Palladium-catalyzed carbonylative synthesis of carboxylic acid anhydrides from Alkenes

Ramakrishnan, A.

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Summary, Conclusions and Outlook

5.1. Summary

In this thesis results are described of an investigation to the feasibility and efficiency of a novel type of catalytic carbonylation reaction involving the use of carboxylic acids as nucleophile, with the ultimate aim to synthesize adipic anhydride from pentenoic acid. **Chapter 1** provides an overall picture of the palladium-catalyzed hydrocarbonylation reaction of alkenes with nucleophiles such as alcohols, water, amines and thiols to synthesize useful acyl-containing molecules such as esters, carboxylic acids, amides and thioesters.

The chapter highlights the remarkable properties of the commonly used phosphine ligand 1,2-bis(di-*tert*-butylphosphanylmethyl)benzene (d^{t}bpx), used in hydroalkoxycarbonylation and hydrocarboxylation reactions with alcohols or water as nucleophiles to synthesize linear esters or carboxylic acids. d^{t}bpx is used in commercial industrial applications such as the Lucite Alpha process for the production of methyl methacrylate. The structural features of d^{t}bpx, the rigid backbone and bulky groups at phosphorus, allow for the formation of linear products even from internal alkenes. Inspired by its exceptional performance, several other ligands have been developed, for example for selective synthesis of adipic acid esters from 1,3-butadiene.

The formation of amides or thioesters *via* catalytic carbonylation reactions requires use of amines, ammonia or thiols as nucleophiles. However, these nucleophiles come with specific challenges, caused by the basicity of the amines (hindering formation of the required palladium-hydride species), or the strong binding of thiols to the catalytic center (poisoning catalysis).

Hydrocarbonylation reactions of alkenes with formic or oxalic acid as reagents have also been reported. The acid reactant serves as a nucleophile to the acyl-palladium intermediate with the formation of highly unstable formate- or oxalate-based anhydrides, which decompose to give the corresponding carboxylic acid with the release of CO (and CO_2 for oxalic acid).

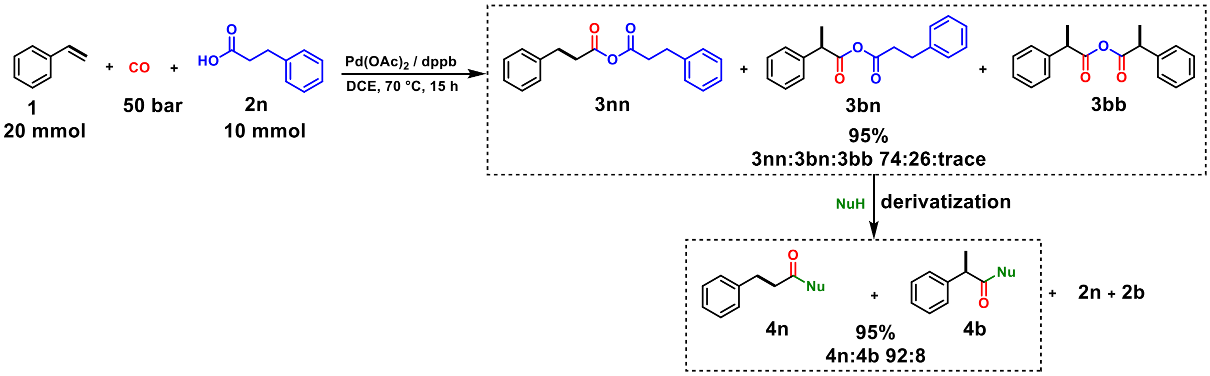
Carboxylic acid (or carboxylates) are considered to be weak nucleophiles, compared to alkoxides and water, and this low nucleophilicity may pose a challenge for their reactivity with an acyl-palladium intermediate. Only few reports describe the use of carboxylic acids as nucleophiles to synthesize acid anhydrides and the substrate scope reported for this challenging reaction is limited. Generally, the yield reported for the synthesis of acid anhydrides is rather low, with the exception for the formation of propionic anhydride from ethene and propionic acid. Hence, to overcome the challenges and develop a synthetic method, this thesis presents the study of the carbonylation reaction with carboxylic acids as nucleophiles (hydroacyloxycarbonylation) to generate acid anhydrides.

