Palladium-catalyzed carbonylative synthesis of carboxylic acid anhydrides from Alkenes

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Introduction

1.1. Alkenes, CO and hydrocarbonylation

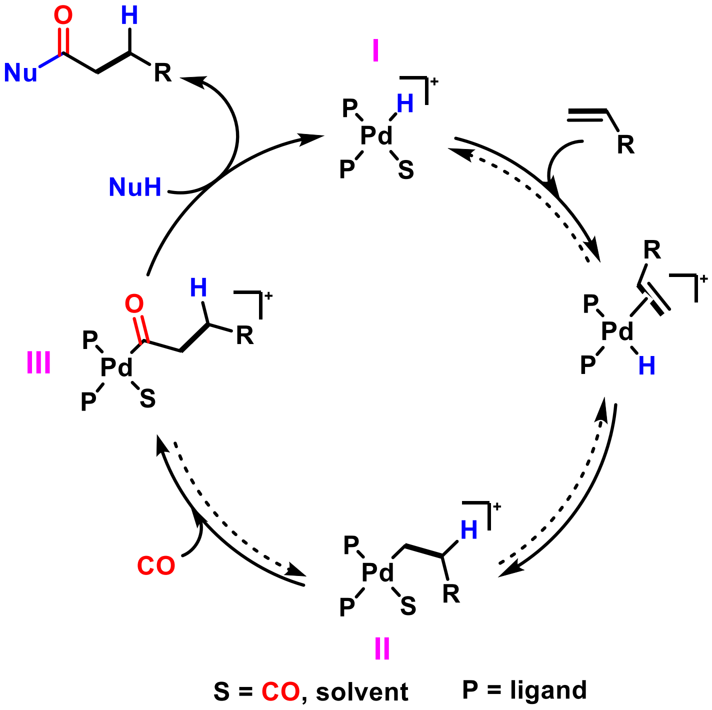
Alkenes are important molecules that can be procured from natural petrochemical or biomass resources, or produced synthetically using known procedures ranging from simple dehydration reactions to more advanced processes such as Wittig, Julia, Tebbe or Peterson olefination reactions. The versatile reactivity of carbon-carbon π bonds with numerous reagents renders them as a highly appealing motif in organic synthesis and catalysis, thus enabling access to a broad spectrum of organic molecules. Transition metals readily interact with alkenes, effectively coordinating with the π bond through σ-donation, where the olefinic C=C π-electrons donate to an empty metal *d* orbital, and subsequently, π-back donation may occur from a filled metal *d* orbital into the unoccupied C=C π^* orbital. This activation of the double bond by transition metals lies at the basis of homogeneous catalysis. Functionalization of alkenes by transition metals represents a highly efficient atom-economical and straightforward approach for generating new C-X (X=C, O, N, Si etc.) bonds. Therefore, metal-catalyzed functionalizations have emerged as powerful synthetic strategies for constructing complex carbon frameworks in recent years.

Carbon monoxide is one of the most important carbon-based reactants used in transition metal-assisted catalysis to form C-C bonds. It serves as a cheap and readily available C1 feedstock. The activation of CO for insertion in organic molecules is a crucial step aided by transition metal catalysts, and reactions involving the addition of CO are commonly known as carbonylation reactions.[1]

From the earliest known pioneering work of Walter Reppe in 1953,[2,3] catalytic carbonylation reactions of unsaturated compounds have found commercial application, with the production of propionic acid, adipic acid and methyl propionate being some of the well-known examples.[4] Classical Reppe-carbonylation reactions are based on three reactants - an unsaturated hydrocarbon (alkene or alkyne), CO and a nucleophile, and are usually catalyzed by a transition metal, mainly Ni, Fe, Ru, Co, Rh, Ir, Pd and Pt. Among these, palladium-based catalysts are the most active and versatile. Palladium(II) is one of several metal ions with d^8 electron configurations that tend to adopt square-planar geometries. With appropriate choice of ligands, one can generate an active palladium-based catalyst and tune the activity and regioselectivity with great ease.

In this Chapter, an overview is provided of important developments reported in recent years concerning palladium-catalyzed hydrocarbonylation reactions of alkenes with the nucleophiles alcohols, water, amines and thiols.

Proposed mechanism. The most generally accepted mechanism in hydrocarbonylation of alkenes is the palladium-hydride pathway (Scheme 1.1).[5,6] The cycle is initiated by formation of the active catalytic species, a palladium-hydride (**I**). The substrate alkene coordinates to the palladium-hydride center, and migration of the hydride results in an alkyl-palladium species (**II**). Coordination of CO and migration of the alkyl group generates an acyl-palladium intermediate (**III**). Finally, a nucleophilic attack results in formation of the product with regeneration of the active palladium-hydride species.



