Palladium-catalyzed carbonylative synthesis of carboxylic acid anhydrides from Alkenes

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Palladium Catalyzed Carbonylative Synthesis of Carboxylic Acid Anhydrides from Alkenes

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Your future is created by what you do today.

To my mother who made sure I never was hungry while I studied and my father who always saw to it I wake up on time to make it to where I am… to the two souls who have supported me in every way…

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List of Abbreviations

ACN	acetonitrile
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
10-CSA	camphorsulfonic acid
5-Cl-SA	5-chlorosalicylic acid
Cy	cyclohexyl
dba	dibenzylideneacetone
DCC	N, N′-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DFT	density functional theory
DME	dimethoxyethane
dppb	1,4-bis(diphenylphosphanyl)butane
dppp	1,3-bis(diphenylphosphanyl)propane
DPEphos	bis[(2-diphenylphosphanyl)phenyl] ether
d^tbpx	1,2-bis(di-*tert*-butylphosphanylmethyl)benzene
equiv.	equivalent(s)
FA	formic acid
GC	gas chromatography
GVL	γ-valerolactone
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HOAc	acetic acid
HOMs	methanesulfonic acid
HOTs(.H_2O)	toluenesulfonic acid (monohydrate)
m-	meta
2,4,6-MBS	2,4,6-trimethylbenzenesulfonic acid
Me	methyl
MZ	mierenzuur
NMP	N-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
o-	ortho
p-	para
PEA	pentenoic acid
Ph	phenyl
PPA	phenylphosphonic acid
TBA	2,4,6-trimethylbenzoic acid
tert-/*t*	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TOF	turn over frequency
TON	turn over number
UPLC	ultra-performance liquid chromatography

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Introduction

1.1. Alkenes, CO and hydrocarbonylation

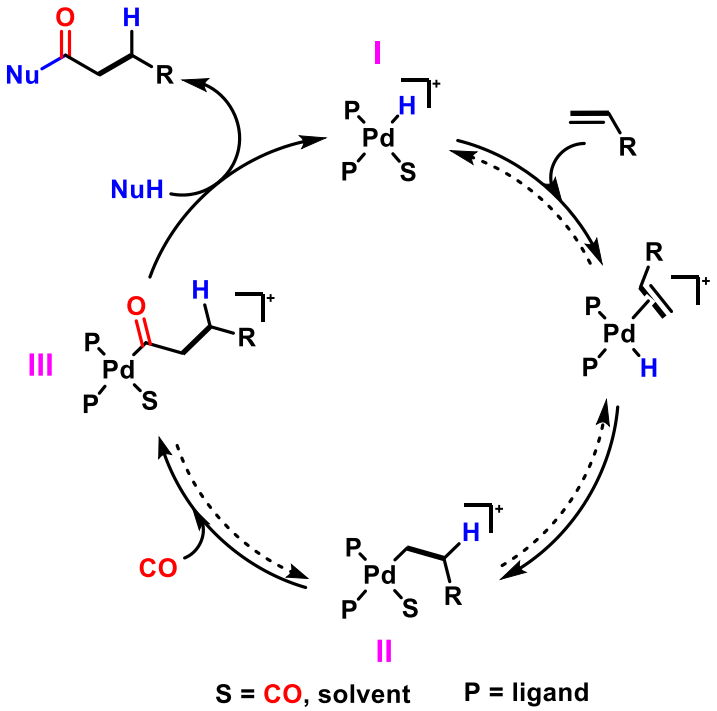
Alkenes are important molecules that can be procured from natural petrochemical or biomass resources, or produced synthetically using known procedures ranging from simple dehydration reactions to more advanced processes such as Wittig, Julia, Tebbe or Peterson olefination reactions. The versatile reactivity 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.

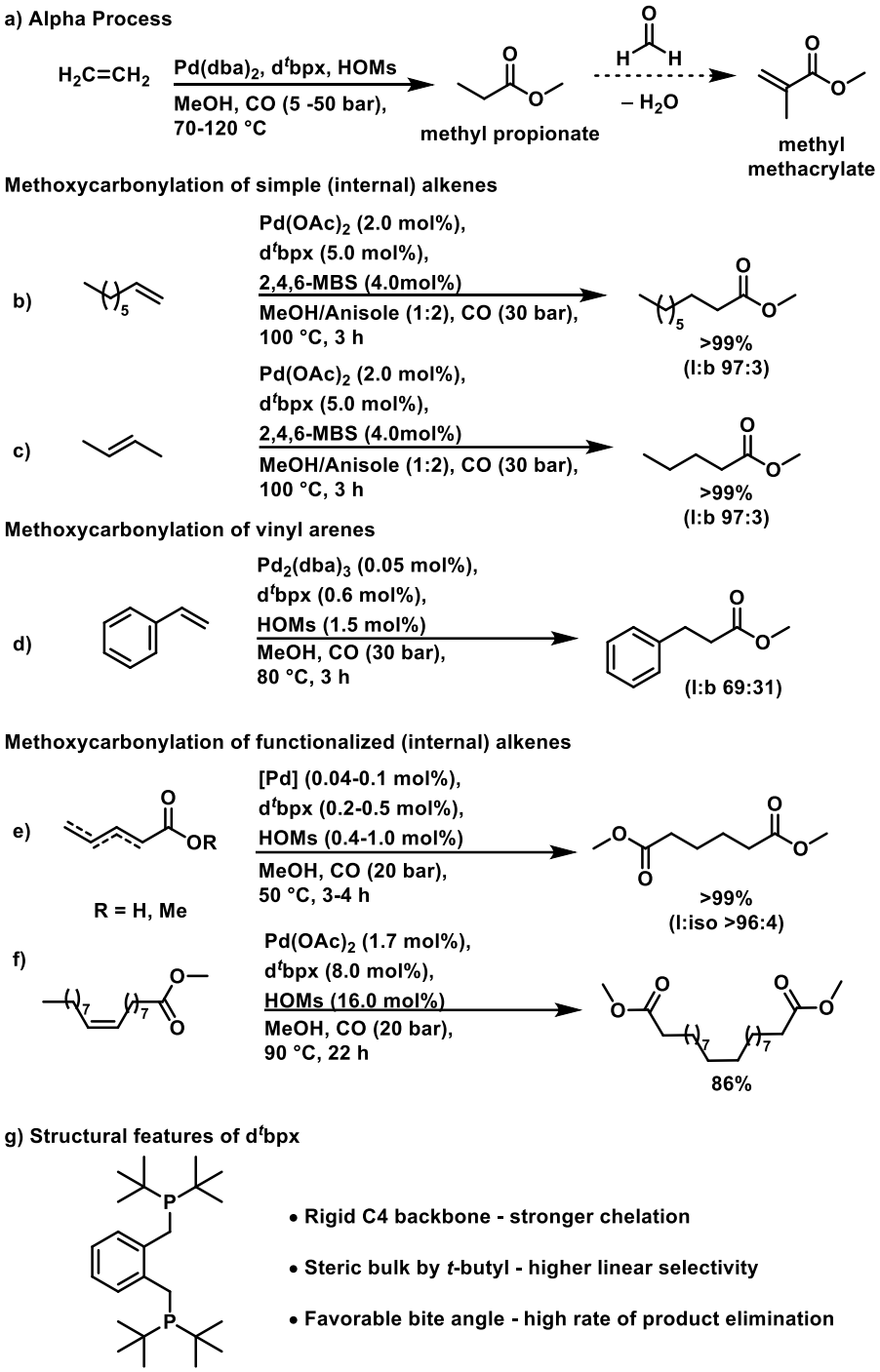
1.2. Hydroalkoxycarbonylation

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]

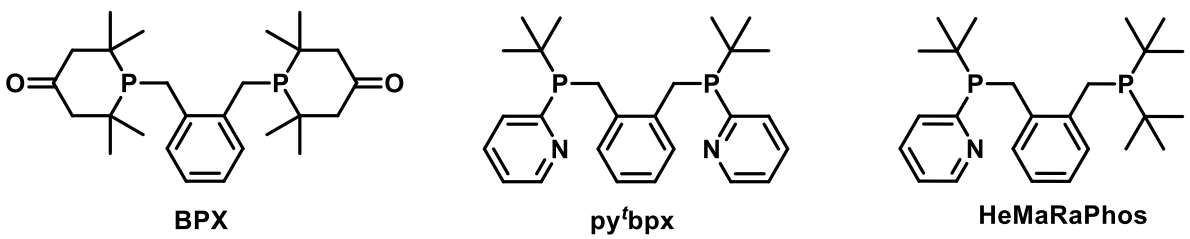
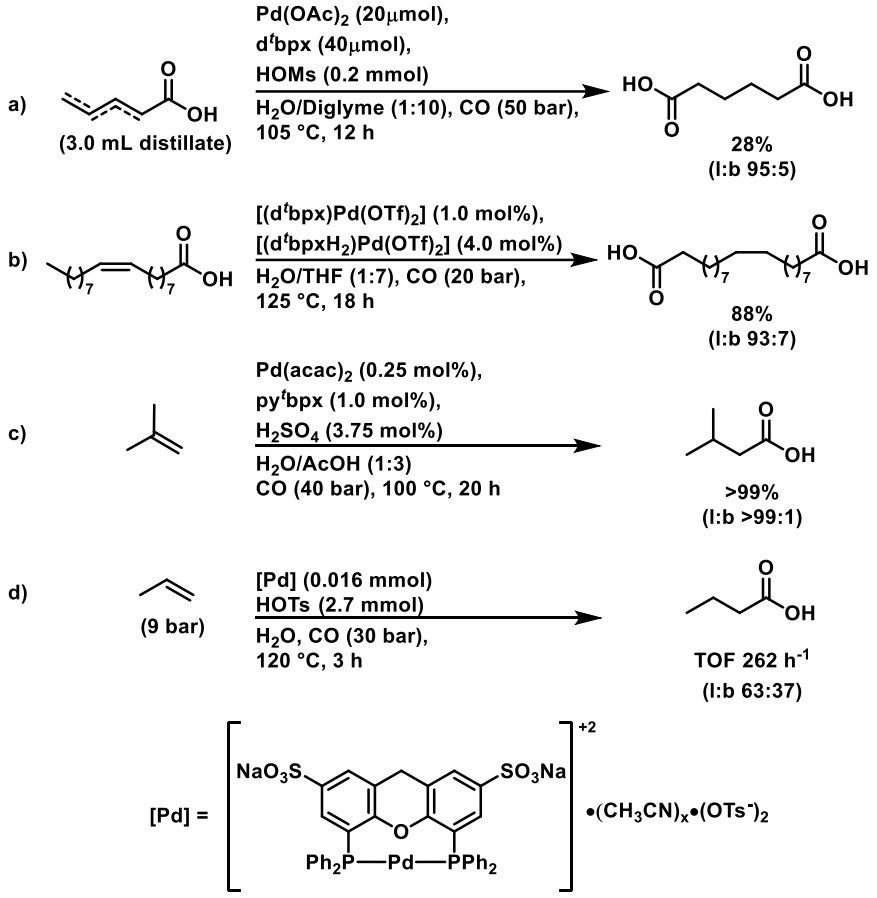


Figure 1.1. Congeners of d^{t}bpx.