A facile and efficient catalytic method to synthesize carboxylic acid anhydrides is reported in **Chapter 2**. Formation of acid anhydrides at temperatures below 85 °C was demonstrated, using a catalytic system of Pd(OAc)$_2$/dppb (dppb = 1,4-bis(diphenylphosphanyl)butane), taking styrene (**1**) and 3-phenylpropionic acid (**2n**) as model substrates. A temperature of 70 °C was found to be optimal using 1,2-dichloroethane (DCE) as the solvent at 50 bar CO pressure, resulting in the desired anhydrides in a yield of ~65% from equimolar amounts of substrates. Temperatures higher than 85 °C led to substantial loss in mass balance, due to polymerization of **1**.

Attempts to improve the yield by increasing catalyst loading or use of acid additives were unsuccessful. The calculated Gibbs free energy ($\Delta G_{\text{gas-phase}}$) of the reaction indicated that the reaction is slightly endergonic, which we ascribe to limitations of the computational method. This outcome essentially suggests that the reaction most likely is an equilibrium. Indeed, increased yields were obtained when using higher CO pressures at equimolar ratio of substrates or by changing the relative substrate ratio at a certain CO pressure. Furthermore, formation of styrene was observed when anhydride **3** was subjected to catalytic conditions, confirming reversibility of the reaction. A total yield of anhydride **3** of 95% was attained when employing a 2:1 ratio of **1**:**2n** (at 50 or 65 bar CO; Scheme 5.1).

NMR analysis of the reaction mixture showed the presence of the linear-linear symmetric (**3nn**) and branched-linear mixed (**3bn**) anhydrides in a ratio of 74:26, with traces of branched-branched symmetric anhydride (**3bb**). Derivatization of the catalytic reaction mixture with pyrrolidine resulted in 95% amide **4** (92:8 **4n**:**4b**), due to preferential activation at the linear acyl group of **3bn**. Several ligands were tested in the optimized catalytic conditions to investigate which features of these ligands dictate conversion and regioselectivity. It was found that use of the electron-rich phosphine ligand d^{t}bpx, unfortunately, did not yield any product. The rate of the reaction appeared to be highest when using common, phenyl-substituted ligands; the use of dppb resulted in the highest conversion and a linearity of ~80%. Use of the rigid, xylene-bridged analog resulted in high selectivity for the linear products, but unfortunately led to lower reaction rates.

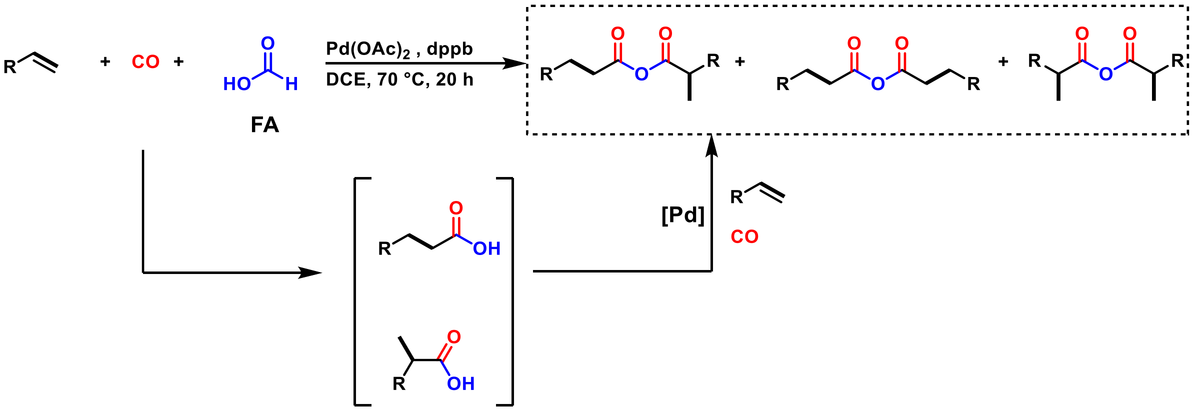
The optimized catalytic conditions were applied to a wide range of alkenes and carboxylic acids, resulting in symmetric as well as mixed anhydrides in moderate to high yields. The utility of this new catalytic procedure was demonstrated by the production of a primary amide and thioester, which are challenging to obtain through a direct hydrocarbonylation reaction, *via* a simple one-pot derivatization reaction of anhydride **3** with ammonia and benzylthiol.



Scheme 5.1. Palladium-catalyzed synthesis of acid anhydrides from alkenes and carboxylic acids.