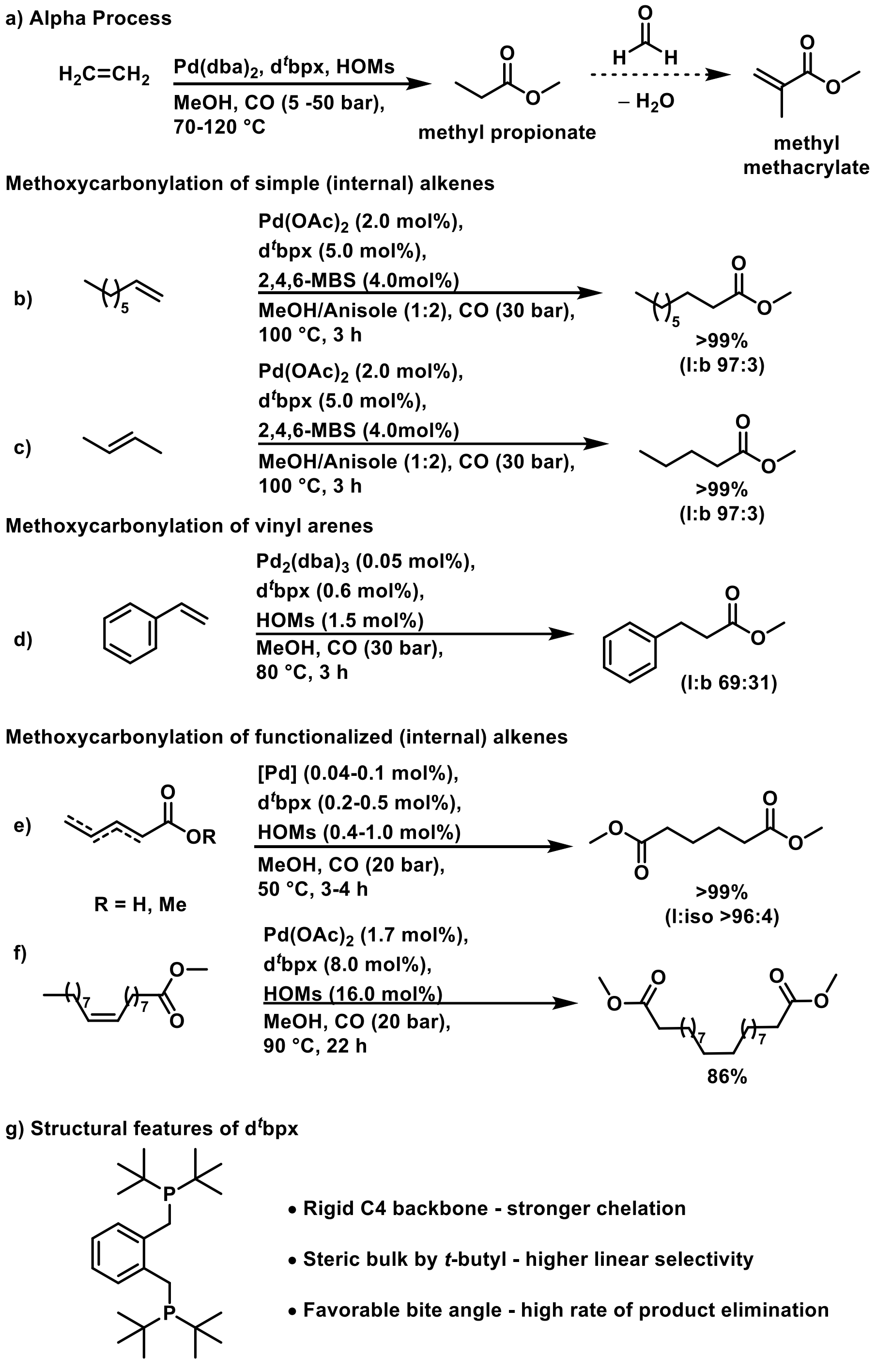
Scheme 1.1. Proposed palladium-hydride pathway as catalytic cycle in catalytic hydrocarbonylation of alkenes.

1.2. Hydroalkoxycarbonylation

Eminence of d^{t}bpx. Palladium-catalyzed hydroalkoxycarbonylation reactions generating esters from alkenes have found their application in synthesis of solvents, flavouring and fragrant agents, and plasticizers. The first step in the Lucite Alpha process, a two-step process to produce methyl methacrylate at 370,000 tonnes a year, involves a palladium-catalyzed hydromethoxycarbonylation of ethene to synthesize methyl propionate (Scheme 1.2.a).[7,8] The ligand used in this catalytic system is 1,2-bis(di-*tert*-butylphosphanylmethyl)-benzene (1,2-dtbpmb or d^{t}bpx). The active catalytic complex is formed by treating a palladium salt as a pre-catalyst with d^{t}bpx and a sulfonic acid, such as methanesulfonic acid (HOMs). Earlier reports by Tooze and co-workers describe high turnover frequencies (TOF) of 12,000 h^{-1} with a selectivity towards the ester product up to 99.9% without formation of any by-products.[9,10]

Drent and Jager investigated the same catalytic system for the hydromethoxycarbonylation of longer alkenes,[11] resulting in 97% selectivity for the linear ester of 1-octene (Scheme 1.2.b). Surprisingly, the same catalytic system aided in formation of linear esters up to 97% selectivity from 2-butene, an internal alkene (Scheme 1.2.c).[11] The ability to isomerize an internal alkene to produce a linear ester added an accolade to the remarkable properties of this ligand. Further, several groups including Cole-Hamilton and co-workers, and Eastham and co-workers demonstrated the high catalytic efficiency of the system and its high linear selectivity of methyl ester formation from 1-octene, 1-hexene and 1-dodecene under mild reaction conditions (pressure below 30 bar and temperature below 50 °C).[12] Some other substrates for which the catalytic system with d^{t}bpx led to high linear selectivities include styrene (Scheme 1.2.d)[13] and internal alkenes including methyl esters of pentenoic acid (Scheme 1.2.e),[14] oleic (Scheme 1.2.f)[15] and linoleic acid.[16] However, challenges arose in hydroalkoxycarbonylation of dienes such as 1,3-butadiene to 1,6-dimethyl adipate due to competing side reactions, notably dimerization and telomerization, and the requirement of higher catalyst loadings due to faster catalyst deactivation.[8]