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 iso-

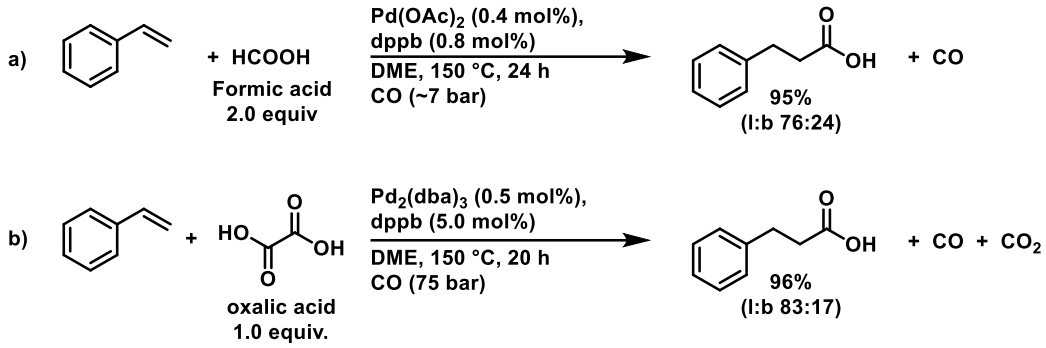
butene (Scheme 1.3.c).[24] Additionally, the acidic aqueous solution of the catalyst could be recycled and was shown to run 26 cycles of reactions without considerable loss of activity. Often hydrocarboxylation is performed in solvents which readily mix with water or in combination with a co-solvent 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^{t}bpx/py^{t}bpx/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]

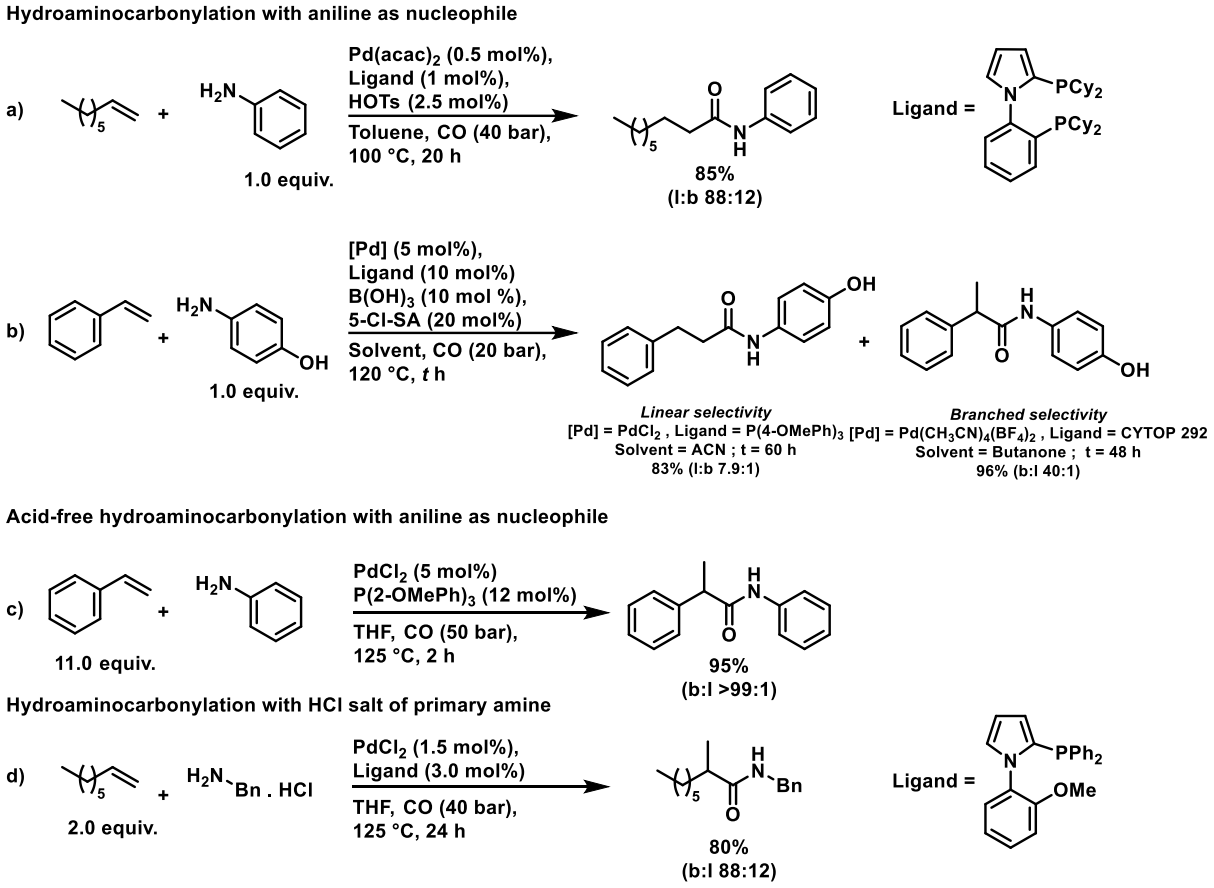
1.4. Hydroaminocarbonylation and hydroamidocabonylation

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 ~ 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

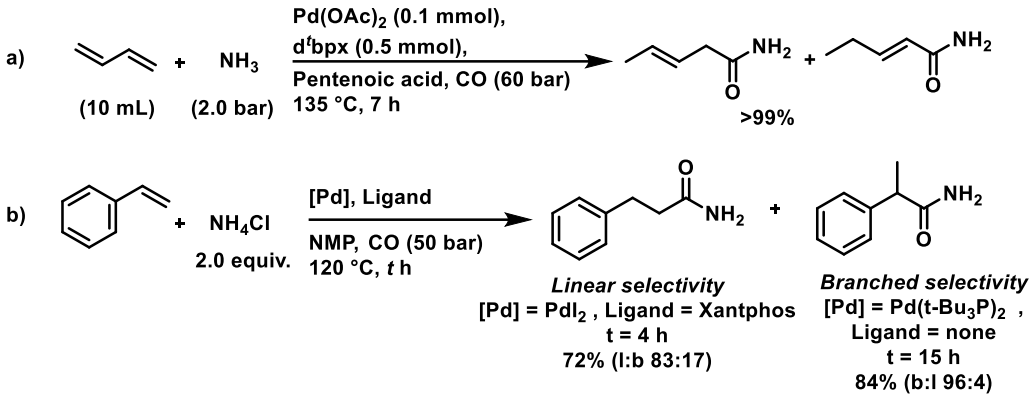
(11:1 alkene:aniline). However, no products were formed with aliphatic amines due to their high basicity. The group of Alper demonstrated hydroaminocarbonylation with aminophenols to prepare linear and branched products in high selectivity (Scheme 1.5.b).[42]

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.



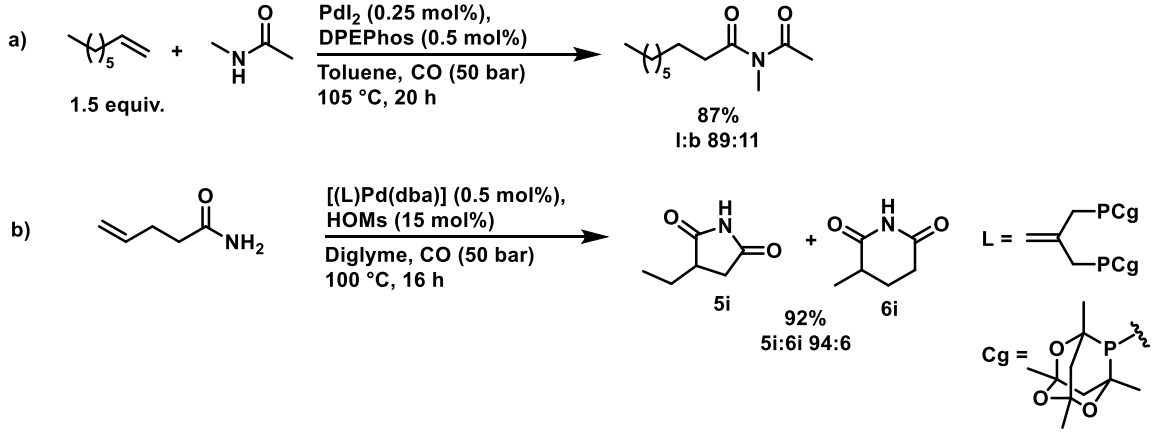
Scheme 1.5. Selected examples of hydroaminocarbonylation of alkenes with primary amines to generate secondary amides.[39,41–43]

*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]

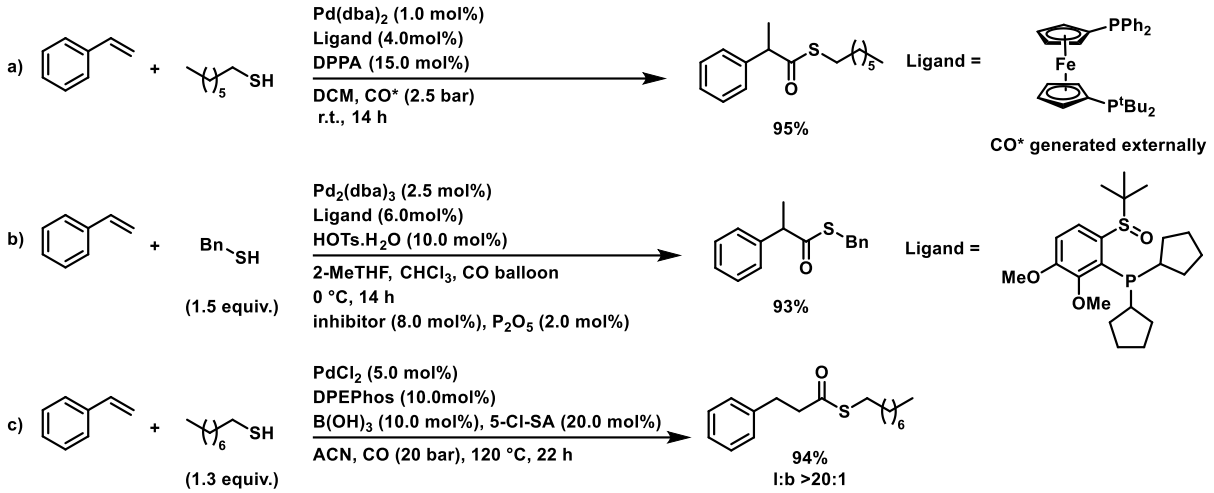


Scheme 1.7. Hydroamidocarbonylation of alkenes with amide to synthesize imides.

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

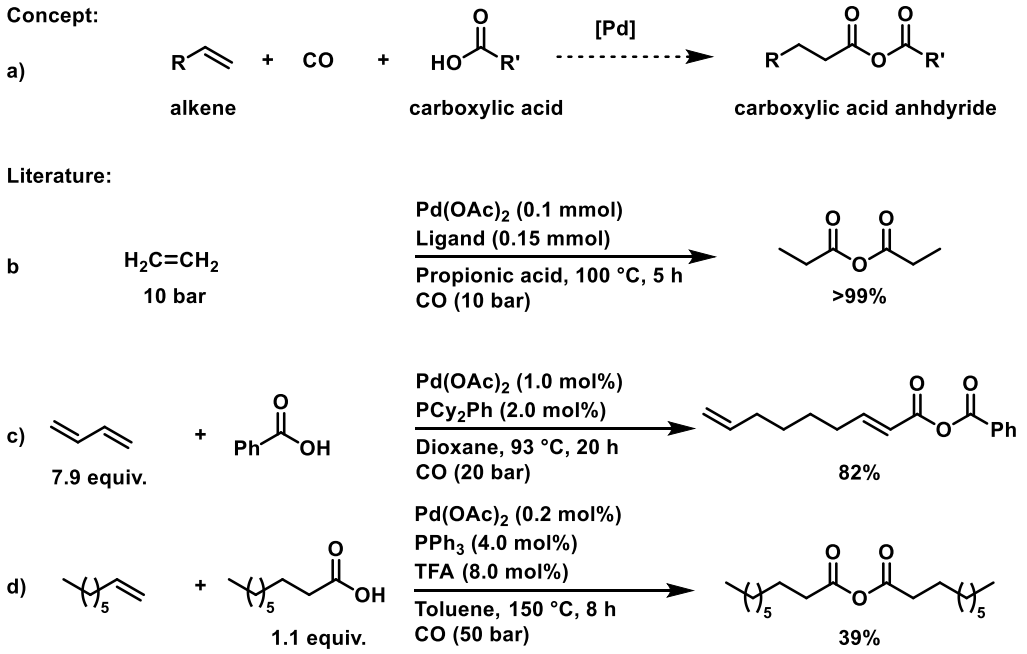
alkenes including vinyl arenes was reported by Wu and co-workers resulting in good yields and selectivity by employing a palladium-based catalytic system containing DPEPhos and a combination of $B(OH)_3$ and 5-chloro-salicylic acid (5-Cl-SA) as acid additives (Scheme 1.8.c).[58]



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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2

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.

