Scheme 56).



Scheme 56: One-Pot synthesis of polysubstituted cyclohexenes, cyclohexadienes and phthalates from alkynes.

As depicted in Figure 9, the present one-pot process was surprisingly versatile. In general, both symmetrical and unsymmetrical alkynes underwent efficient hydroformylation/Diels-

Alder reactions to afford the corresponding multi-substituted cyclohexenes in good yields. Notably, alkynes having different functional groups such as phthalimide and ester were well tolerated, and smoothly transformed to the corresponding functionalized cyclohexenes in good yields (**213** and **214**).

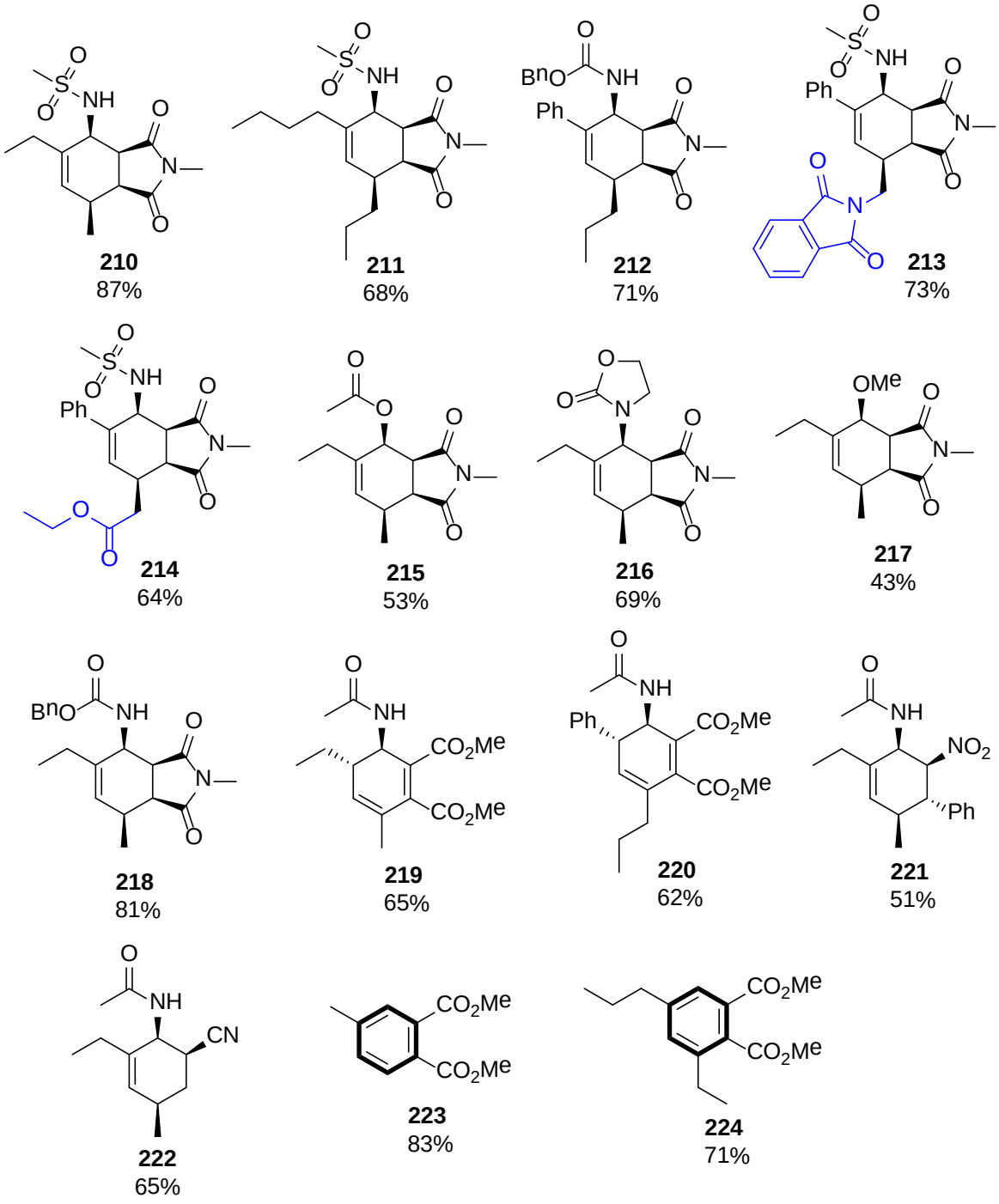


Figure 9: Substrate scope of the one-pot hydroformylation/Diels-Alder process.