Noteworthy features of d^{t}bpx. The efficiency of the palladium-based catalytic system with the ligand d^{t}bpx is attributed to the key features possessed by d^{t}bpx (Scheme 1.2.g). The C4 xylene-bridge backbone provides higher rigidity than a normal alkyl chain, improving the chelation strength of the ligand to the metal center and thereby the stability of the complex. The *tert*-butyl groups on the phosphorus atoms provide large steric bulk leading to preference for isomerization to the least-sterically demanding terminal carbon atom under a CO atmosphere. In addition to steric pressure, the relatively large bite angle of the ligand (~99.3° for a complex with Pd(OTf)$_2$)[8] is favorable to induce product elimination.

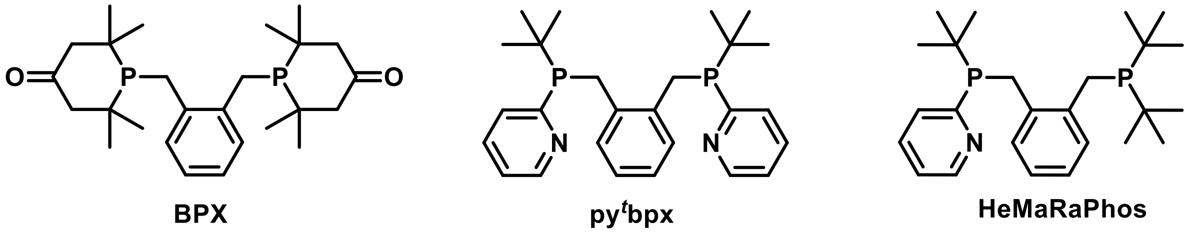


Scheme 1.2. Commercial application and selected examples of hydroalkoxycarbonylation of various alkenes mediated by palladium-d^{t}bpx catalytic system to synthesize linear esters.[9,11,13–15] Structural features of d^{t}bpx are highlighted.[8]

Congeners of d^{t}bpx. Based on the success of the ligand d^{t}bpx, several groups have undertaken endeavors to develop new ligands that give catalytic systems improved activities or selectivities (Figure 1.1.). van Meurs and co-workers introduced the novel diphosphine ligand 1,2-bis(4-phosphorinone)xylene (BPX).[17] Catalytic systems containing BPX gave results that were similar compared to that with d^{t}bpx in terms of isomerization and terminal regioselectivity of internal alkenes, but exhibited higher activity; e.g. in hydromethoxycarbonylation of 4-

octene, the turnover number (TON) reached with BPX and d^{t}bpx was 800 and 280, respectively, under the same catalytic conditions. The authors claimed that the structural features of the P atoms constrained in a six-membered heterocycle and the presence of an electron-withdrawing ketone group increases the electrophilicity of the Pd center, which results in increased catalytic activity.

Beller and co-workers developed the novel ligand 1,2-bis((*tert*-butyl(pyridin-2-yl)phosphanyl)methyl)benzene (py^{t}bpx) that proved effective in hydroalkoxycarbonylation of less-reactive alkenes such as tetramethylethylene.[18] The presence of the bulky *tert*-butyl group facilitates effective isomerization as discussed earlier, whereas the pyridyl group, inspired by the role played by diphenyl(2-pyridyl)phosphine in hydroalkoxycarbonylation of phenylacetylene,[19] would act as a proton-shuttle during the nucleophilic attack of the alcohol, facilitating the alcoholysis of the acyl-palladium species. With this rationale, Beller and co-workers introduced a series of novel diphosphine ligands with *tert*-butyl and pyridyl groups (or other bases) on the phosphorous atoms.[20] Moreover, dicarbonylation of conjugated dienes, considered cumbersome due to multiple challenges associated with its catalytic process, to adipate esters was achieved using a palladium-based catalytic system with the rationally designed, unsymmetrical diphosphine ligand “HeMaRaPhos”.[21]

