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Citation

Ramakrishnan, A. (2023, December 19). *Palladium-catalyzed carbonylative synthesis of carboxylic acid anhydrides from Alkenes*. Retrieved from https://hdl.handle.net/1887/3674100

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Palladium-Catalyzed Synthesis of Carboxylic Acid Anhydrides from Alkenes

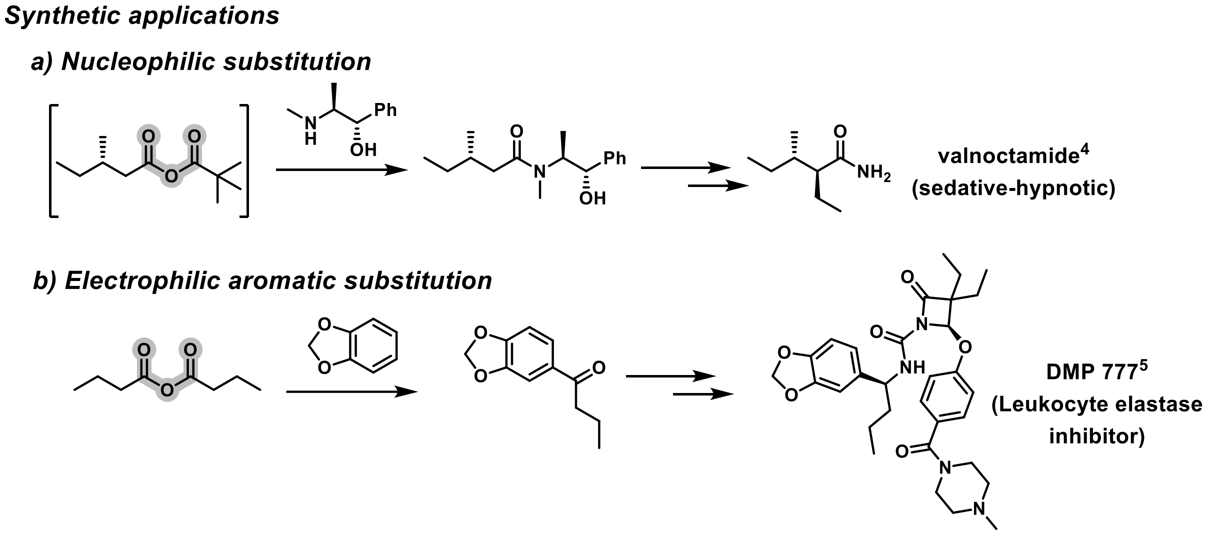
Hydrocarbonylation of alkenes with nucleophiles – water, alcohols and amines, is widely studied and implemented in synthesis of fine chemicals and natural products. Here, an efficient and additive-free palladium-catalyzed hydrocarbonylation reaction of alkenes is described using carboxylic acids as the nucleophile, by which acid anhydrides are obtained in moderate to excellent yields. The relative concentrations of substrate and reagents play an important role in driving the reaction forward, which reaches an equilibrium at equimolar concentrations under a given CO pressure. A ligand-screening study revealed the use of electron-poor phosphine ligands to be crucial for obtaining higher rates of the catalytic reaction. Several substrates including unactivated alkenes were successfully converted to the corresponding symmetric as well as mixed anhydrides. An additional advantage of our synthetic procedure is that the obtained anhydrides can be converted to (primary) amides, thioesters or esters in situ via a simple one-pot derivatization reaction, since acid anhydrides are prone to degradation on isolation.

This chapter has been accepted for publication:

Ramakrishnan A.; Romeijn S.G.; Bouwman E. Palladium-catalyzed synthesis of carboxylic acid anhydrides from alkenes, J. Catal. ***2023****, in press, DOI: 10.1016/j.jcat.2023.115192.*

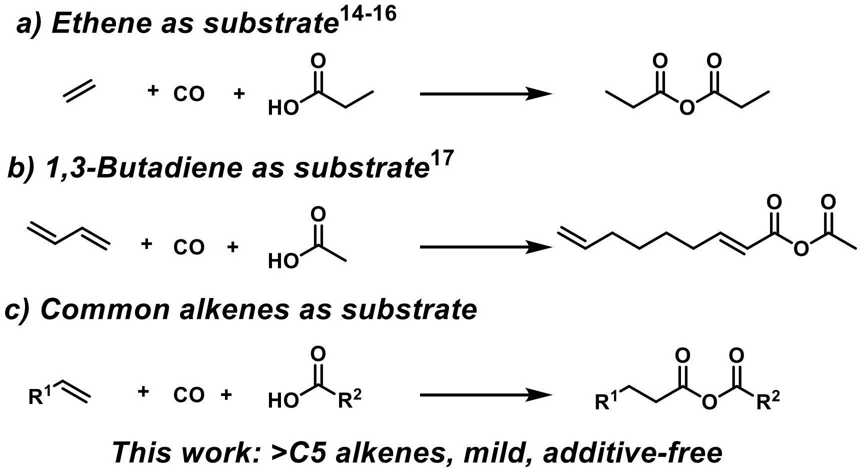
2.1. Introduction

Carboxylic acid anhydrides are important activated forms of carboxylic acids. In a survey reported by Sheppard and co-workers, it was found that 16% of the total procedures for amide bond formation above 300 gram scale within Glaxo-Smith-Kline (GSK) are achieved *via* acid anhydrides.[1] Anhydrides have traditionally served as popular acylating reagents in amide coupling reactions employed in peptide chemistry,[2,3] and the nucleophilic substitution of the acyl group in carboxylic acid anhydrides is one of the classical strategies in synthesis of esters, thioesters and amides. Several pharmaceutically relevant molecules are prepared from mixed anhydrides of the relevant carboxylate with pivalic acid, for cheaper and more selective nucleophilic substitution reactions. For example, Li and co-workers reported activation of a precursor acid by the formation of a mixed anhydride with pivalic acid; reaction of this anhydride with pseudoephedrine is one of the steps in the synthesis of Valnoctamide, a mild sedative (Scheme 2.1.a).[4] Anhydrides can also be used in electrophilic aromatic substitution reactions, as shown for the synthesis of DMP 777 (Scheme 2.1.b).[5]



Scheme 2.1. Examples of acid anhydrides as intermediates or reagents in synthetic procedures.