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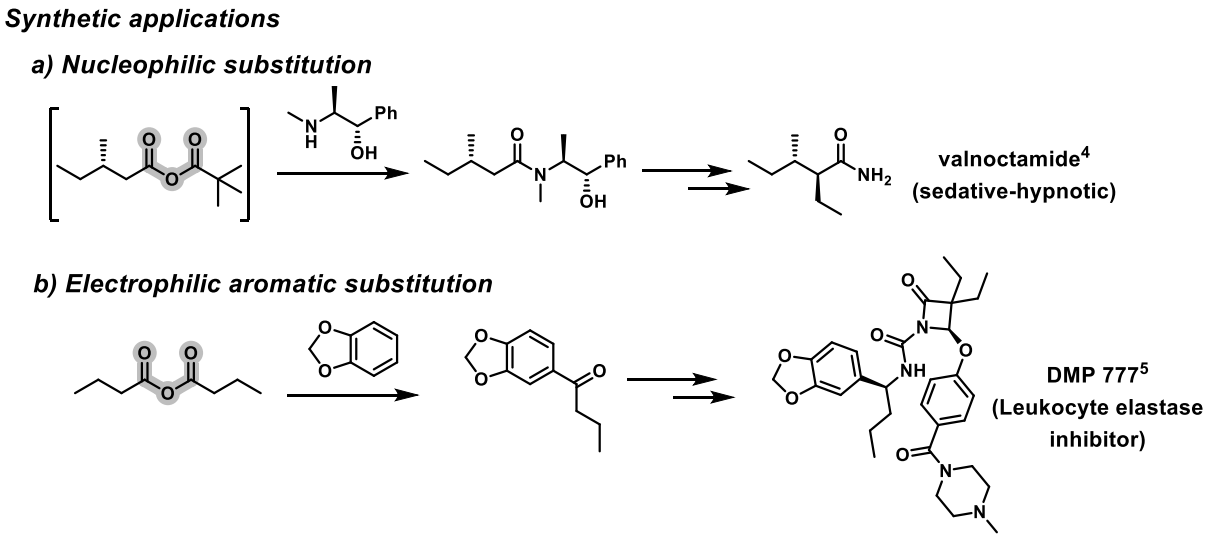
2.1. Introduction

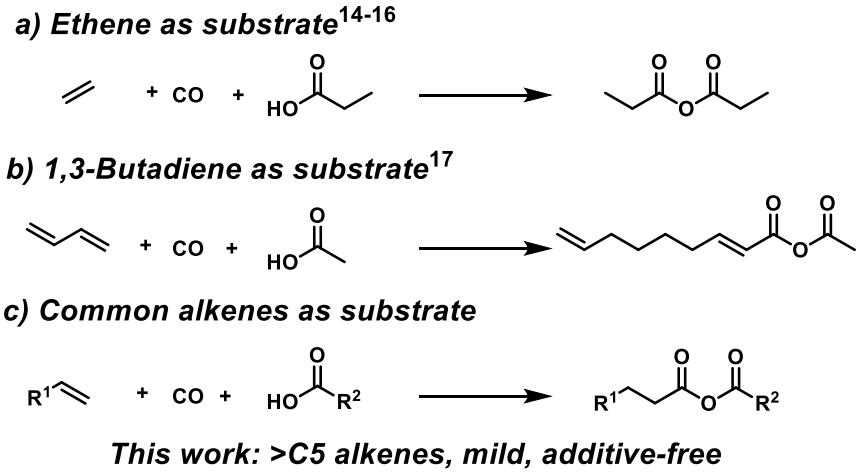
Carboxylic acid anhydrides are important activated forms of carboxylic acids. In a survey reported by Sheppard and co-workers, it was found that 16% of the total procedures for amide bond formation above 300 gram scale within Glaxo-Smith-Kline (GSK) are achieved *via* acid anhydrides.[1] Anhydrides have 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.



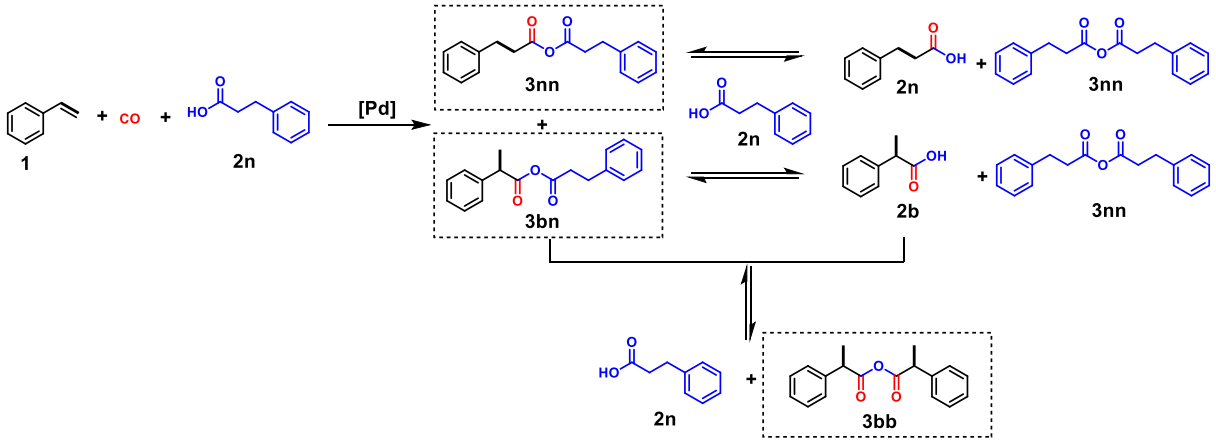
Scheme 2.2. Carbonylation reactions to synthesize carboxylic acid anhydrides.

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.

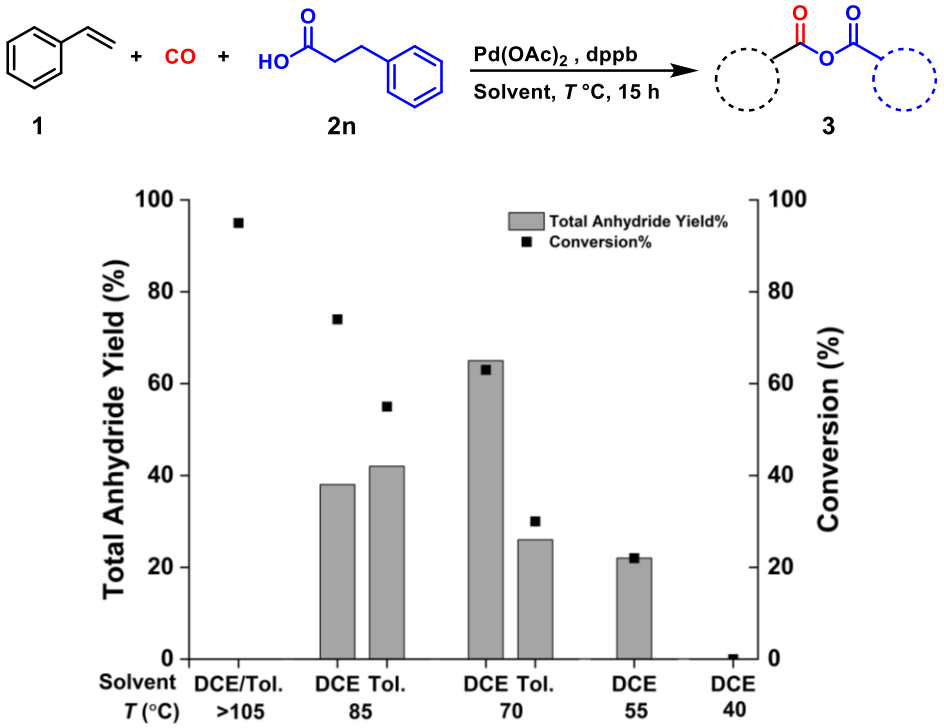


Figure 2.1. Palladium-catalyzed carbonylation of **1** with **2n:** Screening of temperature in DCE and toluene (Tol.). Reaction conditions: **1** (10.5 mmol), **2n** (10 mmol), $Pd(OAc)_2$ (0.05 mmol), dppb (0.1 mmol), CO (50 bar), temperature *T* °C, solvent (6 mL), 15 h. Conversion % based on **1** (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

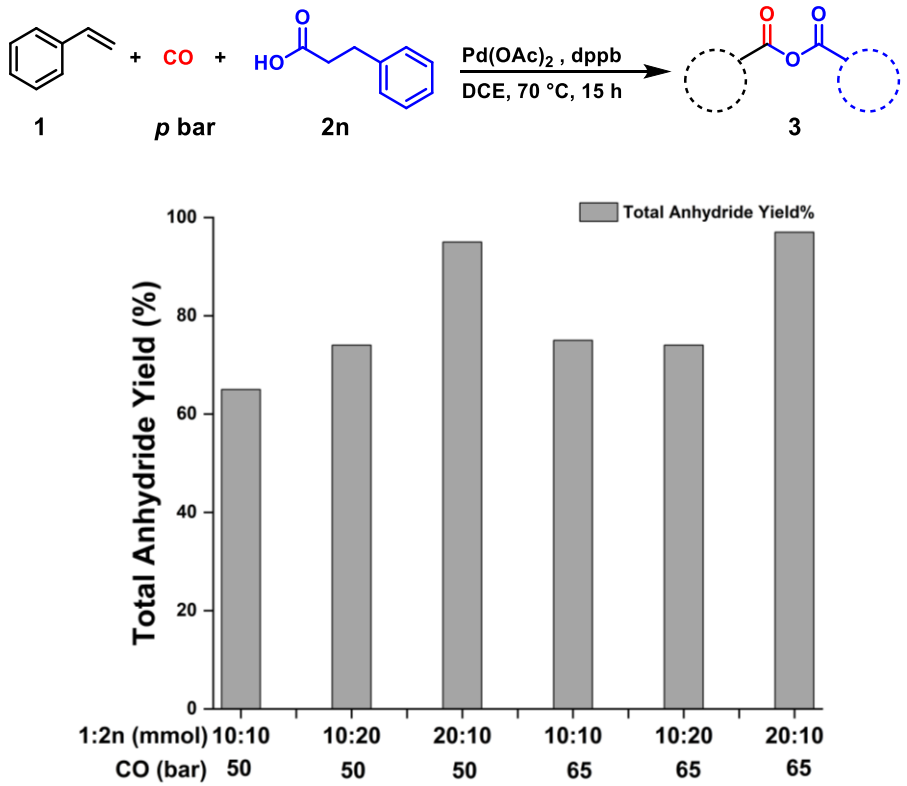


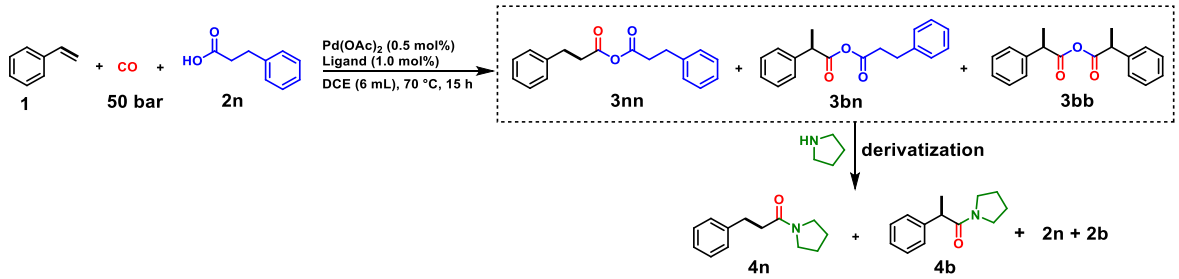
Figure 2.2. Palladium-catalyzed carbonylation of **1** with **2n**: Variation in relative amounts of substrates. Reaction conditions: $Pd(OAc)_2$ (0.05 mmol), dppb (0.1 mmol), 70 °C, DCE (6 mL), 15 h. Total anhydride yield (% based on the limiting reagent, grey bars) determined by UPLC using benzamide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