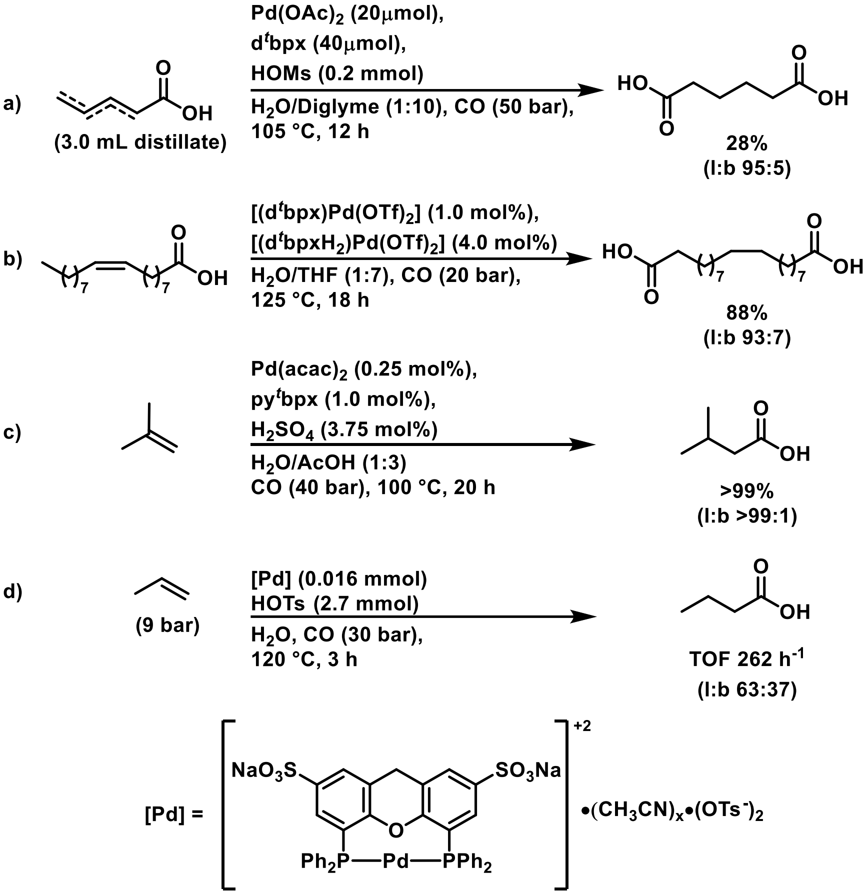


BPX **py^{t}bpx** **HeMaRaPhos**

Figure 1.1. Congeners of d^{t}bpx.

1.3. Hydrocarboxylation

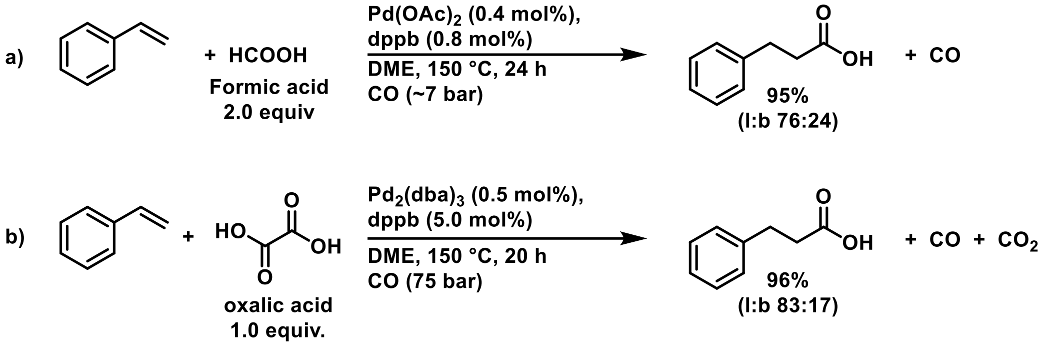
Phosphine ligands in hydrocarboxylation. The catalytic system composition for hydroalkoxycarbonylation has been applied to hydrocarboxylation as well. Catalytic systems involving Pd-d^{t}bpx and sulfonic acids have been demonstrated to be efficient in production of linear carboxylic acids. Rösch and co-wokers reported the use of this catalytic system to synthesize adipic acid from a distillate of pentenoic acid isomers with a selectivity of 95% (Scheme 1.3.a).[22] The catalyst has also been effectively used for the production of linear long-chain carboxylic acids from long-chain alkenoic acids with internal double bonds as reported by Mecking and co-workers (Scheme 1.3.b).[23] The catalytic system with py^{t}bpx introduced by Beller and co-workers was found to be more effective than d^{t}bpx in hydrocarboxylation of isobutene (Scheme 1.3.c).[24] Additionally, the acidic aqueous solution of the catalyst could be recycled and was shown to run 26 cycles of reactions without considerable loss of activity. Often hydrocarboxylation is performed in solvents which readily mix with water or in combination with a co-solvent that helps dissolution of water. Hydrocarboxylation in water as solvent creates issues in solubility of the phosphine ligands. The incorporation of functional groups, such as sulfonate groups (Scheme 1.3.d),[25,26] or guanidinium substituents[27] has led to the development of water-soluble phosphine ligands for the hydrocarboxylation of vinyl arenes. The acidic aqueous catalytic solutions containing sulfonate derivative of phosphine ligands could be recycled for further runs.[26]



Scheme 1.3. Selected examples of hydrocarboxylation of alkenes with water to generate linear carboxylic acids by use of palladium catalytic systems consisting d^tbpx/py^tbpx/a water-soluble phosphine ligand. [22–25]

Formic and oxalic acid as reactants. In hydrocarboxylation reactions the amount of water generally is in large excess to the alkene. Inconveniently, water may cause catalyst deactivation and palladium-black formation by oxidation of the phosphine ligands in the presence of carboxylic acids.[28,29] The use of formic or oxalic acid has allowed for hydrocarboxylation reactions to be performed in organic solvents in the absence of water. These molecules do not generate water *in situ* but produce the desired formation of carboxylic acids with release of CO.