In **Chapter 3**, we describe the results of our investigation to synthesize carboxylic anhydrides from alkenes by *in situ* generation of their corresponding C_{n+1} carboxylic acid by using formic acid (FA) (Scheme 5.2). Carbonylation of an alkene in presence of FA results in formation of an unstable formate anhydride, which decomposes to the desired carboxylic acid. The newly formed carboxylic acid then acts as nucleophile in a second carbonylation reaction of the alkene, ultimately producing an acid anhydride from two equivalents of alkene and one equivalent of FA.

Taking styrene **1** as the model substrate and using **1**:FA at 2:1 ratio yielded 70% acid anhydride **3**, employing the catalytic system developed in Chapter 2. The composition of the anhydrides **3nn**:**3bn**:**3bb** was found to be approximately 60:35:5 based on NMR analysis, indicating an overall linearity of ~80% for the carbonylation reaction. Use of various ligands in the catalytic system resulted in only small differences in regioselectivity of the reaction. However, the conversion varied substantially, with the use of dppb resulting in the highest yield amongst the ligands that were investigated. The catalytic procedure appeared to be applicable to a broad spectrum of alkenes with various functional groups, resulting in moderate to high yields of



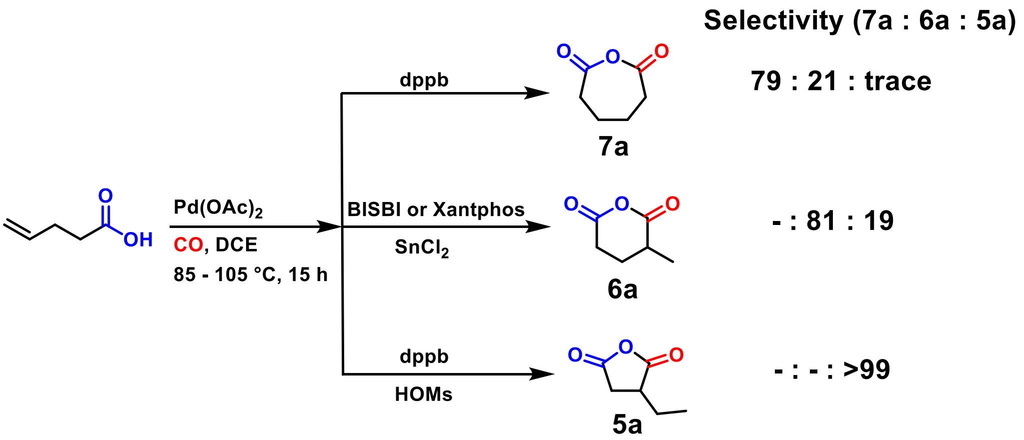
Scheme 5.2. Palladium-catalyzed synthesis of acid anhydrides from alkenes via *in situ* generated carboxylic acids.

linear amides upon derivatization. The practical value of the catalytic procedure was exemplified by one-pot derivatization reactions of the reaction mixtures with various nucleophiles to yield a primary amide, a bulky thioester and phenolic ester, as well as products such as ketones *via* Suzuki coupling or Friedel-Crafts acylation reactions.

A study on the synthesis of cyclic anhydrides from pentenoic acids (PEAs) is described in **Chapter 4**. Cyclocarbonylation of PEA leads to the formation of five-, six- or seven-membered cyclic anhydrides (Scheme 5.3, **5a**, **6a** or **7a**; numbering relates to ring-size), depending on the regioselectivity of the catalytic system. However, undesired intermolecular and disproportionation reactions result also in formation of pentenoic anhydride (4-PEAn), adipic acid, and oligomeric products. An acceptable mass balance with rather good yields of desired cyclic products could be achieved by employing relatively dilute reaction conditions.

Products **7a** and **6a** were obtained in moderate to good yields, starting from 4-PEA as substrate and employing palladium-based catalytic systems in absence of strong acid. Cyclic anhydrides were obtained in 73% yield with **7a**:**6a** selectivity of ~80:20 using $Pd(OAc)_2$/dppb as the catalytic system. Applied to 3-PEA, this catalytic system resulted in the formation of **6a** and **5a** in the ratio 41:59, indicating that the system in absence of acid does not catalyze isomerization of the double bond.