Furthermore, various carboxamides were well tolerated under the standard reaction conditions. Employment of 2-oxazolidinone gave the corresponding product **216** in 69% yield and with a tertiary amide moiety. Benzyloxycarbonyl protection of the amino function was

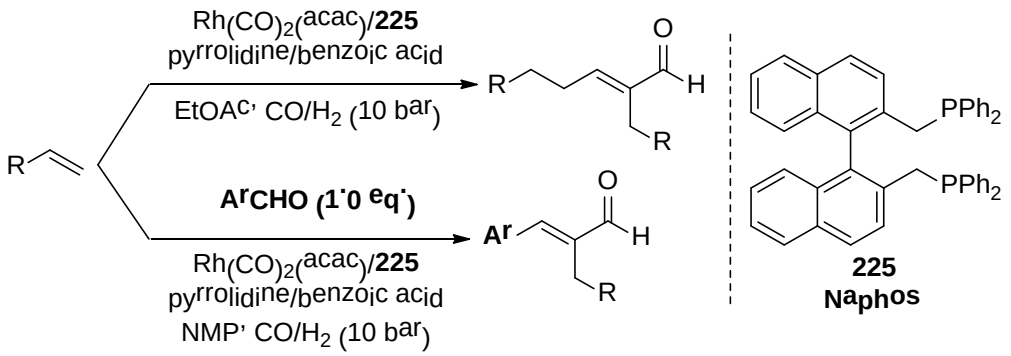
realized for **212** and **218**. In addition to amides, anhydrides (ANAD-reaction) and orthoesters (OAD-reaction) also served as coupling partners and led to an increase of structural diversity (**215** and **217**). In order to study also the influence of other dienophiles, dimethyl acetylenedicarboxylate, trans-*β*-nitrostyrene and acrylonitrile were employed and gave yields of 65, 51, and 65%, respectively (**219**-**222**). For all products, one- and two-dimensional NMR experiments established the stereochemical structure. In all cases, we observed the selective *endo* addition of the dienophile during the Diels-Alder step. To enhance product diversity of present reaction protocol further on, tri- and tetra-substituted dimethyl phthalates (**223** and **224**) were prepared in good yields after 48 h at 160 ^{o}C from alkynes, acetamide and dimethyl acetylenedicarboxylate. Both short- and long-chained symmetrical aliphatic alkynes provided the corresponding substituted dimethyl phthalates in good yields *via* facilitated acylamine elimination from the intermediate cyclohexadienes.

In conclusion, several one-pot procedures for a diversity oriented synthesis of multi-substituted cyclohexenes, cyclohexadienes and phthalates has been developed. Key to success is the combination of hydroformylation of alkynes followed by Diels-Alder reactions. Notably, this methodology provides an interesting option to synthesize new organic products as the corresponding *α,β*-unsaturated aldehydes are traditionally difficult to synthesize and only few examples are commercially available. The detailed results are shown in Publication 4.6.

3.7 Domino Hydroformylation/Aldol Condensation Catalysis

As elaborated in chapter 1.2.1, generally, aldol products are only observed as unwanted side-products in olefin conversions under hydroformylation conditions. However, for a successful domino hydroformylation/aldol condensation sequence efficient and aldol addition of the enolized aldehyde to another aldehyde product has to occur. Even more challenging is the selective cross-aldol reaction of two different aldehydes present under hydroformylation conditions due to the usual problems of chemo- and regioselectivity. In early studies, it has been found that hydroformylation/aldol condensation reaction sequences usually suffer from low chemoselectivity and/or low yield of the desired unsaturated aldehyde, primarily because the formation of the corresponding saturated aldehydes and alcohols can be hardly suppressed under the harsh conditions. Noteworthy, Eilbracht and Breit have made pioneering work in this area. However, until today there exist no general methodology for intermolecular hydroformylation/aldol condensation reactions to give *α,β*-unsaturated aldehydes. Hence, we disclose the combination of a specific rhodium(I) phosphine complex and pyrrolidinium benzoate as an efficient catalyst system for practical intermolecular domino hydroformylation/aldol condensation reactions. Both industrially and synthetically important

olefins are selectively transformed into the desired products under mild conditions (Scheme 57).



Scheme 57: Highly selective synthesis of *α,β*-unsaturated aldehydes from olefins.

Applying optimized conditions good to excellent yields and stereoselectivity (*E/Z* ratios: >95/5) towards the *α,β*-unsaturated aldehydes can be obtained from various terminal olefins as shown in Figure 10. Gratifyingly, substrates having different functional groups such as amine, olefin, halide, and ether were well tolerated and smoothly transformed to the corresponding functionalized *α,β*-unsaturated aldehydes in good yields with high stereoselectivities (**230**-**233**).