The use of formic acid in hydrocarboxylation of alkenes has been reported by several groups (Scheme 1.4.a).[30–36] It is presumed that the catalysis involves a nucleophilic attack of the formate ion on an intermediate acyl-palladium species with the formation of a relatively unstable formyl mixed anhydride, which decomposes to give the corresponding carboxylic acid and CO. Apart from formic acid, oxalic acid has also been used in hydrocarboxylation of alkenes (Scheme 1.4.b).[32,37]



Scheme 1.4. Selected examples of hydrocarboxylation of alkenes with formic and oxalic acid to produce linear carboxylic acids.[30,32]

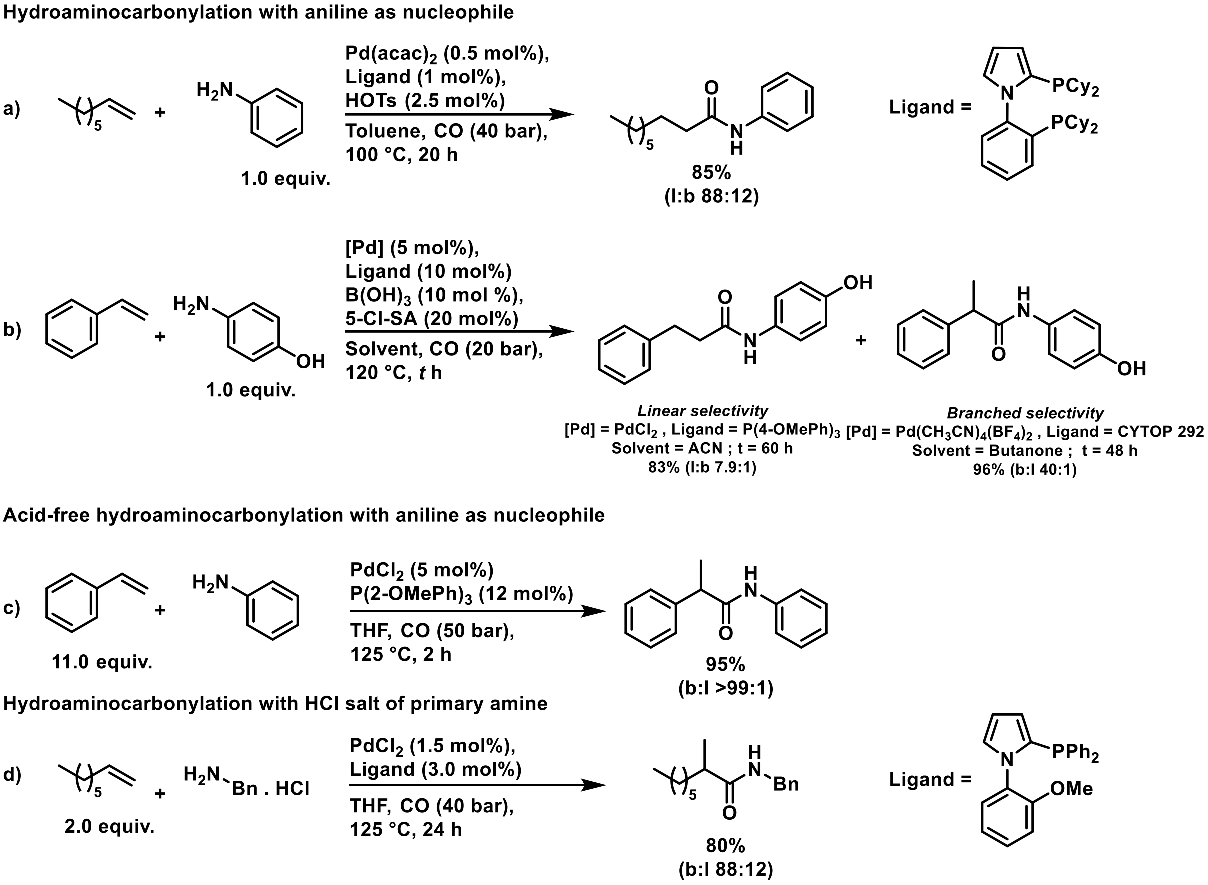
1.4. Hydroaminocarbonylation and hydroamidocabonylation

Secondary or tertiary amide synthesis. In contrast to hydroalkoxycarbonylation and hydrocarboxylation reactions, catalytic hydroaminocarbonylation has presented itself as a challenging task, with several factors playing a crucial role in determining the reaction's progress. Among these factors is the generation of the active palladium-hydride species that readily forms in acidic media, but whose formation may be hampered by the presence of amines. Hence, the basicity imparted by the amines and generation of active catalytic species need to be kept in check for catalysis to occur.

Use of anilines or aromatic amines ($pK_b \sim 9.4$) as nucleophiles do not hinder the formation of palladium-hydride species due to their low basicity. Earlier reports by Alper and co-workers described selective synthesis of five-, six- or seven- membered lactams from 2-vinyl- or allyl anilines.[38] Hydrogen gas rather than acid was used to generate the necessary key palladium-hydride species. Beller and co-workers developed a palladium-catalyzed hydroaminocarbonylation reaction of olefins with aromatic amines resulting in 88% linear selectivity when 1-octene was used as the substrate (Scheme 1.5.a).[39] Additionally, they demonstrated the synthesis of α,β-unsaturated amides from 1,3-diene substrates in a similar manner but without an acid additive.[40] Similarly, Dyson and co-workers also reported an acid-free reaction with the use of monophosphine ligands to yield the branched product selectively (Scheme 1.5.c).[41] The equivalents of alkene used was in large excess with respect to aniline