The conventional synthesis of anhydrides involves a reaction between a carboxylate salt and acyl chloride,[6] although several methods are described using reagents such as DCC,[7] thionyl chloride,[8] Boc-anhydride/$MgCl_2$[9] or by light activation.[10] The process of transition-metal catalyzed carbonylation has gained attention as efficient, environmentally benign and highly atom-economical procedure for the synthesis of complex molecules from alkenes using carbon monoxide as C1 building block. Hydrocarbonylation reactions involving nucleophiles such as alcohols, water, and amines have been studied in great detail.[11–13] Although palladium-catalyzed carbonylation chemistry is well documented, the carbonylative synthesis of anhydrides (hydroacyloxycarbonylation) has never been studied in detail; reports on this reaction are scarce. Drent and co-workers reported the palladium-catalyzed synthesis of propionic anhydride from ethene and propionic acid,[14,15] and Zoeller and co-workers reported the same reaction catalyzed by molybdenum (Scheme 2.2.a).[16] Synthesis of mixed anhydrides by carbonylative telomerization of 1,3-butadiene with benzoic or acetic acid was recently reported by Seidensticker and co-workers (Scheme 2.2.b).[17] In the course of our research, a study was reported on the synthesis of long chain alkyl anhydrides *via* palladium/triphenylphosphine-catalyzed carbonylation of alkenes with carboxylic acids in the presence of acid additives, resulting in nonanoic anhydride in a rather low yield of 40%.[18] The rather limited studies on hydroacyloxycarbonylation till date prompted us to investigate and address the underlying synthetic challenges. The main challenge of the reaction appears to be the low nucleophilicity of the carboxylate ion, to perform the necessary attack at a carbonyl carbon bound to the palladium center. The nucleophilicity of a carboxylate ion can be 10^6 folds lower than that of hydroxide, which by itself is a weaker nucleophile than an alkoxide and amine.[19] Resonance stabilization caused by the delocalization of the negative charge over the two oxygen atoms contributes to the low reactivity. We herein present an efficient and additive-free palladium-catalyzed synthesis of carboxylic acid anhydrides from alkenes that is applicable to a wide range of substrates.

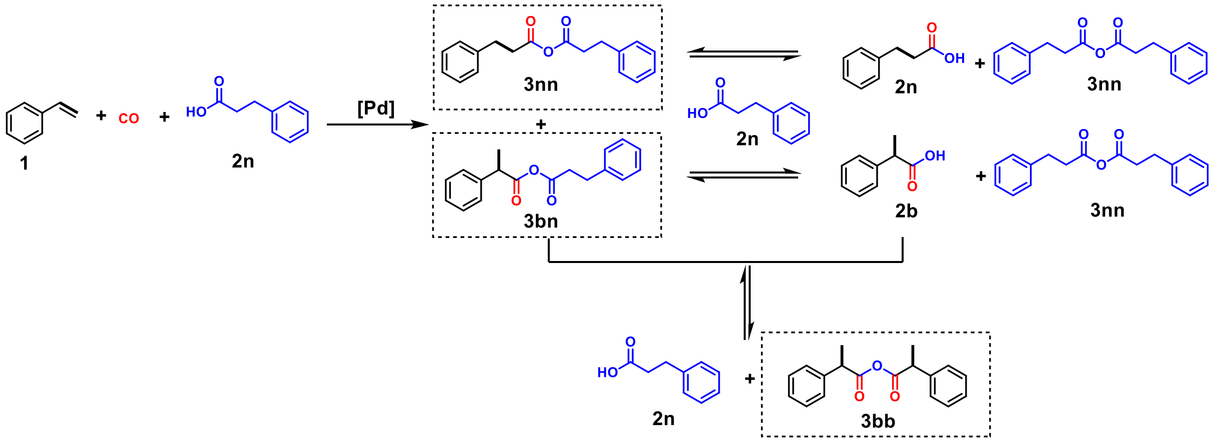


Scheme 2.2. Carbonylation reactions to synthesize carboxylic acid anhydrides.

2.2. Results and Discussion

Reaction considerations. The experimental details of the catalytic procedure are described in Appendix I. Our initial studies were performed using styrene (**1**) and 3-phenylpropionic acid (**2n**) as the substrates; in Scheme 2.3, the products are shown that can be formed in this catalytic carbonylation reaction. Depending on the regioselectivity of the carbonylation step, two products can be formed initially: the linear-linear symmetric anhydride (**3nn**) and the branched-linear mixed anhydride (**3bn**).The mixed anhydride **3bn**, however, is relatively unstable and can undergo disproportionation,[20] by reacting with **2n** to form **3nn** with the release of 2-phenylpropionic acid (**2b**). The thus formed branched acid **2b** may react with **1**, or with **3bn** in a disproportionation reaction to form branched-branched symmetric anhydride **3bb** with the release of **2n**. The latter reaction complicates reporting of conversion, as part of the starting carboxylic acid may be regenerated.

The initial catalytic studies were aimed at formation of the anhydrides and to obtain a condition for optimum yield, after which the selectivity of the reaction was investigated during ligand screening. After catalytic reactions, the reaction mixtures were treated with pyrrolidine in a derivatization reaction to confirm the formation of acid anhydrides. This derivatization was also used as a means to understand selectivity as described later in this article. We implemented UPLC analysis for quantification of total carboxylic acid (**2**) and anhydride (**3**) yield, and GC analysis to quantify conversion of **1** in the catalytic reaction mixture. The calculated conversion of **1** is accounted with an estimated error of ±5%. Treatment of the analytical data is described in Section AI.2.3.



Scheme 2.3. Possible products formed from carbonylation and disproportionation in palladium-catalyzed carbonylation of **1** with **2n**.