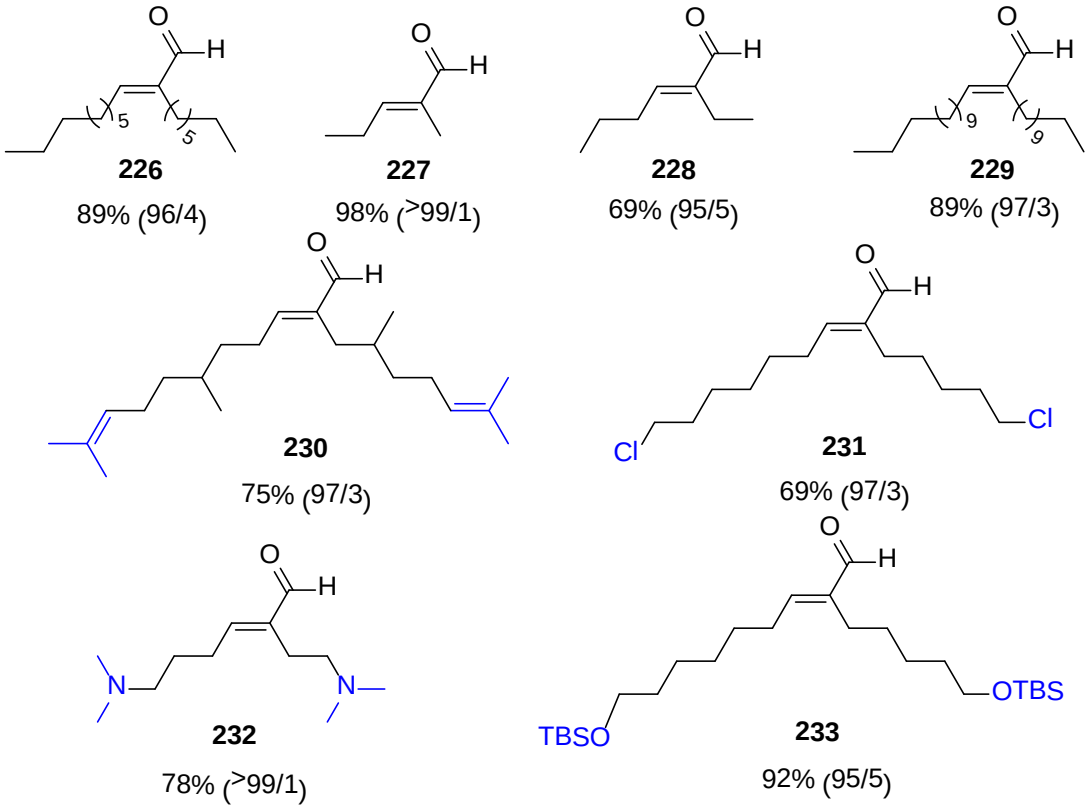


Figure 10: Substrate scope of the domino hydroformylation/homo-aldol condensation of olefins.

More importantly, the present catalyst system was surprisingly versatile for domino hydroformylation/cross-aldol condensation sequence, too. As shown in Figure 11, various benzaldehydes with electron-neutral, electron-deficient and electron-rich substituents underwent efficient transformation to afford the corresponding *α,β*-unsaturated aldehydes in good to excellent yields with high *E*-stereoselectivities. Meanwhile, aldehydes having different functional groups such as halide, nitrile and nitro, were well tolerated, too (**235** and **238**-**239**). Moreover, heterocyclic aldehydes proved also to be efficient coupling partners to generate the corresponding products in good yields (**240**-**242**). From a synthetic point of view, the synthesis of functionalized *α,β*-unsaturated aldehydes from functionalized olefins and aromatic aldehydes is important which is reflected in products **243** and **244**, which are obtained in good yield using our protocol.