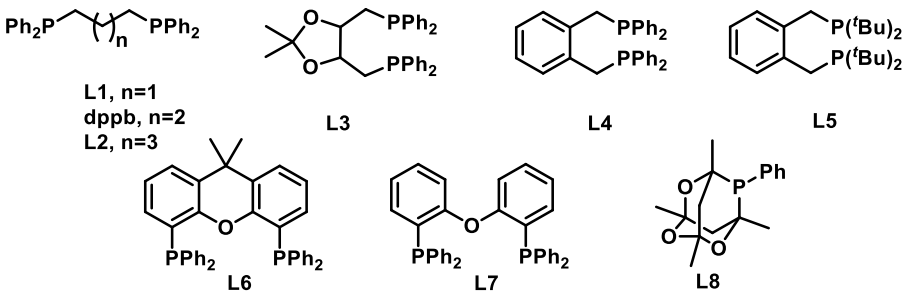
Analysis of a catalytic reaction mixture (**1**:**2n** = 2:1, 50 bar CO; Table AI.7, entry 2) with NMR showed that the produced anhydrides comprised approximately 74% of **3nn**, 26% of **3bn** and only trace amounts of **3bb**. Derivatization of the reaction mixture with pyrrolidine yielded 95% amide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

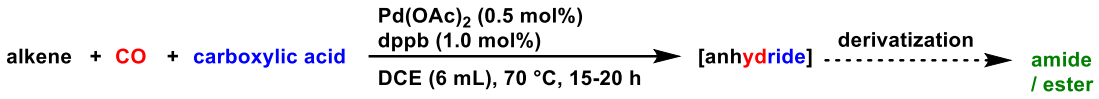
Substrate scope. To investigate the scope of the catalytic reaction, various substrates were subjected to the optimized conditions, using commercially available dppb as the ligand (Table 2.2). The catalytic system was assessed for the synthesis of various symmetric carboxylic anhydrides starting from 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-

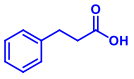
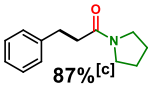
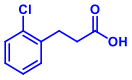
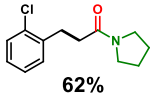
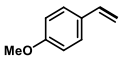
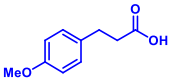
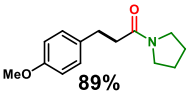
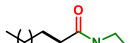
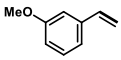
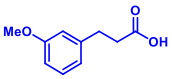
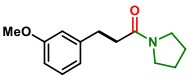
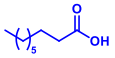
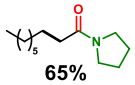
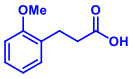
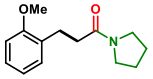
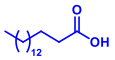
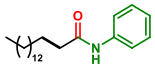
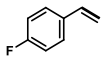
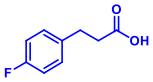
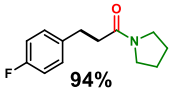
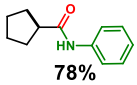
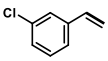
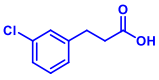
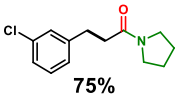
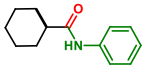
workers[18] for the reaction of 1-octene and nonanoic acid at a 10 mmol scale in our hands resulted in only 12% yield of nonanoic anhydride as determined with NMR.[25]

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%.

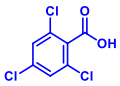
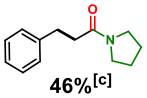
Table 2.2. Palladium-catalyzed carbonylation of alkenes with carboxylic acids : Substrate scope



Symmetric anhydrides[a]

Entry	Alkene	Carboxylic acid	Derivatized product	Entry	Alkene	Carboxylic acid	Derivatized product
[1]			 87%[c] 85%	[7]			 62%
[2]			 89%	[8]			 92%
[3]			 76%	[9]			 65% 94%[e]
[4]			 93%	[10][d]			 46%
[5]			 94%	[11]			 78%
[6]			 75%	[12]			 36%

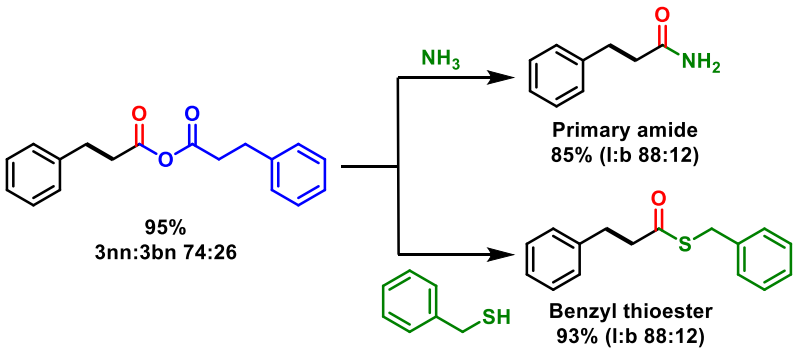
Mixed anhydrides[f]

[13][g]			 46%[c]	[16]			34% 73%[i]
[14]			53%[c] 34%[h]	[17]			0%
[15]			29%	[18]			37%

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]

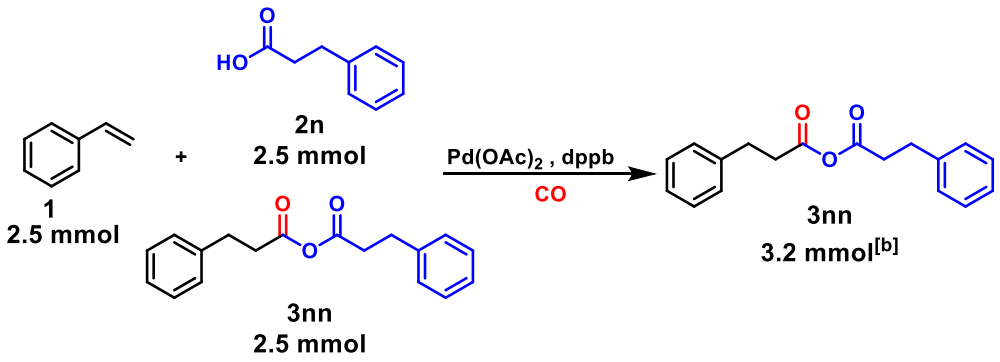


Scheme 2.5. Applications of carbonylative synthesized acid anhydrides to produce primary amide and thioester. (Yield % based on **2n** as limiting reagent).

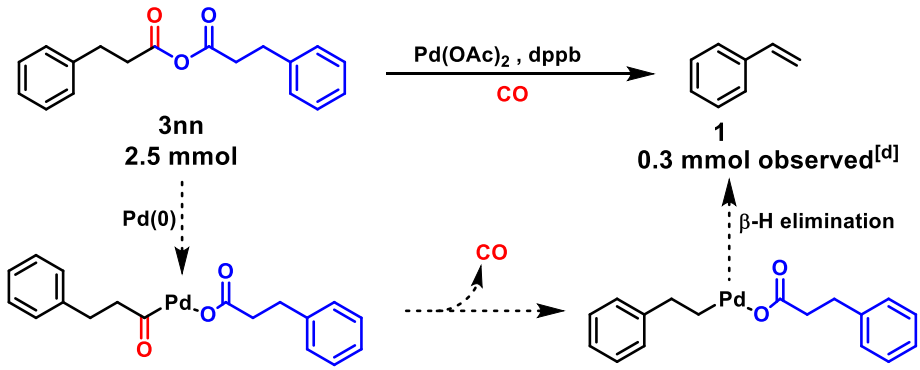
Mechanistic considerations. When **1** and **2n** were used in equivalent amounts the yield of anhydride never exceeded 67%. Our suspicion that the reaction is actually an equilibrium, preventing full conversion of the substrates, is supported by the calculated ΔG of −3.8 kcal/mol for the reaction of 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]



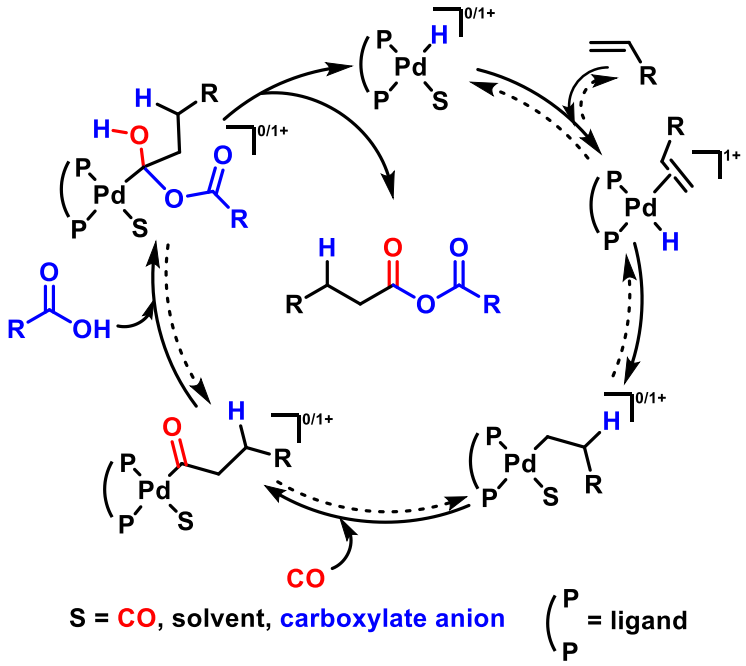
b. *Acid anhydride in catalytic conditions*[c]



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.