Temperature and solvent screening. We began our initial investigations using $Pd(OAc)_2$ in combination with 1,4-bis(diphenylphosphanyl)butane (dppb) as catalytic system. We performed a preliminary screening of solvents and temperatures to find conditions in which anhydrides were formed. In Figure 2.1 a comparison is shown of total anhydride yield and substrate conversion in toluene and 1,2-dichloroethane (DCE) at various temperatures. The formation of anhydrides was observed for reactions that were carried out at a temperature of 85 °C in toluene, diglyme, anisole or DCE (Table AI.1). At temperatures higher than 85 °C polymerization of **1** was the predominant reaction and anhydrides were observed only in trace amounts; also at 85 °C some polymerization took place, but more significantly in DCE than in toluene. As the temperature was lowered to 70 °C, a total anhydride yield of 65% was reached in DCE with full selectivity. The CO-pressure curve recorded during the reaction (Figure AI.1) indicates that after 15 h the reaction stops. At temperatures of 55 °C or lower, the reaction becomes slower and little or no anhydride is formed.

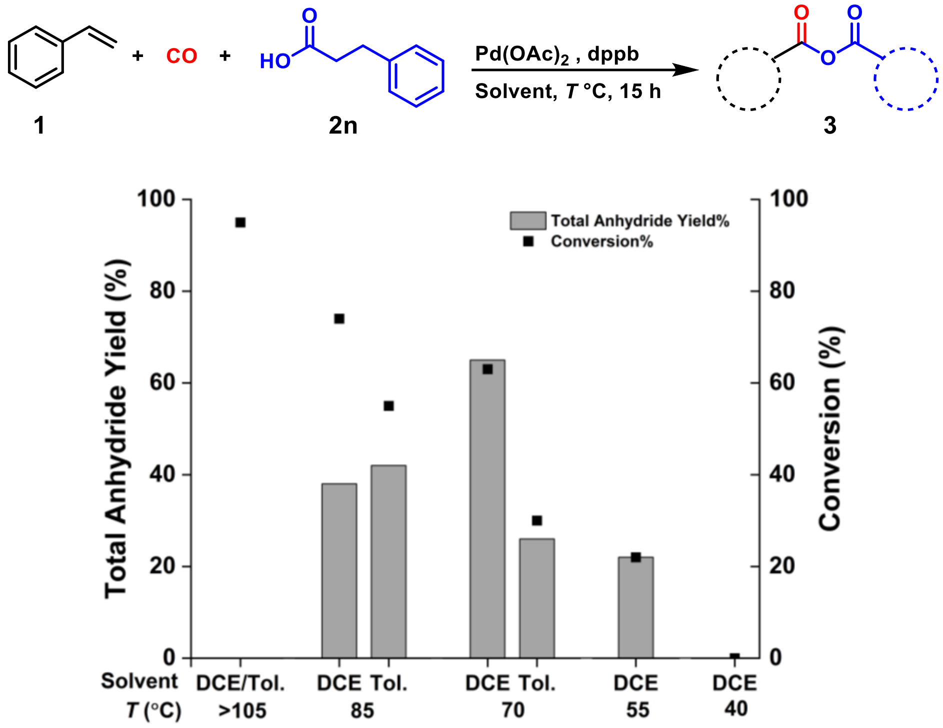


Figure 2.1. Palladium-catalyzed carbonylation of **1** with **2n:** Screening of temperature in DCE and toluene (Tol.). Reaction conditions: **1** (10.5 mmol), **2n** (10 mmol), $Pd(OAc)_2$ (0.05 mmol), dppb (0.1 mmol), CO (50 bar), temperature T °C, solvent (6 mL), 15 h. Conversion % based on **1** (black squares; right y-axis), determined by GC using undecane as internal standard. Total anhydride yield % (grey bars; left y-axis) determined with UPLC using benzamide as internal standard. (See also Table AI.1, AI.2)

Influence of additives and catalyst loading. In attempts to improve the yield, several additives such as *p*-toluenesulfonic acid (*p*-HOTs) and camphorsulfonic acid (10-CSA), commonly used as co-catalyst in hydroalkoxycarbonylation and hydrocarboxylation reactions,[11,12] silver triflate, a Lewis acid used in hydroacylation reactions,[21] and lithium salts were tested at 5 mol% (Table AI.3). The use of sulfonic acids as additives proved deleterious to catalysis. Addition of lithium chloride slowed down the reaction which may be attributed to coordination of the chloride ion to the metal center. In addition, a reaction was carried out with double catalyst loading (Table AI.5), but this did not significantly improve the yield. However, flattening of the CO-pressure curve occurred approximately 5 hours earlier than the usual 15 hours (Figure AI.2), in agreement with a higher reaction rate.

Influence of the relative ratio of substrate and reagents. The calculated Δ*G* (using DFT: BLYP-D3(BJ)/TZ2P) of a simple hydrocarbonylation reaction of ethene and propionic acid in the gas phase is −3.8 kcal/mol, whereas the value of +5.0 kcal/mol for the reaction of **1** with **2n** indicates that this reaction might be endergonic (Section AI.4.8.3). We attribute the apparent positive Δ*G* to limitations of the computational method, as we do observe the reaction to occur. However, these calculated reaction energies being close to zero indicates that the reaction might be an equilibrium. With the aim to drive this equilibrium towards the desired anhydrides, the reaction was thus carried out using different relative ratios of substrates and reagents; the results of these experiments are shown in Figure 2.2. The use of equimolar ratio of substrates **1** and **2n** at a CO pressure of 65 bar resulted in an increased yield of anhydrides up to 75%. Maintaining the CO pressure at 50 bar and doubling the relative amounts of **1** or **2n** with respect to each other also resulted in increased yields. The highest yield of anhydrides of 95-97%, based on **2n** as the limiting reagent, was obtained for reactions using a ratio **1**:**2n** of 2:1. As expected, a CO pressure lower than 50 bar results in lower yields (Table AI.7). For all reactions, the total anhydride yields are based on the limiting reagent (**1** or **2n**). Conversion cannot be calculated