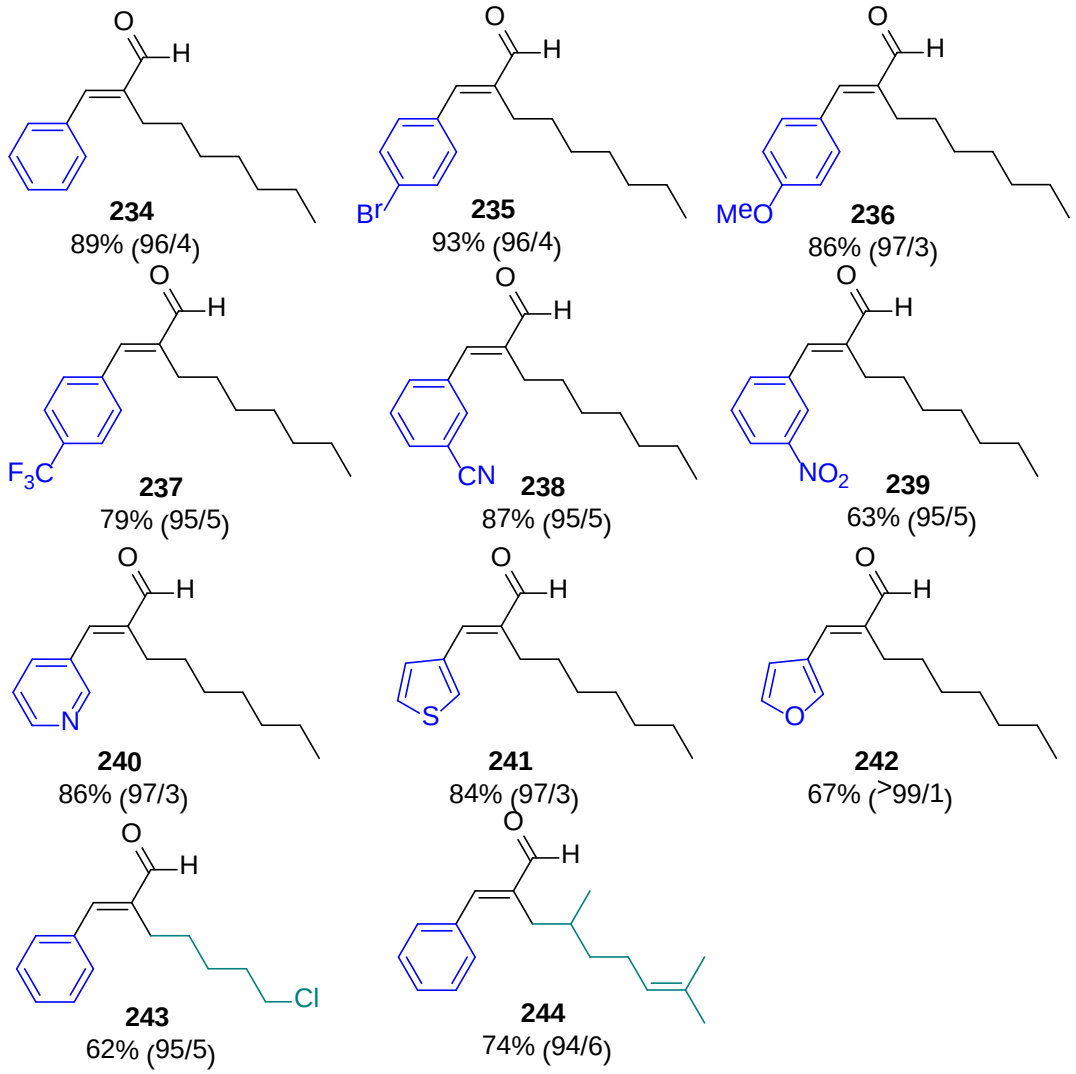


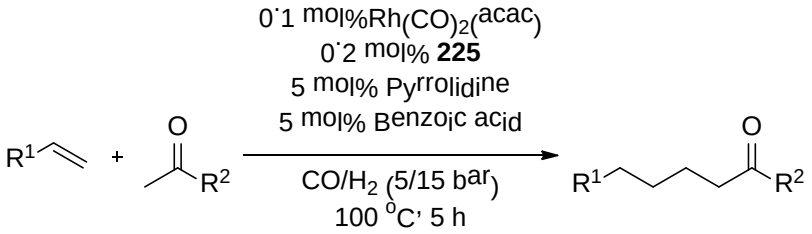
Figure 11: Substrate scope of the domino hydroformylation/cross-aldol condensation of olefins with aromatic aldehydes.

In conclusion, we present an efficient and highly selective intermolecular domino hydroformylation/aldol reaction sequence which allows for the synthesis of *α,β*-unsaturated

aldehydes. Various olefins and aromatic aldehydes underwent efficient transformation in the presence of a cooperative rhodium/phosphine and organocatalyst system to afford the corresponding *α,β*-unsaturated aldehydes in good to excellent yields with high *E*-stereoselectivities. For the first time also excellent chemoselectivity is achieved in intermolecular hydroformylation/cross-aldol condensation reactions and the corresponding *α,β*-unsaturated aldehydes were obtained effectively by suppressing the unwanted homo-aldol condensation side reactions. Key to success is the inherently low concentration of the aldehyde formed in the hydroformylation step. For more details, see Publications 4.7 and 4.9.

3.8 Domino Hydroformylation/Aldol Condensation/Hydrogenation Catalysis

The hydroformylation of olefins is known since 75 years. The reaction is well investigated and constitutes one of the largest homogeneously catalyzed processes in industry. In fact, originally this reaction was named oxo reaction because of the formation of both aldehydes and ketones using ethylene and synthesis gas at high temperature and high pressure. However, soon after the discovery of the reaction it was realized that it mainly delivers aldehydes. Herein, we present a general synthesis of ketones from olefins, synthesis gas and acetone or related substrates. Combination of a specific rhodium(I) phosphine complex and pyrrolidinium benzoate creates an efficient catalyst system for practical domino hydroformylation/aldol condensation/hydrogenation reactions. Both industrially and synthetically important olefins are selectively transformed into the desired ketones in good to excellent yields and regioselectivities (Scheme 58).