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3

Palladium-Catalyzed Synthesis of Symmetric Carboxylic Acid Anhydrides from Alkenes with *in situ* Generated Carboxylic Acids

*Carboxylic acid anhydrides are well known for their non-corrosive and mild acylating nature, and readily react with nucleophiles – alcohols, amines and thiols. We recently reported a carbonylative synthesis of acid anhydrides from alkenes with carboxylic acids as nucleophiles (Chapter 2). However, its synthesis of symmetric anhydrides requires the corresponding C_{n+1} carboxylic acid, which is not readily available in most of the cases. To overcome this challenge, we herein describe a strategy to synthesize symmetric acid anhydrides via in situ generated carboxylic acids from the alkene itself. It is known that the use of cheap and inexpensive formic acid (FA) reacts with alkene and CO to form carboxylic acids. Application of our catalytic conditions and modulating the alkene:formic acid ratio to at least 2:1 resulted in the formation of symmetric acid anhydride up to 70%, which was increased to 88% on varying the ratio to 3:1 - as represented in the case of the model substrate, styrene (**1**). Further studies showed minimal influence of different phosphine ligands on the regioselectivity of the acid anhydrides formed (approximately 60% linear-linear (**3nn**), 35% linear-branched (**3bn**) and 5% branched-branched (**3bb**)) resulting in an overall ~80% linearity. The catalytic process was applied to various alkenes, simple and with functional groups, to produce moderate to excellent yields as observed by their NMR yield or the corresponding amide produced on derivatization. A one-pot derivatization of the reaction mixtures provided access to various acyl molecules including phenolic esters, primary amides, thioesters and ketones, which otherwise require special conditions or are difficult to obtain via carbonylation chemistry.*

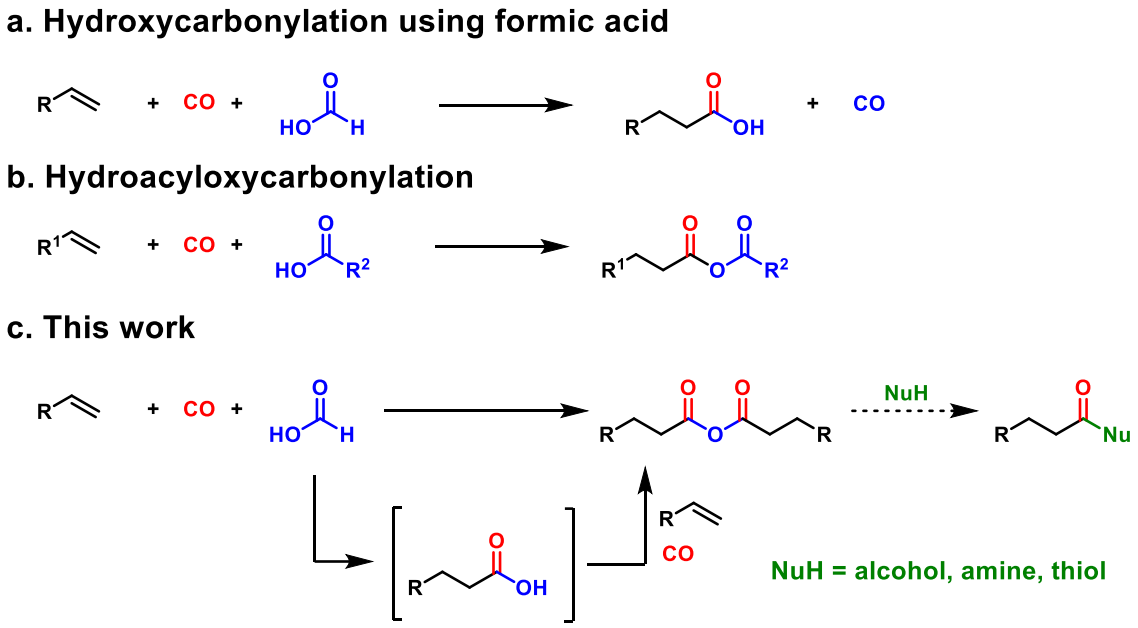
This chapter will be submitted for publication.

3.1. Introduction

Symmetric carboxylic acid anhydrides are vital electrophilic acylating reagents used in chemical synthesis of various fine chemicals, pharmaceuticals and polymers. The mild nature and effective chemical reactivity of anhydrides have established them as widely favored acylating agents in organic synthesis. As a result, they are employed, for example, as reagents in peptide chemistry to facilitate N-acylation processes.[1] It is important to use symmetric acid anhydrides in acylation processes, as it avoids the generation of by-products resulting from an attack on the undesired acyl group in mixed anhydrides.[2]

The conventional synthesis of symmetric anhydrides involves the activation of carboxylic acids by reagents such as thionyl chloride,[3,4] carbodiimides,[5] and triphosgene;[6] the use of these reagents generates by-products, and thus reduce the atom efficiency of the reaction. The development of metal-catalyzed carbonylation of alkenes with carbon monoxide as a cheap and abundant C1 feedstock has emerged as a sustainable and highly atom-economical synthesis for acyl-bearing molecules. Applying this concept, we established a facile palladium-catalyzed carbonylative synthesis of carboxylic acid anhydrides from alkenes with carboxylic acid as co-substrates (hydroacyloxycarbonylation) as described in Chapter 2.[7]

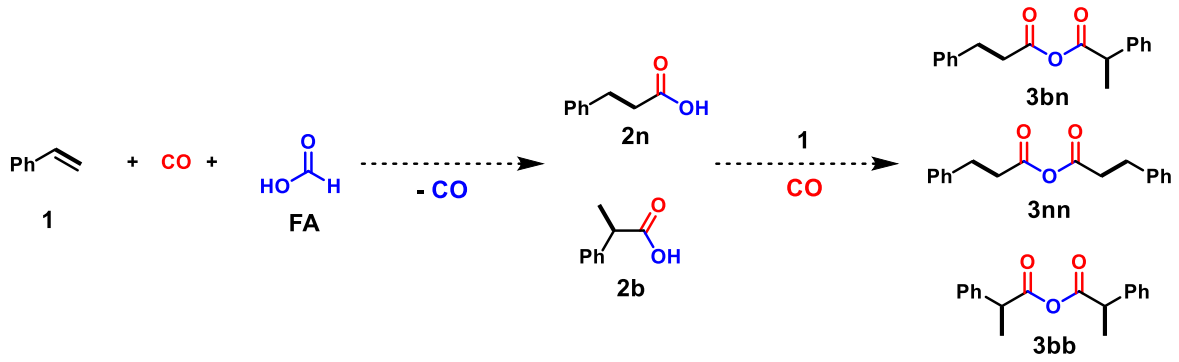
Carbonylative synthesis of carboxylic acids (hydrocarboxylation) is one of the prominent reactions in carbonylation chemistry.[8,9] Hydrocarboxylation of alkenes using formic acid (FA) in excess (at least 2.0 equivalents with respect to alkene) is one of the well-known synthetic strategies established and reported by several groups (Scheme 3.1.a).[10–15] The catalytic cycle involves formation of a mixed anhydride containing FA, which is known to be highly unstable and readily decomposes to release CO with formation of a carboxylic acid derived from the alkene. Taking this into account and based on the established catalytic conditions from our previous report on synthesis of acid anhydrides (Scheme 3.1.b), we envisaged a strategy to produce symmetric carboxylic acid anhydrides from alkenes without the need of an individually synthesized or isolated carboxylic acid co-substrate (Scheme 3.1.c). We herein present a palladium-catalyzed synthesis of symmetric carboxylic acid anhydrides from alkenes with *in situ* produced carboxylic acids.



Scheme 3.1. Proposed concept of carbonylative synthesis of symmetric acid anhydrides from alkenes without the need of corresponding carboxylic acid.

3.2. Results and Discussion

The reaction described in this chapter is a tandem reaction as shown in Scheme 3.2 using styrene (**1**) as a model substrate. In the first step, a carboxylic acid (phenylpropionic acid, **2n** or **2b**) is formed from a reaction of **1** with CO and FA. In the second step, the produced carboxylic acid will act as the nucleophile in the carbonylation of **1**, forming the carboxylic acid anhydride (phenylpropionic acid anhydride, **3nn**, **3bn** or **3bb**). To analyse the reactant and products in this reaction, we implemented NMR analysis to quantify **2** (**2n**, **2b**) and **3** (**3nn**, **3bn**, **3bb**), and GC analysis to quantify **1**. The yield% was calculated with respect to the limiting reagent (in most cases formic acid unless otherwise specified).



Scheme 3.2. Synthesis of anhydrides from styrene (**1**) and formic acid: intermediates and products.

Highly selective formation of linear acids or esters from alkenes can be achieved with a palladium-based catalytic system with the electron-rich and bulky ligand 1,2-bis(di-*tert*-butylphosphanylmethyl)benzene.[16] However, in our previous studies on carbonylative

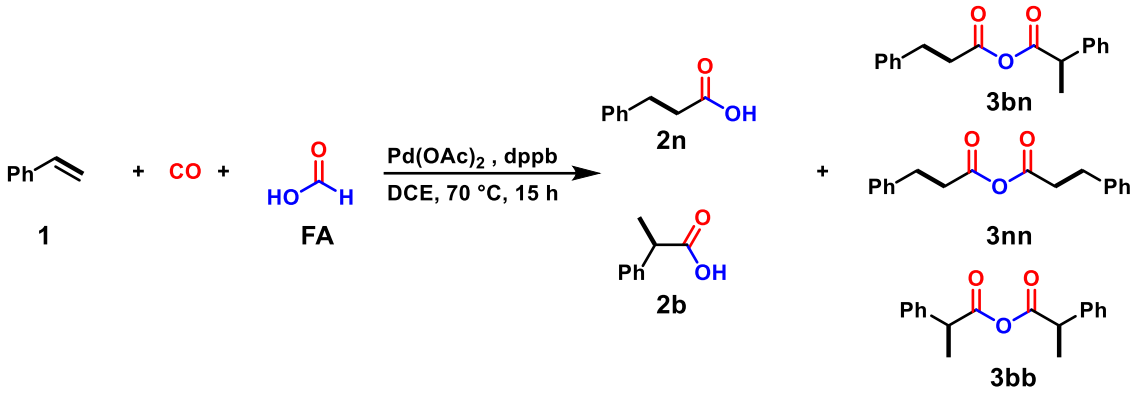
synthesis of imides and acid anhydrides, we found that use of electron-donating ligands in our catalytic system resulted in very slow catalysis and hence electron-withdrawing groups (such as phenyls) on phosphorus atoms was essential.[7,17] We also found that addition of strong acids was detrimental for catalysis; most likely it hampers formation of the carboxylate nucleophile. Based on this prior knowledge, for our initial trials in the current study we used the optimal conditions previously established for the carbonylation reaction of **1** with 3-phenylpropionic acid (**2n**): 1,4-bis(diphenylphosphanyl)butane (dppb) as the phosphine ligand, in combination with $Pd(OAc)_2$ as the pre-catalyst in 1,2-dichloroethane (DCE).

*Varying **1**:FA ratio*. Ideally, the envisioned reaction should be carried out with an alkene to FA ratio of 2:1, as in the first step one equivalent of carboxylic acid **2** should be formed, which then acts as the nucleophile in the second step forming **3**. Thus, we started our investigations with a study to establish the optimal substrate to FA ratio, as we have shown in our previous work that the hydrocarbonylation of **1** with **2n** is an equilibrium reaction (with a calculated $\Delta G_{\text{gas-phase}}$ value close to zero) and benefits from the use of an excess of one of the substrates.

We began with testing our established catalytic conditions for anhydride synthesis from alkenes with FA in excess (Table 3.1, entry 1). As expected, this resulted in ~90% phenylpropionic acid (**2**, 82:18 **2n**:**2b**), which confirmed the instability of the produced formate anhydride. An equimolar ratio of **1**:FA resulted in the same yield of **2** with only a trace amount of **3nn** (Table 3.1, entry 2). As decomposition of the formate anhydride to **2** is accompanied by the formation of CO, overall the net reaction does not consume CO, as is nicely demonstrated by the absence of a CO pressure drop (Figure AII.1). The result of this reaction seems to indicate faster kinetics of the nucleophilic attack by FA than by carboxylic acid **2**, as hardly any anhydride is formed. However, it cannot be excluded that upon formation of **3** a subsequent disproportionation reaction with FA ultimately results in generation of more **2**.

Use of stoichiometric amounts (for the net desired reaction) of **1** and FA of 2:1 resulted in 70% yield of phenylpropionic anhydride (**3**) (Table 3.1, entry 3). This value is similar to the equilibrium yield reported in our previous work.[7] Increasing the molar ratio of **1**:FA to 3:1 led to formation of **3** with a yield of 86% (Table 3.1, entry 4; please note that this yield is calculated with respect to the limiting reagent FA, the yield based on **1** is 57%). With the same amount of catalyst, the reaction could be scaled to 30:10 mmol **1**:FA generating a yield of 88% (Table 3.1, entry 5). Overall, we observe that the linearity obtained in both steps of the reactions is 75 to 80%, as reflected in the approximate 4:1 ratio found for **2n**:**2b**, and **3nn**:**3bn**:**3bb** ratios approaching the statistically expected values of 64:32:4.