The addition of strong acids indeed causes isomerization of 4-PEA to internal alkenes with the formation of smaller rings **5a** or **6a** in relative amounts related to the strength of the acid used; relatively weak acids result in higher selectivity towards **6a,** while addition of strong acids favors formation of **5a**. Since isomerization is an integral feature necessary to obtain **7a** from a mixture of PEA isomers, catalytic systems with bulky phosphine ligands and acid additives are required. Unfortunately, the ligands that were tested in such reaction conditions all resulted in



Scheme 5.3. Carbonylation of pentenoic acid to synthesize cyclic anhydrides.

selectivity for **6a** or **5a** rather than **7a**, as the catalytic system comprising the benchmark ligand with *tert*-butyl groups performs poorly in our reaction.

5.2. General Conclusions

The aim of the research described in this thesis was to develop a hydrocarbonylation reaction to synthesize carboxylic acid anhydrides from alkenes. This reaction appeared to be an equilibrium with low energy gain, depending on the substrate alkenes and carboxylic acid reagents. The major challenge of this hydrocarbonylation reaction is the low nucleophilicity of carboxylic acids and carboxylate ions, and thus their poor reactivity towards carbonyl carbon atoms. Use of a palladium-based catalytic system comprising the well-known ligand d^{t}bpx, with electron-donating *tert*-butyl groups, led to very poor yields of acid anhydrides due to low reaction rates (Chapters 2, 3 and 4). In contrast, use of common, relatively electron-poor, phenyl-substituted phosphine ligands resulted in moderate to good yields of acid anhydrides. It has been suggested that use of electron-poor phosphines are essential for coordination and thus activation of weakly nucleophilic reagents to react with the acyl-palladium species.[1]

The intramolecular reaction described in Chapter 2 is inhibited by the presence of sulfonic acids or chloride salts. With our additive-free procedure, symmetric anhydrides can be prepared in good to excellent yields from alkenes and their corresponding C_{n+1} carboxylic acid as the nucleophilic reagent. If the carboxylic acid corresponding to the alkene is not commercially available, pivalic acid or 2,4,6-trichlorobenzoic acid can be used as the nucleophile yielding mixed anhydrides. Notably, synthesis of symmetric acid anhydrides can also be achieved from two equivalents of the alkene with the use of formic acid as the nucleophile, which aids in the generation of the necessary carboxylic acid *in situ*, as described in Chapter 3.

The catalytic reaction mixtures can be taken further in a one-pot derivatization reaction with various nucleophiles, to access esters, amides, thioesters or ketones. This two-step procedure eliminates the need of different catalytic conditions for the synthesis of each product from the alkene and avoids deactivation of the carbonylation catalyst by nucleophiles such as amines or thiols. The mixed anhydrides obtained with pivalic acid or 2,4,6-trichlorobenzoic acid can selectively be converted to the desired products *via* such derivatization reactions, yielding the amide product derived from the alkene and pivalic acid or 2,4,6-trichlorobenzoic acid as the leaving group.

The synthesis of **7a** from 4-PEA was demonstrated in absence of strong acids (non-isomerizing conditions; Chapter 4). The use of dilute reaction conditions is important in order to avoid mass-balance losses due to formation of 4-PEAn and oligomeric products *via* intermolecular reactions. Interestingly, and in contrast to the intermolecular reaction described in Chapter 2, this intramolecular reaction also proceeds in presence of strong acids. The use of strong acids is necessary to induce isomerization activity of the catalytic system, in order to be able to synthesize the desired **7a** from a mixture of PEA isomers. Unfortunately, so far a suitable ligand for this conversion has not been found. The use of sterically hindered phosphine ligands with electron-donating substituents (d^{t}bpx) in presence of strong acid resulted in formation of **6a** in low yields.

5.3. Outlook

Acid anhydrides may serve as reagents for acylation of various nucleophiles. Transformation of alkenes with formic acid to produce symmetric anhydrides is advantageous if the corresponding carboxylic acid is not readily available, especially when a particular acylating reagent needs to be generated for an expensive nucleophile. On the other hand, when complete conversion of an expensive alkene to an acylated product is required, synthesis of a mixed anhydride of this alkene with e.g. pivalic acid or 2,4,6-trichlorobenzoic acid will be the most efficient strategy. For this specific application, nucleophiles should selectively react at the alkene-derived end of mixed anhydrides with the release of the used carboxylic acid, which then can be reused for the next cycle of catalysis.