Scheme 58: Highly selective synthesis of ketones from olefins.

As depicted in Figure 12, the present domino process is surprisingly versatile. In general, both short- and long-chained terminal aliphatic olefins provided the corresponding saturated ketones in good yields with high regioselectivity (*n*/*iso* ratios: >98/2). Gratifyingly, substrates with different olefinic groups showed high selectivity for the functionalization of the terminal double bond (**248**-**249**). Moreover, functional groups such as amine and ether were well tolerated and the corresponding functionalized ketones were achieved in good yields with excellent regioselectivities (**250**-**251**). On the other hand, various aliphatic and aromatic ketones underwent efficient transformation to afford the corresponding saturated ketones in

good to excellent yields with high regioselectivities. Using 2-butanone demonstrated the high chemoselectivity of the reaction sequence. Hence, functionalization took only place on the methyl group and not on the ethyl part (**252**). An excellent chemoselectivity is also observed for 2,5-hexanedione, which gave led to mono-functionalization (**254**). Moreover, functional groups including ester (**253**) and halides (**256**) are well tolerated, which provide useful handles for further synthetic transformations. The alkylation of easily available methyl levulinate is also of interest as an easy tool for further valorization of biomass (**253**). Similarly, heterocyclic ketones proved also to be efficient coupling partners to generate the corresponding ketone in good yield (**257**).

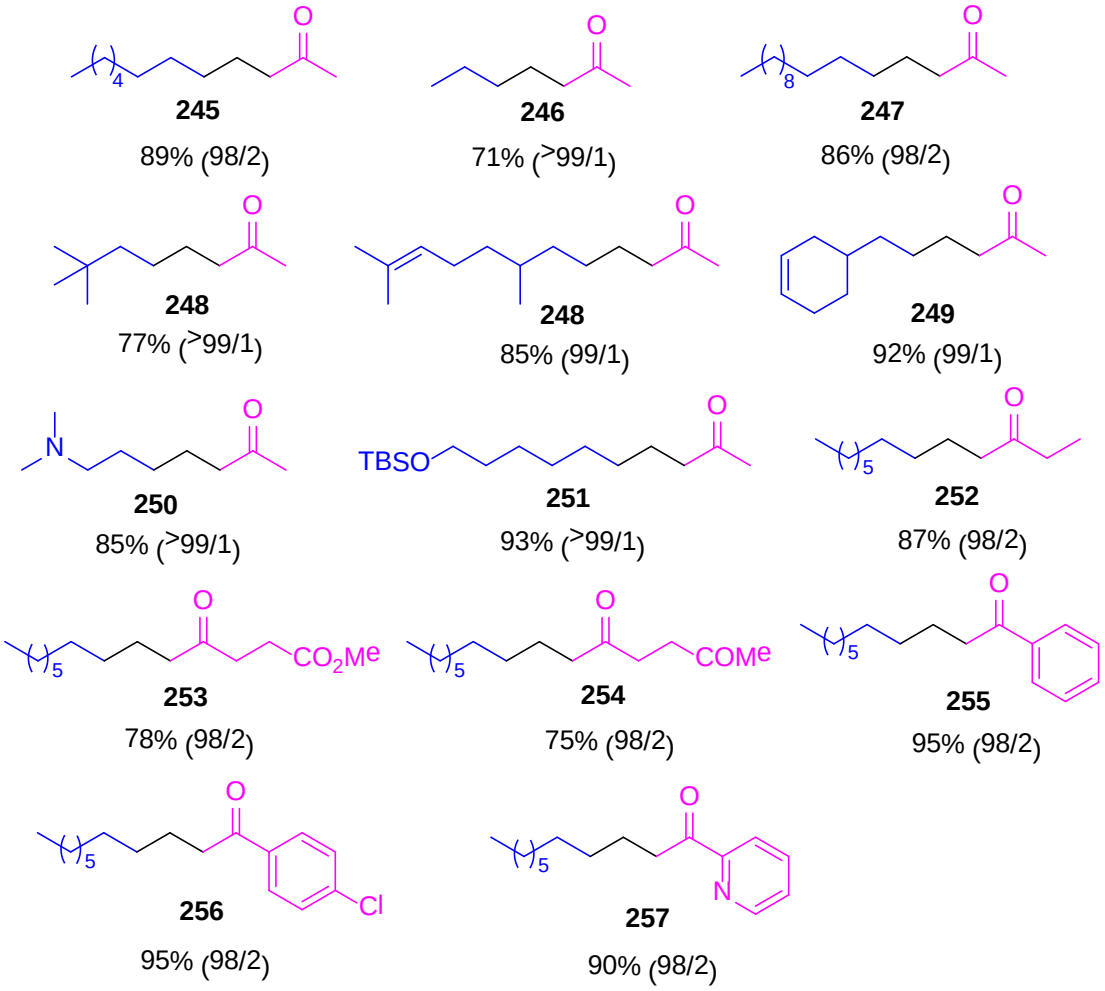


Figure 12: Substrate scope of the domino hydroformylation/aldol condensation/hydrogenation of olefins.