Table 3.1. Influence of relative substrate ratio on product formation.[a]

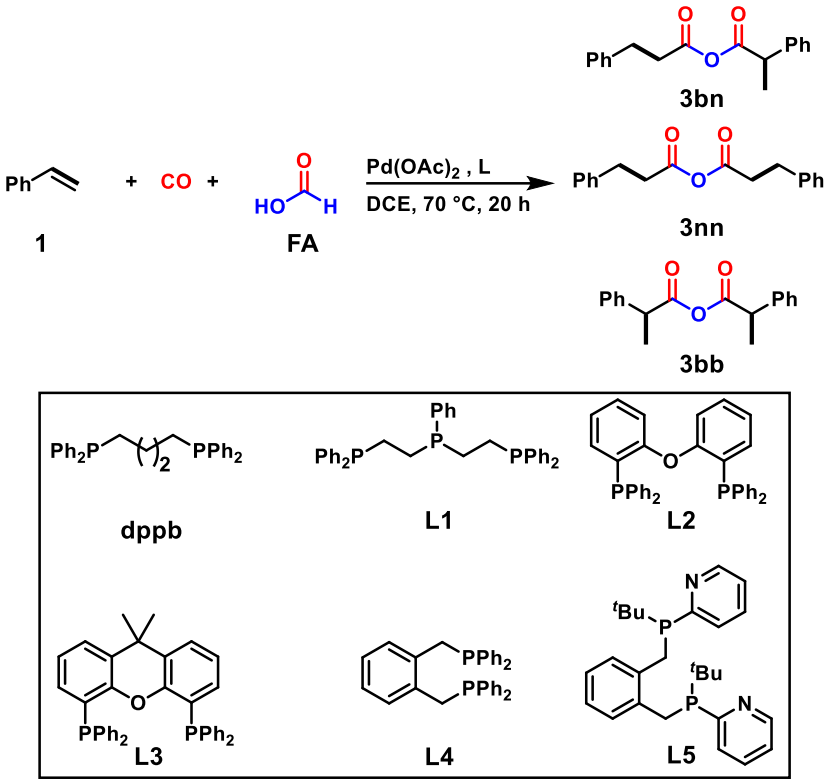


Entry	1:FA (mmol)	2 (mmol)	3 (mmol) (3nn:3bn:3bb)
1	5:10	4.5	0
2	5:5	4.6	Trace
3	10:5	1.3	3.5 (59:34:7)
4	15:5	1.0	4.3 (58:37:5)
5	30:10	1.5	8.8 (54:40:6)

[a] Reaction conditions: CO (50 bar), $Pd(OAc)_2$ (0.05 mmol), dppb (0.10 mmol), DCE (6 mL), 70 °C, 15 h. Amount of products and regioselectivity of **2** and **3** determined by quantitative NMR analysis with dibromomethane as internal standard (error ± 5%).

Influence on regioselectivity by ligands. We tested several phosphine ligands to study their influence on the reactivity and regioselectivity of the catalytic system (Table 3.2). A catalytic system comprising the tridentate ligand **L1** did not yield any product. Use of **L2** resulted in 82% yield of **3**, whereas use of **L3** resulted in a total anhydride yield of 72%, but at a reaction temperature of 85 °C. Rigid backbone, **L4** and **L5**, were tested for their activity. Interestingly, the xylene-based ligand **L4** resulted in 28% yield of **3** and 20% yield of **2** (also see Table AII.2, entry **L4**); apparently, the rigidity of the backbone significantly lowers the rate of the reaction. Similarly, the rate of the reaction comprising the catalytic system with **L5** is even lower, yielding only 16% of **3** and 60% of **2**, with a **2n**:**2b** ratio of 66:34 (also see Table AII.2, entry **L5**). In conclusion, the tested ligands mostly affect the rate of the reactions. Use of the more rigid **L4** or more electron-donating **L5** result in low yields of anhydride **3** and build-up of intermediate **2**. The linearity in products is approximately the same (75-80%) in all reactions with catalytic systems comprising phenyl-containing ligands, whereas use of **L5** leads to a lower linearity of about 65-70%.

Table 3.2. Influence of ligands on the yield and regioselectivity in the formation of anhydrides.



Entry	Ligand	Yield% of 3	3nn:3bn:3bb
1[a]	**dppb**	86	58:37:5
2	**L1**	0	-
3	**L2**	82	61:34:5
4[b]	**L3**	72	58:35:7
5[c]	**L4**	28	57:43:trace
6[c]	**L5**	16	47:53:trace

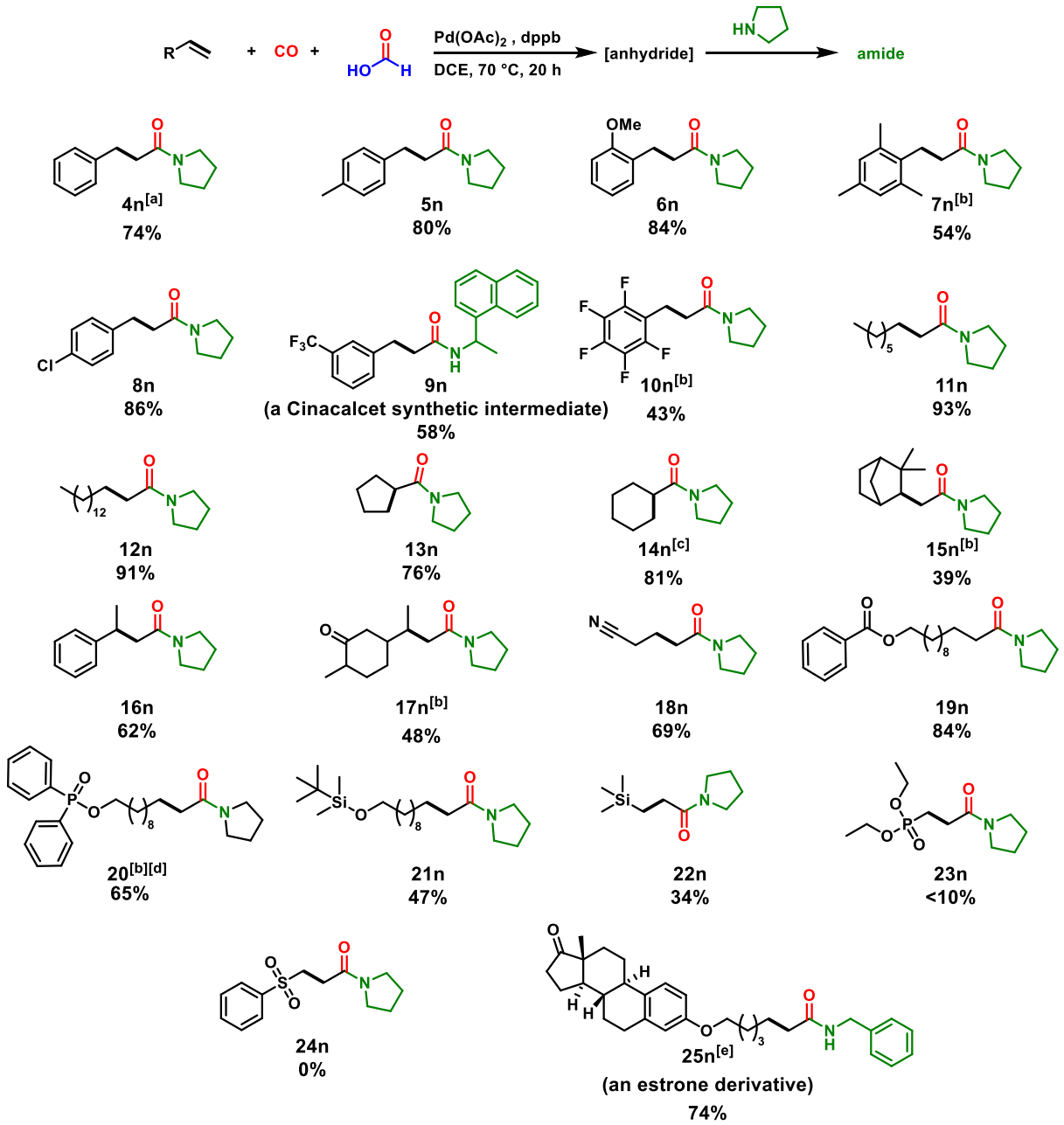
Reaction conditions: **1** (15.0 mmol), FA (5.0 mmol), CO (50 bar), $Pd(OAc)_2$ (0.05 mmol), ligand (0.10 mmol), DCE (6 mL), 70 °C, 20 h. Yield% (based on FA) and regioselectivity of **3** determined by NMR analysis with dibromomethane as internal standard. [a] 15 h instead of 20 h. [b] 85 °C instead of 70 °C. [c] **1** (7.5 mmol), FA (2.5 mmol), $Pd(OAc)_2$ (0.025 mmol), ligand (0.325 mmol).

Substrate Scope. Based on the commercial availability of the ligand dppb, and the fact that the different ligands result in more or less the same selectivity, a series of substrates were screened using the most active catalytic system dppb/$Pd(OAc)_2$ at an alkene:FA ratio of 3:1 and a catalyst loading of 1.0 mol% (Scheme 3.3). Since acid anhydrides are prone to degradation on isolation, the reaction mixtures were derivatized with pyrrolidine (unless specified otherwise) in basic conditions (see Section AII.5) to produce amides **4**; the amount of pure linear amide isolated by column chromatography is reported (provided yield% is related to FA as the limiting reagent, the numbers should be multiplied with 0.67 to obtain the yield% relative to alkene).

Linear amide **4n** was isolated in 74% yield from our benchmark reaction with **1**. The reaction can be applied to a large variety of styrene-based substrates, resulting in **5n**–**10n** in reasonable to high yields of 43-86%. In some of the reactions the NMR yield of the intermediate anhydride was significantly higher (Table AII.3), indicating that either the derivatization reaction or the isolation of the amide product is more difficult. The reaction with trimethylstyrene as the substrate appeared to be significantly slower, as observed from the CO pressure drop (still dropping after a reaction time of 36 h), leading to a yield of 54% **7n** on derivatization. The reaction with *m*-CF_3-styrene resulted in 68% of anhydride and was derivatized with another amine, (1R)-(+)-1-naphthylethylamine, providing **9n** in a yield of 58%. This compound **9n** is an intermediate in the synthesis of the Cinacalcet,[18,19] a drug used to treat hyperparathyroidism in patients on dialysis with chronic kidney disease.

Unactivated long-chain alkenes such as 1-octene and 1-pentadecene yielded 93% **11n** and 91% **12n**, respectively. Cyclic alkenes are also efficiently converted into their corresponding amides, yielding 76% **13n** and 81% **14n**. The sterically demanding substrate (±)camphene yielded 39% **15n** (2:1 endo:exo) after a reaction time of 36 h. The CO pressure drop indicated that the catalysis was slow. Geminal disubstituted alkenes, α-methylstyrene and dihydrocarvone, yielded 62% **16n** and 48% **17n** (after 36 h), respectively. The catalytic system was found to be tolerant to functional groups such as ether (**6n**), ketone (**17n**), nitrile (**18n**), ester (**19n**), phosphinate ester (**20**) and silyl-/silylether (**21n**, **22n**), and gave modest (34% **22n**) to excellent (84% **19n**) yields. However, vinyl-based substrates containing a sulfone or phosphate group at the vicinal position generated little (<10%) or no anhydride. Palladium black formation was observed in catalytic reactions with substrates containing silyl or silylether functional groups.