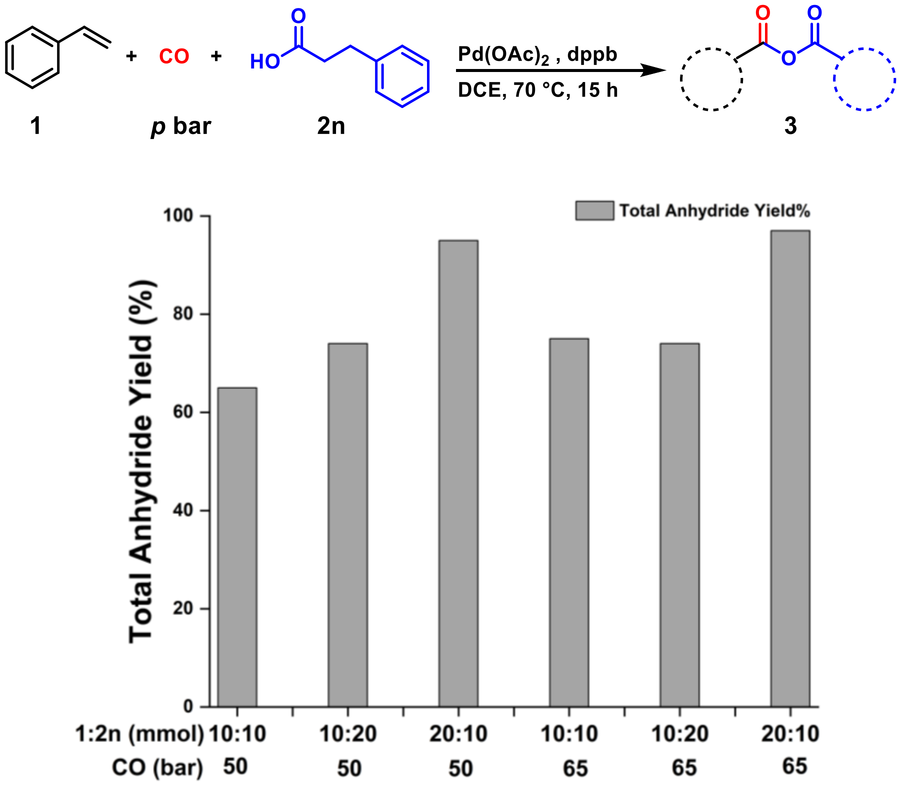


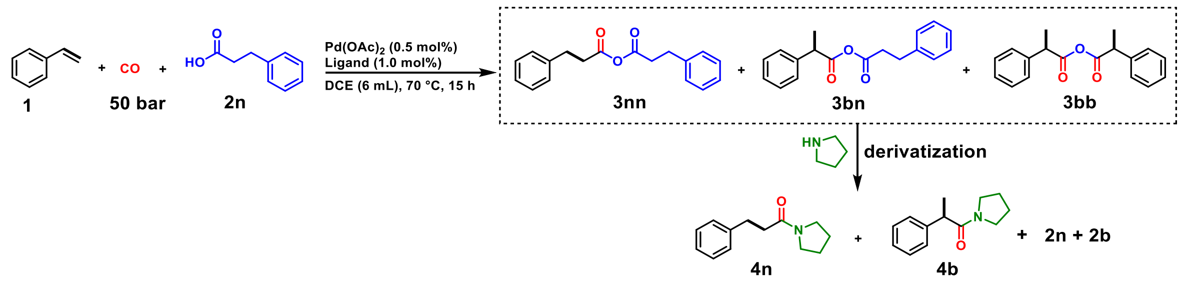
Figure 2.2. Palladium-catalyzed carbonylation of **1** with **2n**: Variation in relative amounts of substrates. Reaction conditions: Pd(OAc)$_2$ (0.05 mmol), dppb (0.1 mmol), 70 °C, DCE (6 mL), 15 h. Total anhydride yield (% based on the limiting reagent, grey bars) determined by UPLC using benzamide as internal standard. (See also Table AI.7., AI.8.)

on the limiting reagent **2n** in reactions using **1** in excess, since **2n** can be regenerated *via* disproportionation reactions as explained previously, whilst the overall mass balance is maintained. Thus, the conversion of **1** in these reactions can be larger than 50%, owing to the formation of **2n**/**2b**. Conversion based on **1** in reactions using **2n** in excess was in agreement with the product formation (within experimental error).

Reaction analysis and regioselectivity. Having established a catalytic system producing anhydrides in good yield and selectivity, we set out to analyze the regioselectivity of the reaction. The reaction mixtures were analyzed with ^{1}H NMR, and the signals for **3nn**, **3bn** and **3bb** could be clearly distinguished (Figure AI.9). For further analysis of the regioselectivity, the reaction mixtures were treated with pyrrolidine in basic conditions (see Scheme 2.4, and Section AI.3c for the procedure). The formed anhydrides are expected to react fully to form one equivalent of amide and one equivalent of carboxylic acid. Derivatization of conventionally prepared **3bn** with pyrrolidine yielded 69% selectivity towards the linear amide (**4n**), indicating a slight preference of the amidation reaction to occur at the least hindered carbonyl group. This allowed us to calculate and validate the selectivity of catalytic reactions by looking at the composition of the amides formed on derivatization using gas chromatography (Section AI.4.7).

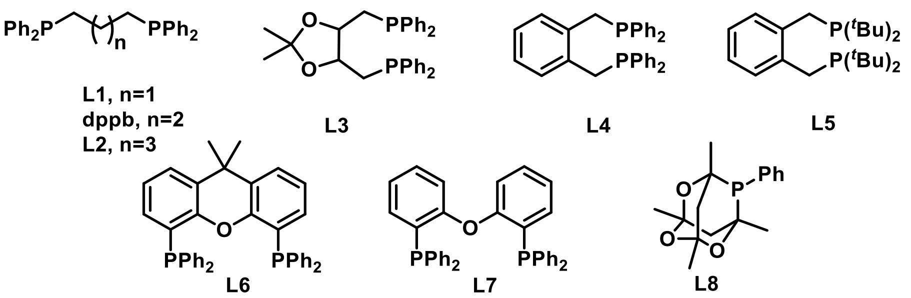
Analysis of a catalytic reaction mixture (**1**:**2n** = 2:1, 50 bar CO; Table AI.7, entry 2) with NMR showed that the produced anhydrides comprised approximately 74% of **3nn**, 26% of **3bn** and only trace amounts of **3bb**. Derivatization of the reaction mixture with pyrrolidine yielded 95% amide **4**, with a selectivity for **4n**:**4b** of 92:8, in agreement with the 69% selectivity for **4n** in the derivatization of pure **3bn**.