In conclusion, we developed a highly selective intermolecular domino hydroformylation/aldol condensation/hydrogenation reaction sequence which allows for an efficient synthesis of ketones. Key to success for this transformation are the use of a specific cooperative rhodium/phosphine and organocatalytic system and the inherently low

concentration of the aldehyde formed in the hydroformylation step. For details, see Publications 4.8 and 4.10.

4. Publications

4.1 Selective Palladium-Catalyzed Hydroformylation of Alkynes to *α,β*-Unsaturated Aldehydes

Xianjie Fang, Min Zhang, Ralf Jackstell, Matthias Beller

Angewandte Chemie **2013**, *125*, 4743-4747; *Angewandte Chemie International Edition* **2013**, *52*, 4645–4649.

Contributions

In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 85%.

4.2 Synthesis of New Diphosphine Ligands and their Application in Pd-Catalyzed Alkoxycarbonylation Reactions

Anahit Pews-Davtyan, Xianjie Fang, Ralf Jackstell, Anke Spannenberg, Wolfgang Baumann, Robert Franke, Matthias Beller

Chemistry – An Asian Journal **2014**, *9*, 1168-1174.

Contributions

In this paper, I planned and performed reactions described in Table 2. My contribution as co-author of this paper is approximately 25%.

4.3 Selective Palladium-Catalyzed Aminocarbonylation of Olefins with Aromatic Amines and Nitroarenes

Xianjie Fang, Ralf Jackstell, Matthias Beller

Angewandte Chemie **2013**, *125*, 14339-14343; *Angewandte Chemie International Edition* **2013**, *52*, 14089-14093.

Contributions

In this paper, I planned, performed and analyzed all the experiments for this manuscript. I wrote the manuscript. My contribution as co-author of this paper is approximately 90%.

4.4 Palladium-Catalyzed Alkoxycarbonylation of Conjugated Dienes under Acid-Free Conditions: Atom-Economic Synthesis of *β,γ*-Unsaturated Esters

Xianjie Fang, Haoquan Li, Ralf Jackstell, Matthias Beller

Angewandte Chemie **2014**, *126*, 9176-9180; *Angewandte Chemie International Edition* **2014**, *53*, 9030-9034.

Contributions

In this paper, I planned and performed half of the experiments. I wrote the manuscript. My contribution as co-author of this paper is approximately 50%.

4.5 Selective Palladium-Catalyzed Aminocarbonylation of 1,3-Dienes: Atom-Efficient Synthesis of *β,γ*-Unsaturated Amides

Xianjie Fang, Haoquan Li, Ralf Jackstell, Matthias Beller

J. Am. Chem. Soc. **2014**, *136*, DOI: 10.1021/ja507530f

Contributions

In this paper, I planned and performed almost half of the experiments. I wrote the manuscript. My contribution as co-author of this paper is approximately 50%.

4.6 Sequential Hydroformylation/Diels–Alder Processes: One-Pot Synthesis of Polysubstituted Cyclohexenes, Cyclohexadienes, and Phthalates from Alkynes

Xianjie Fang, Ralf Jackstell, Matthias Beller

Chemistry - A European Journal **2014**, *20*, 7939-7942.

Contributions

In this paper, I planned, performed and analyzed all the experiments for this manuscript. I prepared the manuscript. My contribution as co-author of this paper is approximately 90%.

4.7 Domino Hydroformylation/Aldol Condensation Catalysis: Highly Selective Synthesis of *α,β*-Unsaturated Aldehydes from Olefins

Xianjie Fang, Ralf Jackstell, Robert Franke, Matthias Beller

Chemistry - A European Journal **2014**, *20*, 13210-13216.

Contributions

In this paper, I planned, performed and analyzed all the experiments for this manuscript. I prepared the manuscript. My contribution as co-author of this paper is approximately 85%.

4.8 Domino Hydroformylation/Aldol Condensation/Hydrogenation Catalysis: Highly Selective Synthesis of Ketones from Olefins

Xianjie Fang, Ralf Jackstell, Armin Börner, Matthias Beller

Chemistry - A European Journal **2014**, *20*, DOI: 10.1002/chem.201404294

Contributions

In this paper, I planned, performed and analyzed all the experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 85%.