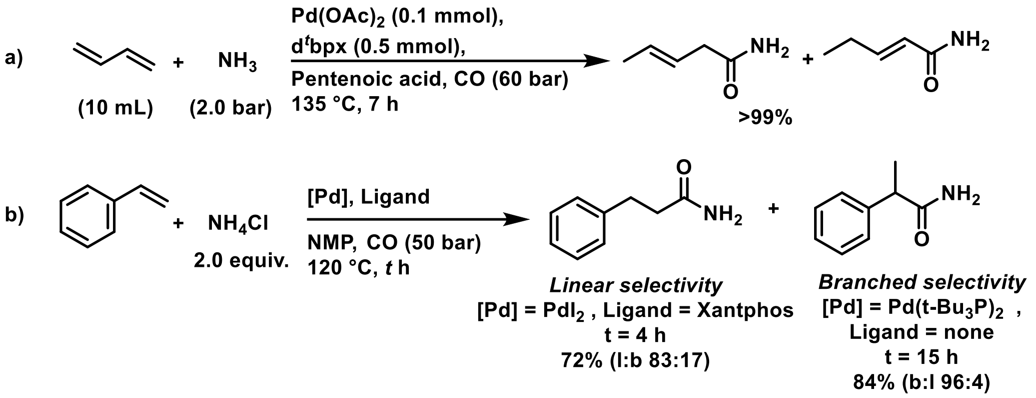
(11:1 alkene:aniline). However, no products were formed with aliphatic amines due to their high basicity. The group of Alper demonstrated hydroaminocarbonylation with aminophenols to prepare linear and branched products in high selectivity (Scheme 1.5.b).[42]

Beller and co-workers developed a new strategy for hydroaminocarbonylation, based on the use of the HCl salt of aliphatic amines rather than the amine alone or in the presence of additional acid (Scheme 1.5.d).[43] The selectivity for linear and branched products was determined by selection of the appropriate ligand.



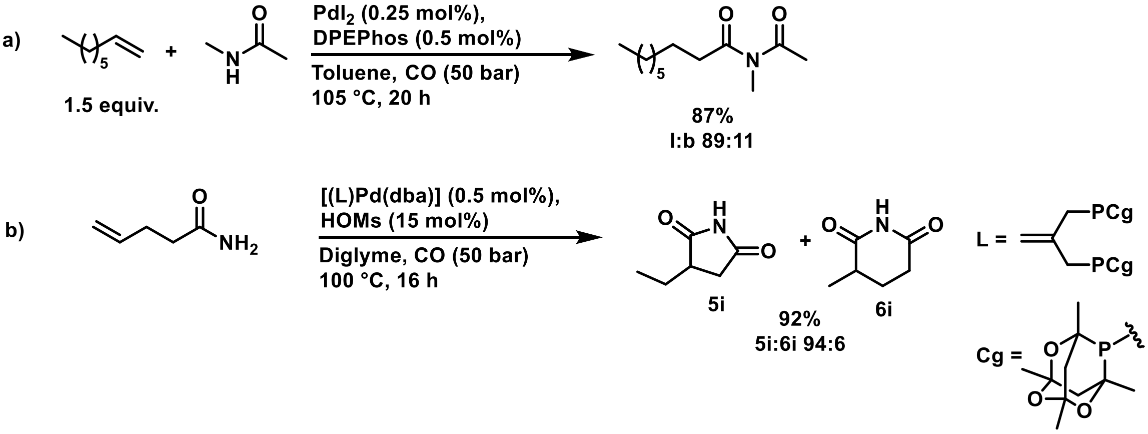
Scheme 1.5. Selected examples of hydroaminocarbonylation of alkenes with primary amines to generate secondary amides.[39,41–43]

*Primary amide synthesis. S*ynthesis of primary amides with ammonia comes with further challenges. Use of ammonia in transition-metal catalysis is limited due to formation of unreactive metal complexes.[44,45] Drent and co-workers reported successful hydroaminocarbonylation reaction of 1,3-butadiene with ammonia and CO in the presence of pentenoic acid as intermediate as well as solvent (Scheme 1.6.a).[46] Huang and co-workers reported the selective formation of primary amides from alkenes by using ammonium chloride instead of ammonia (Scheme 1.6.b).[47]



Scheme 1.6. Hydroaminocarbonylation of alkenes with ammonia (surrogate) to synthesize primary amides.[46,47]