Several ligands were tested in our optimized catalytic conditions to investigate which features of these ligands dictate conversion and regioselectivity (Table 2.1). Changing the chain length of the backbone of dppb (**L1** and **L2**) resulted in decreased yields. Use of the four-carbon bridged ligand **L3** resulted in a similar yield to dppb but with a selectivity of 67% towards **3nn**. The catalytic system containing **L4** with a xylene backbone, essentially providing a rigid *cis*-coordination, resulted in lower reaction rate, producing a lower yield of 32%, but with exclusive selectivity for **3nn**. Unfortunately, a temperature of 85 °C did not



Scheme 2.4. Products obtained on derivatization of palladium-catalyzed hydroacyloxycarbonylation reactions of **1** and **2n** with pyrrolidine.

Table 2.1. Palladium-catalyzed carbonylation of **1** with **2n** : Influence of ligands.[a]



Ligand	Total Anhydride (3) Yield (%)[b]	3nn:3bn[c]	Yield (%) of 4 and regioselectivity (4n:4b) based on derivatization[d]
None	0	0	0
dppb	95	74:26	95 (92:8)
L1	40	>99:-	40 (>99:-)
L2	58	74:26	59 (91:9)
L3	91	67:33	92 (91:9)
L4[f]	32	>99:-	33 (>99:-)
L4[e][f]	28	>99:-	28 (>99:-)
L5[f]	0	0	0
L6	32	>99:-	32 (>99:-)
L6[e]	78	80:20	79 (94:6)
L7	70	82:18	71 (95:5)
L8	62[h]	42:44:14[i]	62 (80:20)
L8[g]	65[h]	-:>99 (**3bb**)[j]	65 (-:>99)

[a] Reaction conditions: **1** (20.2 mmol), **2n** (10 mmol), CO (50 bar), $Pd(OAc)_2$ (0.05 mmol), diphosphine (0.1 mmol) or monophosphine ligand (0.2 mmol), 70 °C, DCE (6 mL), 15 h; [b] Total anhydride **3** yield (%; based on carboxylic acid as limiting reagent) determined by UPLC using benzamide as internal standard; [c] **3nn**:**3bn** ratio determined with NMR of crude reaction mixture; **3bb** was found in trace amounts in all reactions unless mentioned otherwise; [d] Yield (%; based on carboxylic acid as limiting reagent) and regioselectivity (**4n**:**4b**) on derivatization determined by GC using undecane as internal standard; [e] Temperature of 85 °C instead of 70 °C; [f] Ligand used at 0.075 mmol instead of 0.1 mmol; [g] 2-Phenylpropionic acid (**2b**) was used instead of **2n**, 20 h instead of 15 h; [h] Total anhydride yield (%; based on carboxylic acid as limiting reagent) determined by NMR with dibromomethane as internal standard; [i] **3nn**:**3bn**:**3bb** reported instead of **3nn**:**3bn**; [j] Amount of **3bb** determined with NMR with dibromomethane as internal standard; **3bn** and **3nn** found in traces. (See also Table AI.9, AI.10)

improve the yield; instead the catalytic system with **L4** deactivated by formation of palladium black.

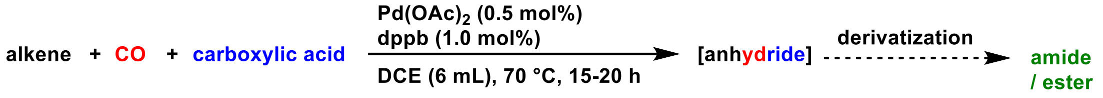
The ligand **L5** with electron-donating *tert*-butyl groups is well-known for its use in the palladium catalytic system for methoxycarbonylation.[22,23] However, its use in our reaction yielded no product. Catalytic reactions using ligands **L6** and **L7** resulted in 32% and 70% of total anhydride yield. With **L6**, the selectivity for **3nn** was more than 99%, and although the yield increased to 78% on performing the reaction at 85 °C, the selectivity for **3nn** decreased to 80%. A catalytic system involving the monodentate ligand **L8**,[24] produced all the three anhydrides in the ratio 42:44:14 (**3nn**:**3bn**:**3bb**) with a total yield of 62%. A reaction using 2-phenylpropionic acid (**2b**) as carboxylic acid co-substrate with the catalytic system comprising **L8** selectively produced **3bb** in a total yield of 65% after 20 hours.