4.9 Patent: Verfahren zur katalytischen Herstellung von ungesättigten Aldehyden

Xianjie Fang, Ralf Jackstell, Matthias Beller

Patent **2014**, 102014201122DE.

Contributions

I performed all of the experiments. I was involved in the planning of experiments, discussions and argumentation of the results. I have done the major part of writing of the manuscript. My contribution as co-author of this patent is approximately 85%.

4.10 Patent: Verfahren zur katalytischen Herstellung von symmetrischen und unsymmetrischen Ketonen

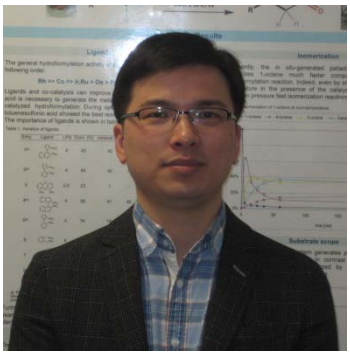
Xianjie Fang, Ralf Jackstell, Armin Börner, Matthias Beller

Patent **2014**, 102014201126.4DE.

Contributions

I performed all of the experiments. I was involved in the planning of experiments, discussions and argumentation of the results. I wrote the experiment part of the manuscript. My contribution as co-author of this patent is approximately 80%.

Xianjie Fang



Curriculum Vitae

Personal details

Name	Xianjie
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Education

09/2011 – Present	**Research Doctorate** **Leibniz-Institute for Catalysis at the University of Rostock** Topic: *Catalytic Carbonylative Functionalization of Multiple Carbon-Carbon Bonds* Supervisor: Prof. Matthias Beller
09/2008 – 03/2011	**Master of Applied Chemistry, East China University of Science and Technology (ECUST),** Shanghai, China Topic: *Palladium and Rhodium-Catalyzed Cyclization Reactions* Supervisor: Prof. Xiaofeng Tong
09/2004 – 06/2008	**Bachelor of Chemical Engineering, Jiangnan University,** Wuxi, China

Award

04/2010	BASF Scholarship in ECUST
05/2011	LORD Education Scholarship in ECUST
09/2011	Leibniz Scholarship in Leibniz Institute for Catalysis

Working experience

04/2011-08/2011 Associate research fellow of Shanghai ChemExplorer Company Ltd.

Research experiences

09/2011-Present	**Doctoral research experiences**
	1 Utilization of alternative metals (beyond Rh and Co) for hydroformylation
	2 Synthesis bulk chemicals by tandem hydroformylation reactions
	3 Transition metal-catalyzed carbonylation of alkenes and alkynes as well as 1,3-dienes
	4 Design and synthesis new ligands for hydroformylation and carbonylation reactions
	5 Methylation of amines using CO_2 and hydrogenation of CO_2
	6 Synthesis of fine chemicals *via* ruthenium-catalyzed hydrogen-borrowing reactions
09/2008-03/2011	**Master research experiences**
	7 Palladium-catalyzed cyclization reactions
	8 Rhodium-catalyzed annulations in the presence of bifunctional organoboron reagents

Relevant skills

Experimental: Proficient with the construction and operation of Schlenk system as well as high pressure equipment (i.e. different scale of autoclaves), experience in handling air and water-sensitive chemicals and purification of organic materials
Technical: Skilled in operation and analysis of some analytical instruments, for example NMR, GC-MS, IR, and HPLC
IT: Excellent ability with MS Office, Origin, experienced in the use of SciFinder, Reaxys database, NMR Topspin, Chemdraw etc and various graphic application tools

List of Publications

[1] Xianjie Fang, Ralf Jackstell, Matthias Beller,* Selective Palladium-Catalyzed Aminocarbonylation of Olefins with Aromatic Amines and Nitroarenes *Angew. Chem. Int. Ed.* **2013**, *52*, 14089-14093. (*hot paper*)

[2] Xianjie Fang, Min Zhang, Ralf Jackstell, Matthias Beller,* Selective Palladium-Catalyzed Hydroformylation of Alkynes to *α,β*-Unsaturated Aldehydes. *Angew. Chem. Int. Ed.* **2013**, *52*, 4645-4649.

[3] Xianjie Fang, Ralf Jackstell, Matthias Beller,* Sequential Hydroformylation/Diels–Alder Processes: One-Pot Synthesis of Polysubstituted Cyclohexenes, Cyclohexadienes, and Phthalates from Alkynes. *Chem. Eur. J.* **2014**, *20*, 7939-7942.

[4] Xianjie Fang, Haoquan Li, Ralf Jackstell, Matthias Beller,* Palladium-Catalyzed Alkoxycarbonylation of Conjugated Dienes under Acid-Free Conditions: Atom-Economic Synthesis of *β,γ*-Unsaturated Esters. *Angew. Chem. Int. Ed.* **2014**, *53*, 9030-9034.