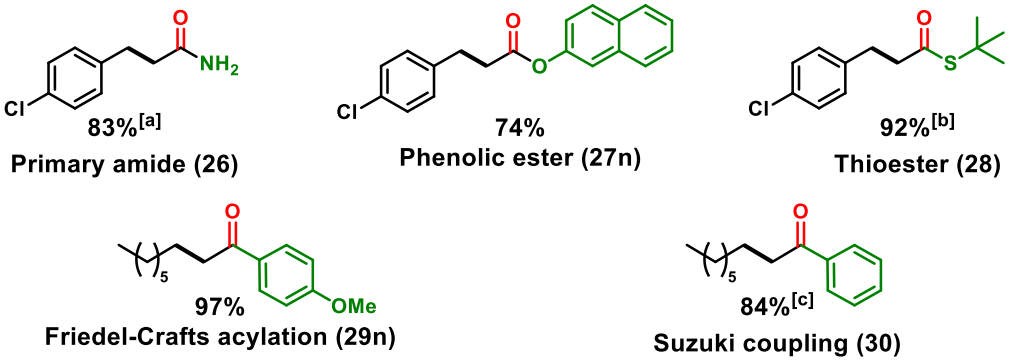
The reactions in this substrate scope were carried out using an excess of alkene (alkene:FA of 3:1), in order to drive the equilibrium to completion. However, whereas FA is readily available, very often the substrate alkenes are expensive or obtained after a multi-step synthetic route. The catalytic procedure was applied to an estrone derivative (scale: 2:1 mmol). For this reaction a catalyst loading of 2.5 mol% was used in order to obtain a reasonable rate for this dilute reaction, and 74% benzylamide **25n** was attained on derivatization with benzylamine.



Scheme 3.3. Synthesis of amides from alkenes and *in situ* generated carboxylic acid *via* carbonylation. Reaction conditions: alkene (3.0 equiv.; 15 or 7.5 mmol), FA (1.0 equiv.; 5 or 2.5 mmol), CO (50 bar), $Pd(OAc)_2$ (1.0 mol%), dppb (2.0 mol%), DCE (6.0 mL), 70 °C, 20 h. [a] 15 h instead of 20 h. [b] 36 h instead of 20 h. [c] alkene (3.0 equiv.; 30 mmol), FA (1.0 equiv.; 10 mmol), CO (50 bar), $Pd(OAc)_2$ (0.5 mol%), dppb (1.0 mol%), DCE (6.0 mL), 70 °C, 24 h. [d] presence of branched product, ratio of l:b 79:21. [e] alkene (2.0 mmol), FA (1.0 mmol), CO (50 bar), $Pd(OAc)_2$ (2.5 mol%), dppb (5.0 mol%), DCE (6.0 mL), 70 °C, 20 h. Yield% are based on FA.

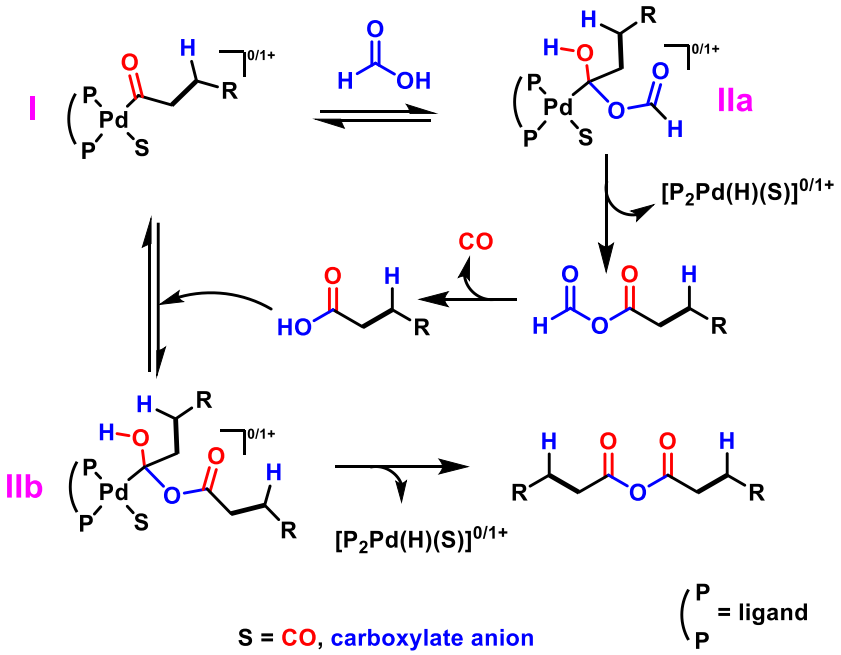
Applications. The reactivity of acid anhydrides allows access to molecules that may be otherwise difficult to obtain *via* classical hydrocarbonylation reactions, either due to low reactivity of the nucleophile or poisoning of the catalyst by the nucleophile. The synthesis of primary amides using ammonia as nucleophile in carbonylation reactions is challenging, owing to the basicity of ammonia hindering metal-hydride formation, and the deactivation of the metal catalyst by formation of unreactive ammine complexes.[20,21] With our catalytic procedure

generating intermediate anhydrides from alkenes and FA, a one-pot derivatization with ammonia resulted in 83% of the primary amide **26** in 79% linearity. Poorly nucleophilic alcohols such as β-naphthol reacted with our catalytic mixture to form ester **27n** in a yield of 74%. Thiols, which are often considered as poisons in palladium-mediated catalysis, can be used as nucleophiles to produce thioesters,[22] and indeed derivatization of a reaction mixture with *tert*-butylthiol resulted in 92% thioester **28** with 85% linear selectivity Finally, we were able to generate ketones in excellent yields *via* a Friedel-Crafts acylation with anisole (97%, **29n**), and a metal-catalyzed Suzuki coupling with phenylboronic acid (84%, **30**).



Scheme 3. 4. One-pot derivatizations of catalytic reaction mixtures to synthesis amide, ester, thioester and ketones. [a] presence of branched product, l:b 79:21. [b] presence of branched product, l:b 85:15. [c] presence of branched product, l:b 92:8. Yield% is based on FA.

Mechanism. The carbonylation reaction with carboxylic acids as the nucleophiles most likely proceeds *via* the classical palladium-hydride[23,24] mechanism for the two cycles, first with FA as the nucleophile forming the formate anhydride that decomposes to a carboxylic acid, which then acts as the nucleophile in the second reaction (Scheme 3.5). Thus, in the first cycle acyl-palladium species **I** undergoes a nucleophilic attack by FA to form a formate-mixed anhydride *via* intermediate **IIa**. This formate acid anhydride is unstable at higher temperatures, decomposing to release CO and carboxylic acid. The CO released in this case compensates for the CO consumed and hence, we do not observe a drop in CO pressure when we use equimolar amounts of **1**:FA to form **2** (see Figure AII.1). The formed carboxylic acid may then act as a nucleophile reacting with **I** to form **IIb**, which yields the acid anhydride fully derived from two molecules of the alkene. Since the acid anhydride formed in the reaction may equilibrate with the regeneration of the reactants, an excess of the alkene may promote the reaction in the forward direction towards the desired product.



Scheme 3.5. Postulated mechanism of tandem hydroacyloxycarbonylation of alkenes to synthesize acid anhydrides.

3.3. Conclusion

In summary, a carbonylative synthesis is reported for the production of symmetric anhydrides from alkenes *via* tandem reaction using FA for *in situ* generation of a carboxylic acid. The catalytic procedure is applicable to a wide range of substrates and is tolerant to various functional groups to produce moderate to excellent yields of anhydrides that are derived from two molecules of the alkene substrate. Further, the anhydrides formed can be derivatized to amides, esters, thioesters and ketones by simple one-pot derivatization reactions. Moreover, a recent report on formation of two molecules of acyl derivative, instead of one, by electrophilic activation of symmetric acid anhydrides[25] further adds to the future scope for sustainability of this reaction.

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4

Regioselectivity in Carbonylation of Pentenoic Acid to Synthesize Cyclic Anhydrides

*Pentenoic acids (PEA) obtained from lignocellulosic biomass derived γ-valerolactone (GVL) can be used as a platform for sustainable and atom-economic synthesis of adipic acid and its derivatives. Herein, a study is reported on the cyclocarbonylation reaction of PEA to synthesize five- (**5a**), six- (**6a**) or seven (**7a**) membered cyclic anhydrides, with the aim to drive the reaction towards potential nylon-6 intermediate **7a** (adipic anhydride). Carbonylation of 4-PEA yielded up to 73% cyclic anhydrides with a **7a**:**6a** selectivity of 79:21, using a palladium-based catalytic system with simple chelating diphenylphosphine ligands in the absence of strong acids. Use of the same catalytic system on the substrate 3-PEA resulted in the formation of **6a** and **5a** in a ratio of 41:59 with a total yield of 61%, showing that the catalytic system in absence of a strong acid is not active in isomerization. The reaction also yielded the side products 4-pentenoic anhydride (4-PEAn) and adipic acid, whose formation can be partially controlled by modulating the [Pd]:substrate ratio and concentration of the reaction mixture. In the presence of strong acids, isomerization was prevalent and led predominantly to the formation of smaller rings (**6a** and **5a**) from 4-PEA. However, isomerization is necessary in order to obtain **7a** from the mixture of PEA isomers that is derived from GVL. Unfortunately, mostly **6a** and trace amounts of **7a** was obtained in very low yields, using a catalytic system containing a ligand with bulky tert-butyl substituents, which has been reported to be highly selective for the formation of terminal carbonyl products, indicating that electron-poor ligands are necessary for obtaining higher activity. Although **7a** can be obtained from 4-PEA in reasonable selectivity, there still remains a challenge to selectively synthesize **7a** from a mixture of PEA isomers. In order to reach this goal, attempts must be undertaken to design the ideal ligand, which is electron-withdrawing for higher activity and bulky enough to enforce selectivity*

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Regioselectivity in Carbonylation of Pentenoic Acid to Synthesize Cyclic Anhydrides. *A. Ramakrishnan, E. Bouwman.*

4.1. Introduction

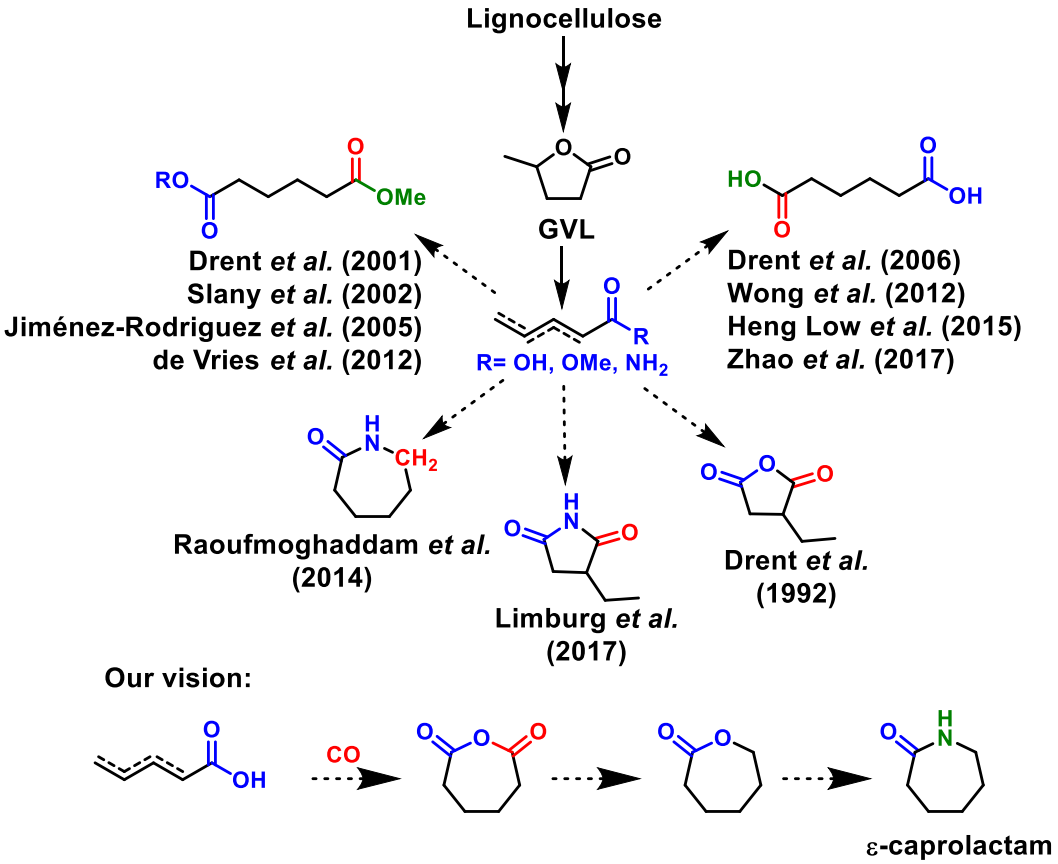
Depletion of fossil fuels has intensified the search for bio-based alternatives from renewable resources that can effectively be used for synthesis of commodity chemicals. A pivotal example in this regard is the pursuit of a sustainable route for the synthesis of adipic acid. Adipic acid is considered the most industrially important dicarboxylic acid by International Energy Agency (IEA) with a production of 3 million tonnes per year worldwide.[1] Its major use lies in the production of nylon, although a significant percentage of its derivatives is used in the manufacture of plasticizers, polyurethanes, pharmaceuticals and food-related products. Its synthetic route relies on petrochemical precursors, mainly benzene, and a bio-based and sustainable approach for its production would be highly desirable.[1–3]