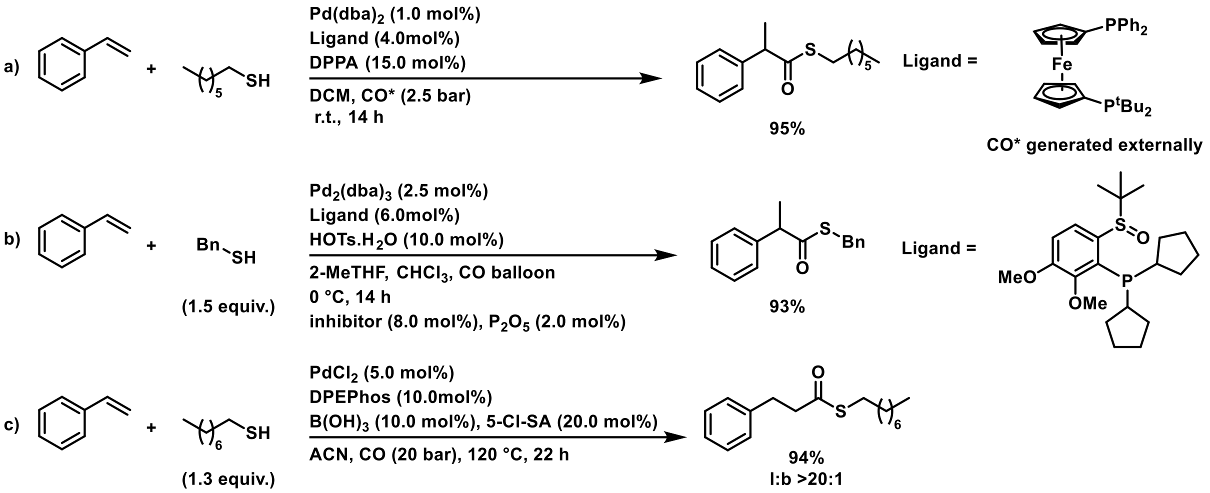
Imide synthesis. Amides as nucleophiles have been reported in the carbonylative synthesis of imides from alkenes (hydroamidocarbonylation). Beller and co-workers demonstrated hydrocarbonylation of simple alkenes[48] (Scheme 1.7.a) and 1,3-butadiene[49] based substrates with amides to form the corresponding imides. Bouwman and co-workers reported a cyclocarbonylation of pentenamides to synthesize cyclic imides (Scheme 1.7.b).[50]



Scheme 1.7. Hydroamidocarbonylation of alkenes with amide to synthesize imides.

1.5. Hydrothiocarbonylation

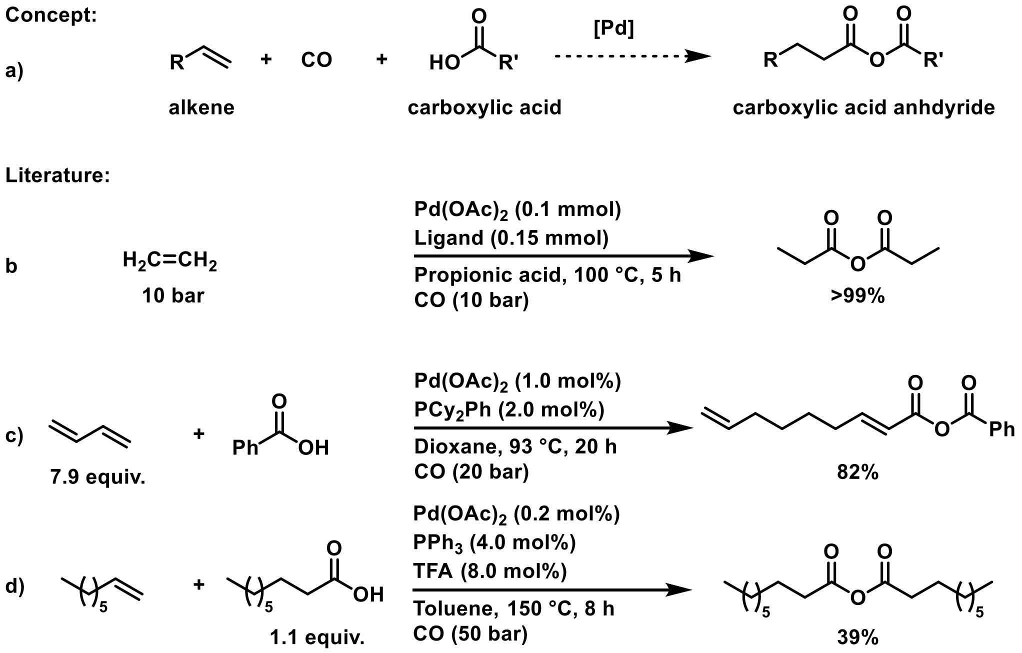
Hydrothiocarbonylation of alkenes to form thioesters has scarcely been reported due to the deleterious effect of thiols on palladium catalysts causing deactivation.[51,52] The reports by Drent and co-workers and Alper and co-workers describe thiocarbonylation of ethene with 1-pentanethiol (catalytic system: $Pd(OAc)_2/(4\text{-}MeOPh)_3P/HOTs$),[53] and of isoprene with thiophenol (catalytic system: $Pd(OAc)_2$/dppp),[54,55] respectively. Fleischer and co-workers demonstrated thiocarbonylation of vinyl arenes in ambient conditions (CO generated *ex situ*) achieving high yields of the branched product (Scheme 1.8.a).[56] Liao and co-workers reported enantioselective thiocarbonylation of styrene employing the chiral ligand, (P-dialkyl)-phosphines with a chiral sulfoxide group (Scheme 1.8.b).[57] Synthesis of linear thioesters from alkenes including vinyl arenes was reported by Wu and co-workers resulting in good yields and selectivity by employing a palladium-based catalytic system containing DPEPhos and a combination of $B(OH)_3$ and 5-chloro-salicylic acid (5-Cl-SA) as acid additives (Scheme 1.8.c).[58]



Scheme 1.8. Recent examples of thiocarbonylation of alkenes with thiols.[56,58,59]