[5] Xianjie Fang, Ralf Jackstell, Robert Franke, Matthias Beller,* Domino Hydroformylation/Aldol Condensation Catalysis: Highly Selective Synthesis of *α,β*-Unsaturated Aldehydes from Olefins. *Chem. Eur. J.* **2014**, *20*, 13210-13216.

[6] Xianjie Fang, Haoquan Li, Ralf Jackstell, Matthias Beller,* Selective Palladium-Catalyzed Aminocarbonylation of 1,3-Dienes: Atom-Efficient Synthesis of β,γ-Unsaturated Amides. *J. Am. Chem. Soc.* **2014**, *136*, DOI: 10.1021/ja507530f

[7] Xianjie Fang, Ralf Jackstell, Armin Börner, Matthias Beller,* Domino Hydroformylation/Aldol Condensation/Hydrogenation Catalysis: Highly Selective Synthesis of Ketones from Olefins. *Chem. Eur. J.* **2014**, *20*, DOI: 10.1002/chem.201404294 (*hot paper*)

[8] Xiao-Feng Wu,* Xianjie Fang, Lipeng Wu, Ralf Jackstell, Helfried Neumann, Matthias Beller,* Transition Metal-Catalyzed Carbonylation Reactions of Olefins and Alkynes: A Personal Account. *Acc. Chem. Res.* **2014**, *47*, 1041-1053.

[9] Yuehui Li, Xianjie Fang, Kathrin Junge, Matthias Beller,* A General Catalytic Methylation of Amines Using Carbon Dioxide. *Angew. Chem. Int. Ed.* **2013**, *52*, 9568-9571.

[10] Min Zhang, Xianjie Fang, Helfried Neumann, Matthias Beller,* General and Regioselective Synthesis of Pyrroles via Ruthenium-Catalyzed Multicomponent

Reactions. *J. Am. Chem. Soc.* **2013**, *135*, 11384-11388.

[11] Lipeng Wu, Xianjie Fang, Qiang Liu, Ralf Jackstell, Matthias Beller,* Xiao-Feng Wu,* Palladium-Catalyzed Carbonylative Transformation of C(sp^3)–X Bonds. *ACS Catal.* **2014**, *4*, 2977-2989.

[12] Anahit Pews-Davtyan, Xianjie Fang, Ralf Jackstell, Anke Spannenberg, Wolfgang Baumann, Robert Franke, Matthias Beller,* Synthesis of new diphosphine ligands and their application in Pd-catalyzed alkoxycarbonylation reactions. *Chem. Asian J.* **2014**, *9*, 1168-1174.

[13] Qiang Liu, Lipeng Wu, Haijun Jiao, Xianjie Fang, Ralf Jackstell, Matthias Beller,* Domino Catalysis: Palladium-Catalyzed Carbonylation of Allylic Alcohols to *β,γ*-Unsaturated Esters. *Angew. Chem. Int. Ed.* **2013**, *52*, 8064-8068. (*VIP*)

[14] Xianjie Fang, Chaolong Li, Xiaofeng Tong,* Rhodium-catalyzed cycloaddition of 1,6-enynes with 2-bromophenylboronic acids: synthesis of a multi-substituted dihydronaphthalene scaffold. *Chem. Commun.* **2009**, 5311-5313.

[15] Xianjie Fang, Xiaofeng Tong,* Palladium-Catalyzed Cyclization of 1,6-Enyne with 2-Bromoarylaldehyde: Domino Sequence to [5-7-6] Tricyclic Ring Systems. *Tetrahedron Lett.* **2010**, *51*, 317-320.

[16] Xianjie Fang, Junyao Sun and Xiaofeng Tong,* Rh(I)-catalyzed formal [2+2+2] cycloadditions of 1,6-diynes with potassium (*Z*)-(2-bromovinyl)trifluoroborate: a new strategy and a facile entry to polysubstituented benzene derivatives. *Chem. Commun.* **2010**, *46*, 3800-3802.

Patents

[1] Xianjie Fang, Ralf Jackstell, Matthias Beller, **102014201122DE** "Verfahren zur Katalytischen Herstellung von ungesättigten Aldehyden"

[2] Xianjie Fang, Ralf Jackstell, Armin Börner, Matthias Beller, **102014201126.4DE** "Verfahren zur Katalytischen Herstellung von symmetrischen und unsymmetrischen Ketonen"

Conference participations

[1] Poster "**Selective Palladium-Catalyzed Hydroformylation of Alkynes: Atom-Efficient Synthesis of *α,β*-Unsaturated Aldehydes**"
Xianjie Fang, Ralf Jackstell, Matthias Beller

at the 2nd International Symposium on C-H Activation, Rennes, France, June 30 – July 3 **2014**.