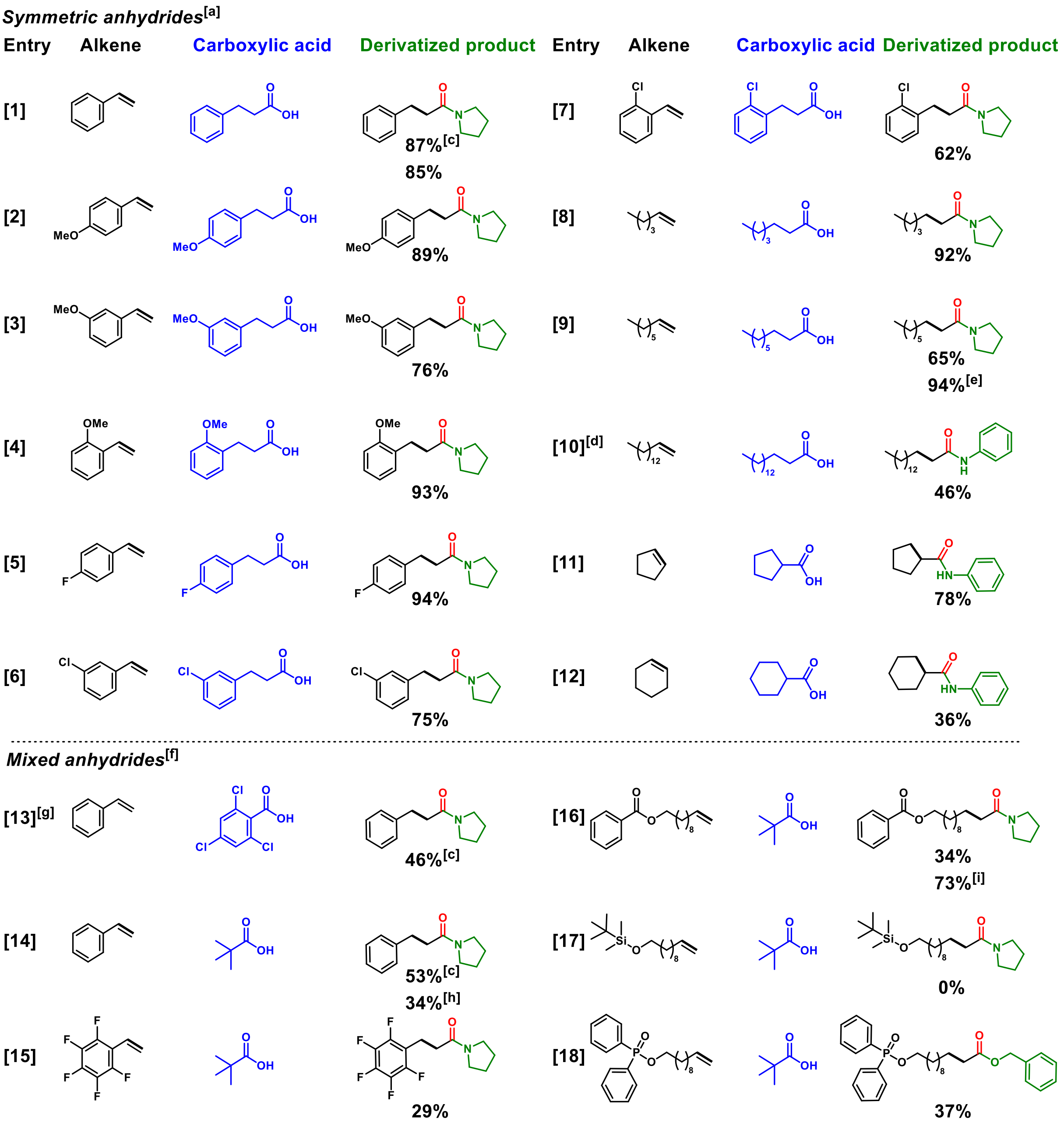
Substrate scope. To investigate the scope of the catalytic reaction, various substrates were subjected to the optimized conditions, using commercially available dppb as the ligand (Table 2.2). The catalytic system was assessed for the synthesis of various symmetric carboxylic anhydrides starting from alkenes and their corresponding carboxylic acids. The anhydrides formed in the reactions, without isolation, were reacted with amine (pyrrolidine/aniline) or alcohol (benzyl alcohol) to form amides or esters which were isolated as proof of anhydride formation.

Styrene-based substrates with electron-donating groups at *para* or *ortho* positions gave excellent yields with high selectivity towards linear amide on derivatization (entries 2 and 4). The use of *m*-methoxystyrene resulted in a slightly lower yield of 76% linear derivatized amide (entry 3), due to lower reaction rate as observed from the CO pressure drop. The reaction works also for substrates with electron-withdrawing substituents; *p*-fluorostyrene, *m*-chlorostyrene, and *o*-chlorostyrene yielded 94%, 75% and 62% linear amide product, respectively (entries 5-7). Symmetric anhydride formation starting from unactivated aliphatic alkenes (C6 to C15) gave moderate to excellent yields of 46-92% of the derivatized amides (entries 8-10). NMR analysis of the catalytic reaction mixture of entry 8 showed no presence of mixed or symmetric branched anhydrides. Cyclic alkenes, such as cyclohexene and cyclopentene with their corresponding carboxylic acids resulted in 36% and 78% yield of the aniline amides on derivatization (entries 11 and 12). In most of the reactions, the CO pressure was still decreasing at the end of 15 h reaction time, indicating that the catalysis was still ongoing. Hence, yields could be further improved just on prolonging the reaction time as demonstrated for the reaction of 1-octene over a time of 24 h (entry 9). The catalytic conditions described by Leitner and co-workers[18] for the reaction of 1-octene and nonanoic acid at a 10 mmol scale in our hands resulted in only 12% yield of nonanoic anhydride as determined with NMR.[25]

We investigated the use of 2,4,6-trichlorobenzoic acid and pivalic acid for the synthesis of mixed anhydrides, beneficial for alkenes of which the corresponding carboxylic acids are not commercially available. A recognized method in organic synthesis of esters or amides is the Yamaguchi protocol which involves 2,4,6-trichlorobenzoyl-based mixed anhydride serving as a precursor.[26–28] The synthesis of a Yamaguchi-based mixed anhydride required use of a different solvent system due to low solubility of 2,4,6-trichlorobenzoic acid in various solvents. Starting from **1** and 2,4,6-trichlorobenzoic acid in a solvent system containing 14% diethyl ether in DCE, we obtained only amide **4** in a total yield of 58% (**4n**:**4b** 79:21) after derivatization, with the yield of linear amide **4n** accounting to 46% (entry 13). Reaction of **1** with pivalic acid in equimolar and 2:1 ratio resulted in 44 and 68% amide **4** (**4n**:**4b** as 78:22 in both cases) after derivatization, with the yield of linear amide **4n** as 34 and 53% respectively (entry 14). An estimated 7-11% of **3nn** was observed on NMR analysis of the reaction mixtures of **1** and pivalic acid, indicating disproportionation to occur during the reaction. The reaction of pentafluorostyrene with pivalic acid (entry 15) produced 29% linear amide on derivatization. The use of pivalic acid for the synthesis of mixed anhydrides was investigated for several derivatives of 10-undecenol. Use of the benzoate ester of 10-undecenol resulted in 34% of the corresponding linear amide (entry 16). *tert*-Butyldimethylsilyl ether of 10-undecenol as the substrate resulted in formation of palladium black and not a trace of desired product was obtained (entry 17). The phosphinate ester of 10-undecenol resulted in 37% of the desired benzyl ester on derivatization with benzyl alcohol (entry 18). In the reactions of deactivated alkenes (entries 15,16 and 18) with pivalic acid, the CO pressures were still dropping after the reactions of 20 h, indicating that catalysis was still in progress but at lower rates. A higher catalyst loading accelerates catalysis as shown for entry 16, wherein a yield of 73% derivatized amide was achieved at a catalyst loading of 2 mol%.