1.6. Hydroacyloxycarbonylation – concept and scope

Carbonylative synthesis of acid anhydrides from alkenes (hydroacyloxycarbonylation, Scheme 1.9.a) involves the use of carboxylic acids as a nucleophile and this comes with its own challenges. Compared to alkoxides or hydroxides, carboxylates are relatively weak nucleophiles. Although the acidity of the reaction mixture for generation of palladium-hydride is maintained, the major challenge lies in the activation of the carboxylic acid. Literature pertaining to carbonylative synthesis of acid anhydrides from alkenes is limited till date. To the best of our knowledge, three palladium-catalyzed synthesis of linear alkyl acid anhydrides from alkenes have been reported. These include i) preparation of propionic acid from ethene demonstrated by Drent and co-workers (Scheme 1.9.b),[60,61] ii) carbonylative telomerization of 1,3-butadiene with benzoic or acetic acid recently reported by Seidensticker and co-workers (Scheme 1.9.c),[62] and iii) synthesis of nonanoic anhydride reported by Leitner and co-workers (Scheme 1.9.d).[63] Though detailed investigation on carbonylative telomerization of 1,3-butadiene has been reported, formation of acid anhydrides from simple alkenes have not been studied in great detail. Some of the unexplored studies include the reason for low yields in synthesis of symmetric linear alkyl anhydrides (except in case of ethene), regioselectivity of catalysis or composition of the anhydrides formed in the reaction mixture, a substrate scope – tolerance of the catalytic system to functional groups and differences in reaction conditions from established alkoxy- or hydroxycarbonylation reactions.



Scheme 1.9. Concept and reported palladium-catalyzed methods of hydroacyloxycarbonylation.

1.7. Aims and outline of this thesis

Carboxylic acid anhydrides portray an array of interesting molecules to access. Carbonylative synthesis of acid anhydrides offers a highly atom-economic and sustainable alternative for classical organic approaches by minimizing use of hazardous reagents, reducing waste generation and promoting energy efficiency. The aim of the research described in this thesis is three-fold:

i) To study and investigate the factors governing the palladium-catalyzed synthesis of acid anhydrides from alkenes.

ii) To optimize the reaction conditions to achieve good yields and selectivity.

iii) To overcome synthetic challenges faced in hydrocarbonylation chemistry with nucleophiles that deactivate the catalytic system by providing a one-pot derivatization of the formed anhydrides.

The development of a palladium catalyzed carbonylative synthesis of carboxylic acid anhydrides from alkenes and carboxylic acids is described in **Chapter 2**. It was found that the reaction for the substrate styrene with 3-phenylpropionic acid is an equilibrium, which could be shifted further to the product side by changing the relative amounts of alkene and carboxylic acid. A ligand-screening study revealed the use of electron-poor phosphine ligands to be crucial for obtaining higher rates of the catalytic reaction. The results described in Chapter 2 also highlight the complications that arise by disproportionation of the acid anhydrides and their effect on analysis of the reaction mixtures. The developed synthetic method was applied to the synthesis of symmetric and mixed carboxylic acid anhydrides. It was shown that by a simple one-pot derivatization, the anhydrides formed can be converted to an amide, ester or thioester.

In **Chapter 3**, formation of carboxylic acid anhydrides from alkenes without the need of the corresponding carboxylic acid is described. Formic acid was used to prepare highly unstable formate-based mixed anhydrides from alkenes, using the optimized conditions described in Chapter 2. These formate-based mixed anhydrides decompose to form the carboxylic acid and CO, as described in Section 1.3, and the formed acid subsequently acts as a nucleophile to form the acid anhydrides - overall from at least two equivalents of the alkene and one equivalent of formic acid. It is shown that the acid anhydrides formed from this catalytic reaction can be converted by simple derivatization reactions, to form amides, esters, thioesters and ketones.

The knowledge gained in hydrocarbonylation catalysis with carboxylic acid as the nucleophile was applied to the cyclocarbonylation of pentenoic acids (PEA), as described In **Chapter 4**. The sustainable formation of adipic anhydride, a potential intermediate in caprolactam synthesis for nylon-6 production, from biomass-derived pentenoic acid is our target of interest. The study describes the parameters, phosphine ligands and anions (also derived from using acid additives), that influence the selective formation of ethyl succinic anhydride (five-membered ring, **5a**), methyl glutaric anhydride (six-membered ring, **6a**) and adipic anhydride (seven-membered ring, **7a**) from 4-pentenoic acid (4-PEA). **7a** could be obtained up to 73% yield with a **7a**:**6a** selectivity of 79:21 using a palladium catalytic system in absence of strong acids. However, the same catalytic system produces **6a**:**5a** in a ratio of 41:59 from 3-pentenoic acid (3-PEA) as substrate, deeming the catalytic system "non-isomerizing". In the presence of strong acids, isomerization occurs and results in the formation of predominantly **5a** and **6a**. Isomerizing catalysts consisting phosphines containing bulky *tert*-butyl groups, known for their selectivity in formation of linear carboxylic/ester from PEA, did not assist in formation of **7a**, but resulted in very low activity of the catalyst. In addition, Chapter 4 also highlights the side reactions that occur in the selective carbonylative synthesis of adipic anhydride which leads to loss in yield and mass balance, and how varying [Pd]:substrate ratio can lower the extent of these losses.

Finally, in **Chapter 5**, an overview is provided of the notable findings obtained from this research, followed by a conclusion and an outlook on future perspectives.

1.8. References

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