The reaction of **1** with **2n**, formic acid, pivalic acid or 2,4,6-trichlorobenzoic acid (Chapters 2 and 3) resulted in different yields of the respective anhydrides, as reflected in the different yields of the amide derivatives after workup. These different yields might be caused by steric bulk of the carboxylic acid (e.g. pivalic acid) leading to lower reaction rates. Additionally, the various mixed anhydrides may be prone to faster or slower disproportionation reactions, leading to different ratios of symmetric and mixed anhydrides. Finally, the outcome and efficiency of the derivatization reaction will be determined by the steric or electronic properties of the carboxylic acid that acts as leaving group. A future study should be directed to the use of different (commercially available) carboxylic acids as reagent in the formation of mixed anhydrides, in order to find the optimal acid nucleophile for achieving high conversion of alkene substrates. Furthermore, use of this ideal acid should result in mixed anhydrides that do not disproportionate under catalytic conditions, and that react with nucleophiles selectively at the alkene-derived acyl group.

For application of both the inter- and intramolecular carbonylation reaction with carboxylic acid nucleophiles, primarily the catalytic conditions and catalytic system need further investigation. The solvent employed in our studies, DCE, is a potential environmental pollutant and undesirable for application in industrial processes; a search for a greener solvent for use in these carbonylation reactions is essential. Catalyst loadings were used up to 2.5 mol% for the synthesis of mixed anhydrides with pivalic acid or unactivated alkenes and 5 mol% for the formation of **7a** in cyclocarbonylation of 4-PEA. Although the use of relatively high catalyst loadings may be acceptable for synthesis and application of anhydrides as acylation reagents in the fine-chemical industry, e.g. for the synthesis of drugs, significantly lower catalyst loadings are crucial for potential industrial development of cyclocarbonylation of pentenoic acids or pentenamides as alternative routes for the production of caprolactam.

Relatively high catalyst loadings were used in order to attain sufficiently high reaction rates and conversion within an acceptable reaction time. It was shown that the rate of the reactions is strongly influenced by the electronic properties of the ligand used in the catalytic system. Use of electron-donating ligands with *tert*-butyl-substituted phosphorus atoms lead to very slow reactions, whereas relatively electron-poor ligands with phenyl-substituted ligands lead to higher reaction rates.

Thus, in order to be able to lower the catalyst loading and still achieve an acceptable rate of reactions, future investigations should be directed to the development and application of ligands that combine strongly electron-withdrawing electronic properties with the steric bulkiness of *tert*-butyl groups. We envision that the desired phosphine ligand should have a similar backbone to d^{t}bpx in structure, i.e. a xylyl bridge for rigid *cis*-coordination and a relatively large coordination angle. In addition, the ligand should have substituents on the phosphorous atoms with the following properties: i) electron-withdrawing nature – prerequisite for activation of poorly nucleophilic carboxylic acids or amides; ii) sterically bulky – for isomerization to terminal products under isomerizing conditions.

A large number of bidentate ligands with large coordination angles and electron-withdrawing phosphite groups have been developed for hydroformylation catalysis.[2,3] The use of these phosphite ligands in hydrocarbonylation reactions with poor nucleophiles such as carboxylic acids and amides should be investigated, determining their stability in the acidic reaction conditions and their efficiency in catalysis. On the other hand, new phosphine ligands may be developed in which the common -CH$_3$ groups are substituted, leading to d^{t}bpx-derived ligands with one or more -CF$_3$ groups, such as shown in Figure 5.1. Another alternative structural modification to be tested would be replacing $-P(^{t}Bu)_2$ with $-P(CF_6)_2$ based on the similar Tolman cone angle of their corresponding monophosphines, $P(^{t}Bu)_3$ and $P(CF_6)_3$. Perhaps such phosphine ligands may not only assist in converting PEA mixtures selectively to **7a**, but also aid in carbonylation of internal alkenes with weak nucleophiles to synthesize linear products.

Only by addressing these general challenges (lower catalyst loading and greener solvent such as anisole or Me-THF), the production of **7a** from PEA isomers can serve as a potential bio-based derived route to caprolactone or caprolactam on an industrial scale.

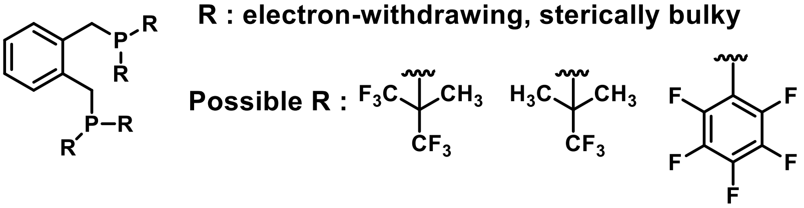


Figure 5.1. Postulated desired phosphine ligand for selective synthesis of **7a** under isomerizing conditions.

5.4. References

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