Table 2.2. Palladium-catalyzed carbonylation of alkenes with carboxylic acids : Substrate scope

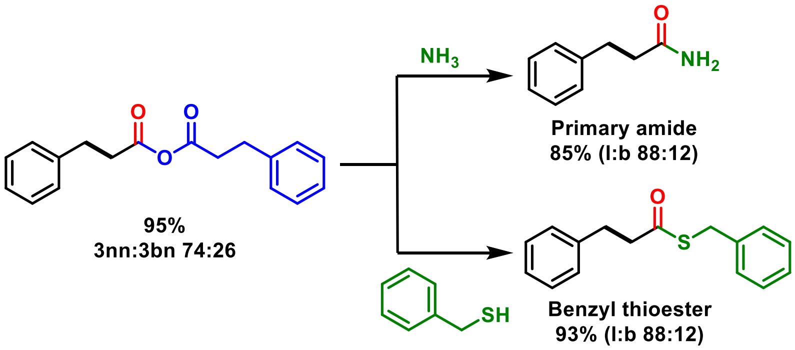




Reaction conditions: [a] alkene (20 mmol), carboxylic acid (10 mmol), CO (50 bar), $Pd(OAc)_2$ (0.05 mmol), dppb (0.1 mmol), 70 °C, DCE (6 mL), 15 h; [b] isolated yield (%; based on carboxylic acid as limiting reagent); [c] Yield (%; based on carboxylic acid as limiting reagent) of linear amide determined by GC using undecane as internal standard; [d] alkene (5 mmol) and carboxylic acid (2.5 mmol) scale; [e] 24 h instead of 15 h; [f] alkene (10 mmol), pivalic acid (5 mmol), CO (50 bar), $Pd(OAc)_2$ (0.025 mmol), dppb (0.05 mmol), 70 °C, DCE (6 mL), 20 h; [g] **1** (5 mmol), 2,4,6-trichlorobenzoic acid (2.5 mmol), $Pd(OAc)_2$ (0.025 mmol), dppb (0.05 mmol), 70 °C, diethyl ether/DCE (1/6 mL), 20 h. [h] alkene:pivalic acid used at 5:5 mmol instead of 10:5 mmol. [i] $Pd(OAc)_2$ (0.10 mmol), dppb (0.20 mmol).

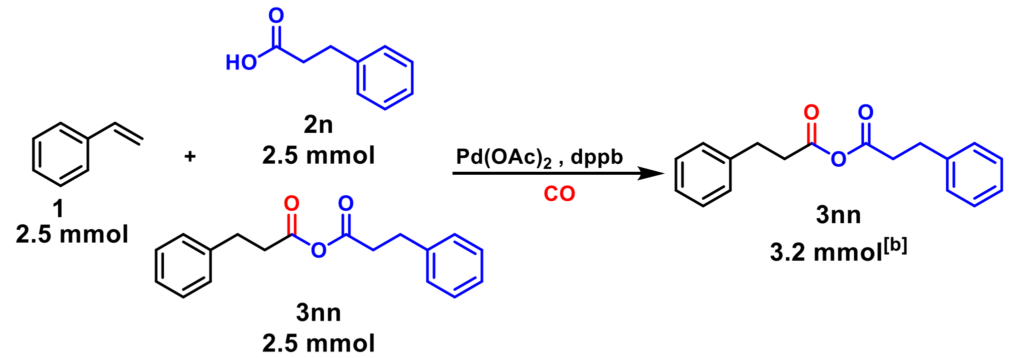
Other synthetic applications. The catalytic synthesis of primary amides from alkenes in hydroaminocarbonylation reactions, using ammonia as the nucleophile, is challenging for several reasons. In the presence of ammonia it is difficult to create the metal-hydride species necessary for catalysis, and the use of a strong acid as co-catalyst results in formation of ammonium salts. Additionally, formation of ammine complexes may cause deactivation of transition metal catalysts.[29,30] Primary amides may be used in synthesis of primary amines which are otherwise difficult to obtain *via* hydroaminomethylation reactions as they readily alkylate resulting in formation of secondary and/or tertiary amines.[31]

Addition of ammonia to the reaction mixture after formation of the anhydrides **3** results in the formation of the corresponding primary amide in a yield of 85% (l:b 88:12) (Scheme 2.5). Similarly, thioesters are obtained in a yield of 93% (l:b 88:12) upon reaction of the anhydrides with thiols, which are known poisons for transition metal catalysts.[32,33] The benzyl thioesters that are thus formed can be debenzylated to form thiocarboxylic acids. The carboxylic acid that is released on derivatization of acid anhydrides can be recycled, thus ensuring an overall sustainable process. Recently, a strategy to derivatize anhydrides yielding two equivalents of derivatized products without generation of carboxylic acids was reported, expanding the utility of our new catalytic procedure for the synthesis of acid anhydrides.[34]

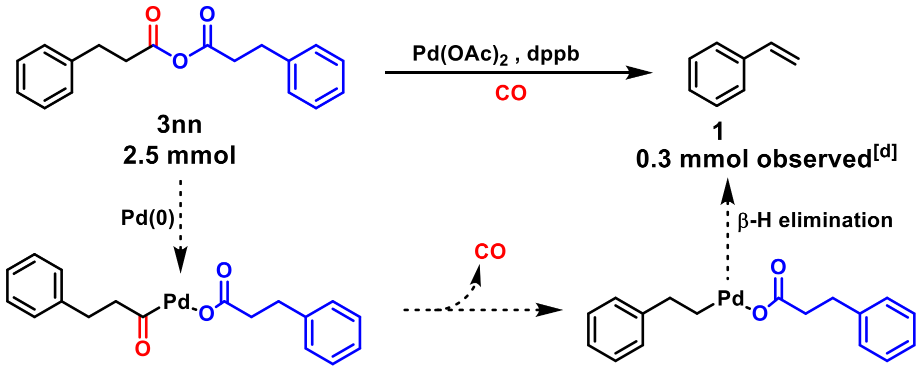


Scheme 2.5. Applications of carbonylative synthesized acid anhydrides to produce primary amide and thioester. (Yield % based on **2n** as limiting reagent).

Mechanistic considerations. When **1** and **2n** were used in equivalent amounts the yield of anhydride never exceeded 67%. Our suspicion that the reaction is actually an equilibrium, preventing full conversion of the substrates, is supported by the calculated Δ*G* of −3.8 kcal/mol for the reaction of ethene and propionic acid and the effects of changing the relative ratios of the reactants on the yield of the reaction. To further investigate this reaction equilibrium, a mixture of equivalent amounts (2.5 mmol) of **1**, **2n** and **3nn** was subjected to our catalytic conditions. This resulted in formation of only an additional 0.7 mmol of anhydride at the end of 15 hours reaction time, thus yielding a total anhydride content of 3.2 mmol (total anhydride yield of 64%) (Scheme 2.6.a). Moreover, catalytic reaction conditions applied to pure **3nn** resulted in the formation of a small amount of **1**, confirming the reversibility of the hydrocarbonylation reaction. The reversed reaction most likely occurs *via* oxidative addition of **3nn** to a Pd(0) species,[35,36] which upon release of CO and subsequent β-hydrogen elimination results in formation of **1** (Scheme 2.6.b).



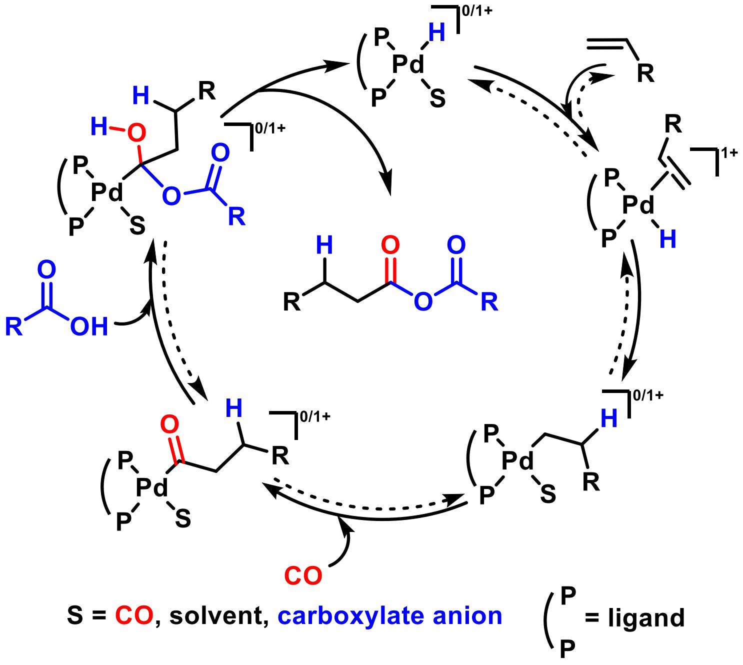
a. *Catalysis with pre-mixed acid anhydride and substrates*[a]



b. *Acid anhydride in catalytic conditions*[c]

Scheme 2.6. Control experiments. [a] reaction conditions: **1** (2.5 mmol), **2n** (2.5 mmol), **3nn** (2.5 mmol), CO (50 bar), Pd(OAc)$_2$ (0.025 mmol), dppb (0.05 mmol), 70 °C, DCE (6 mL), 15 h. [b] Yield determined by UPLC using benzamide as internal standard. [c] reaction conditions: **3nn** (2.5 mmol), CO (50 bar), Pd(OAc)$_2$ (0.025 mmol), dppb (0.05 mmol), 70 °C, DCE (6 mL), 15 h. [d] Yield determined by GC using undecane as internal standard.

A plausible catalytic cycle of the reaction is shown in Scheme 2.7 following the conventional hydride pathway.[37–39] The carboxylic acid substrate in the reaction mixture aids in the formation of a palladium−hydride containing a carboxylate counter anion by protonation of an intermediate Pd(0) species. Coordination of the alkene followed by hydride migration results in the formation of an alkyl-palladium intermediate, and subsequent coordination of CO and migration of the alkyl group forms an acyl-palladium intermediate. The final anhydride product may be formed *via* coordination of the carboxylate ion followed by reductive elimination, or by a direct nucleophilic attack at the acyl group by the carboxylic acid or carboxylate ion to produce an intermediate hydroxy-acyloxy-alkyl palladium intermediate which upon β-hydrogen elimination releases the product and regenerates the palladium hydride.[40] The deleterious effect on catalysis of the addition of chloride salts may indicate that coordination of the carboxylate ion is essential for catalysis. The addition of sulfonic acids as co-catalyst hampers the formation of carboxylate ions, and either inhibits nucleophilic attack or coordination of the carboxylate ion.



Scheme 2.7. Proposed mechanism of the palladium-catalyzed hydroacyloxycarbonylation reaction.

2.3. Conclusion

In summary, we developed a novel catalytic way to synthesize acid anhydrides from alkenes. Using different alkenes and carboxylic acid co-substrates, symmetric as well as mixed anhydrides could be synthesized in moderate to excellent yields. The low ΔG of the reaction causes an equilibrium of the reactants and products and hence, a change in relative amounts of reagents is necessary to drive the reaction forward. The presence of electron-withdrawing groups on the phosphorus atom of the ligand in the catalytic system is crucial for this catalytic reaction. The electron-poor phosphorus ligands make the palladium center more electrophilic, facilitating coordination of weak nucleophiles,[41] and thus activating the poorly nucleophilic carboxylate anion (or carboxylic acid) to react with the acyl-palladium intermediate. From the reactions of **1** with **2n**, pivalic acid and 2,4,6-trichlorobenzoic acid we observe a difference in the linearity of the amide produced on derivatization, which is indicative of the different composition of anhydrides formed in each of the reactions. Therefore, a screening study using different carboxylic acid co-substrates may provide more insight on how these co-substrates influence the regioselectivity in product formation. Generally, isolation of acid anhydrides from a reaction mixture is difficult since they are susceptible to hydrolysis, and especially mixed anhydrides may also undergo disproportionation. The catalytic procedure reported herein provides a general two-step, one-pot procedure to add various functional groups to alkenes, including primary or secondary amides as well as esters or thioesters, which otherwise might require special conditions for each conversion.

2.4. References

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