An inexpensive, readily available, and multi-functional source of biomass is lignocellulose – a mixture of cellulose, hemi-cellulose and lignin.[4] γ-Valerolactone (GVL) is one of the chemical platforms that can be derived from lignocellulose, and which is obtained *via* a two-stage hydrolysis process of cellulose to produce levulinic acid followed by its hydrogenation.[5–7] Acid-catalyzed ring opening of GVL produces a mixture of pentenoic acids (PEA).[8,9] Transition-metal catalyzed carbonylation of pentenoic acids grants access to six-carbon diacyl molecules including adipic acid and its derivatives, thereby providing an atom-economical and sustainable route to their synthesis.

Catalytic hydrocarboxylation and hydroalkoxycarbonylation reactions of PEA (or its methyl esters) have been extensively studied by several groups to synthesize adipic acid,[10–13] or its corresponding mono- and diesters (Scheme 4.1).[14–17] A palladium-based catalytic system with the electron-rich and bulky ligand 1,2-bis(di-*tert*-butylphosphanylmethyl)benzene (**L7**) has been reported to be highly selective for formation of linear acids or esters, even from internal alkenes by isomerization under a CO atmosphere.[18] The bulkiness of the ligand also accelerates the rate-determining nucleophilic attack giving the final product.[19,20]

Pentenamides – amide derivatives of PEA, have been used as substrates in Rh-catalyzed intramolecular hydroamidomethylation reactions with the aim to synthesize ε-caprolactam.[21] The use of a palladium-based catalytic system for this carbonylation reaction results in intramolecular amidocarbonylation instead of cycloamidomethylation, giving rise to the formation of 2-ethylsuccinimide and 2-methylglutarimide, rather than the desired adipimide.[22] These reactions require use of electron-withdrawing phosphine ligands for activation of the poorly nucleophilic amide group. 2-Ethylsuccinic anhydride can be formed with high selectivity from 3-pentenoic acid (3-PEA), using a similar palladium-catalyzed carbonylation reaction.[23]

To the best of our knowledge, a catalytic methodology to selectively synthesize seven- or six-membered cyclic anhydrides has not yet been reported. Recently, we developed a palladium-based catalytic system to synthesize carboxylic acid anhydrides from alkenes and carboxylic acids.[24] This prompted us to investigate the factors that govern selective formation of the three cyclic anhydrides that can be obtained from cyclocarbonylation of PEA. A keen interest lies in the selective formation of the seven-membered ring adipic anhydride as it may serve as a valuable intermediate to produce ε-caprolactam for the production of biobased nylon-6.



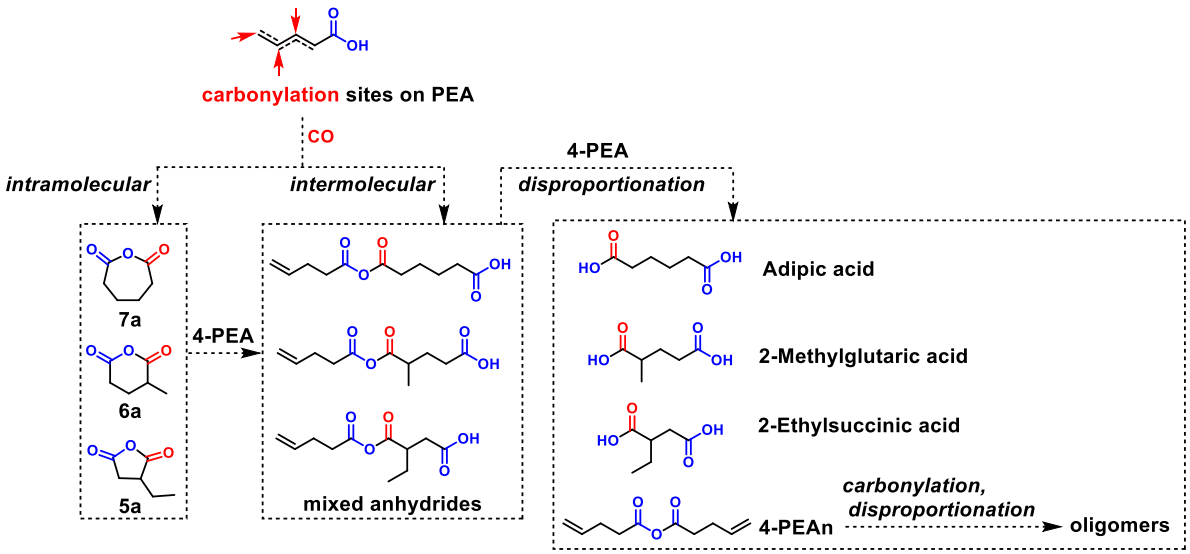
Scheme 4.1. Reported carbonylation reactions of pentenoic acid, ester or amide (ref. 10-17 and 21-23) (top) and envisioned route to synthesize ε-caprolactam from pentenoic acid (bottom).

4.2. Results and Discussion

General reaction considerations. As the product derived from GVL consists of different isomers of pentenoic acid, we chose 4-pentenoic acid (4-PEA) as a model substrate to study the cyclocarbonylation reaction. 4-PEA constitutes a fraction of ~30% of a PEA mixture derived from GVL, and it is cheap and abundantly available.[9,12,13] The potential products expected from carbonylation of 4-PEA are outlined in Scheme 4.2. Based on the regioselectivity of the reaction, adipic anhydride (**7a**; the numbering is related to the ring size), 2-methylglutaric anhydride (**6a**) and 2-ethylsuccinic anhydride (**5a**) are the expected products of cyclocarbonylation. Apart from the desired intramolecular cyclization reaction, 4-PEA (or PEA

isomers) may also undergo intermolecular reactions resulting in the formation of undesired mixed anhydrides. These reactive anhydrides can disproportionate by reacting with another molecule of 4-PEA to produce 4-pentenoic anhydride (4-PEAn) with the release of a diacid (adipic acid, 2-methylglutaric acid, 2-ethylsuccinic acid).[24] 4-PEAn, having a double bond at both ends, may undergo sequential intermolecular carbonylation and disproportionation to form higher molecular weight oligomers with subsequent release of diacids. It is important to note that the diacids are highly soluble in polar solvents (water, methanol) and poorly soluble in less-polar solvents, unlike the cyclic anhydrides that are readily soluble in most of the solvents.

Dilute reaction conditions are often essential for obtaining high selectivity in intramolecular reactions. We tested catalysis at different substrate loadings to establish the optimal concentrations of catalyst and substrates (Table AIII.4). Reactions were carried out with increasing substrate concentrations with the same amount of catalyst ($Pd(OAc)_2$ / **L2**, see next section) and solvent (1,2-dichloroethane, DCE), using 1, 2.5 or 5 mmol of 4-PEA, corresponding with approximately 0.1, 0.25 and 0.5 M concentrations of substrate and 5, 2 and 1 mol% of catalyst, respectively. The conversion of substrate in these reactions was rather comparable, but the mass balance (from 93 to 69%) and the total yield of desired cyclic anhydrides (from 73 to 16%) dropped considerably with higher substrate concentrations. With higher concentrations of substrate in the reaction mixtures the relative selectivity for **7a** over **6a** dropped (from 80:20 to 65:35), and increasing amounts of adipic acid and 4-PEAn were formed, indicating that yield and selectivity towards the desired product **7a** are limited by increased probability of intermolecular reactions at higher concentrations and higher conversion. Despite the observation that the reaction at 1 mol% still proceeds, we chose to



Scheme 4.2. Carbonylation of 4-PEA : possible products from intra- and intermolecular carbonylation.

continue our investigations with a substrate concentration of 0.1 M and with 5 mol% of catalyst, as the reaction rates become very low at lower catalyst concentrations.

Influence of ligands. We started our investigations on cyclocarbonylation of 4-PEA using $Pd(OAc)_2$ at 5 mol% as the pre-catalyst at 105 °C in 1,2-dichloroethane (DCE) as solvent for 15 h. Various ligands were tested to examine their effect on the regioselectivity in the formation of **5a**, **6a** and **7a**. The substrate and products were quantified by GC analysis and the results of the experiments are shown in Figure 4.1. The use of diphosphines with an alkyl backbone (**L1** to **L4**) resulted in formation of **7a** and **6a** with different regioselectivities. Use of **L1** yielded 21% cyclic anhydrides with poor selectivity of 57:43 for **7a**:**6a** while use of **L3** gave a yield of 49% with a good selectivity of 78:22 for **7a**:**6a**. Use of the ligand **L2** resulted in the highest yield up to 73% cyclic anhydrides with a **7a**:**6a** selectivity of 79:21. A palladium-based system containing **L2** has been reported to catalyze intramolecular carbonylation of 3-allyl-4-hydroxycoumarin to seven-membered cyclic lactones.[25] The use of **L4** in our reaction did not yield anhydrides in detectable amounts.

The results with **L2** encouraged us to test other ligands with C4 backbones. We envisioned that replacing the flexible alkyl backbone with a rigid xylene structure might improve selectivity for **7a**. The use of **L5** and **L6** indeed resulted in excellent regioselectivity of 88:12 and >99:- for **7a**:**6a** but the total yield dropped to 40 and 17%, respectively. At a higher temperature of 135 °C, a reaction using **L6** resulted in the isomerization of 4-PEA to internal alkenes along with little formation of **6a** and **7a** (Table AIII.1, entry 7). The use of **L7**, with electron-donating *tert*-butyl groups on phosphorus, yielded no anhydrides at all.

Diphosphine ligands having larger bite angles were also tested. The catalytic system containing **L8** at 135 °C resulted in a total anhydride yield of 49% with **7a**:**6a** selectivity of 79:21. Unexpectedly, use of **L9** resulted in higher selectivity for **6a** (ratio of 36:64) without any sign of isomerization of 4-PEA. The catalytic system comprising **L10** showed high selectivity for **6a** although the overall yield was poor.

A palladium-based catalytic system containing the monodentate ligand **L11** has been shown to catalyze intramolecular hydroalkoxycarbonylation of 2-allylphenols to synthesize 6-membered lactones;[26] in our reaction, this catalytic system selectively yielded **6a**. The catalytic system with **L12** resulted in trace formation of **7a** and yielded 4% **6a**. It is important to note that the amounts of **5a** formed in each of the reactions was low (trace to none), indicating that isomerization did not take place. In accordance with this observation, application of the

catalytic system $Pd(OAc)_2$/**L2** on the substrate 3-PEA resulted in the formation of **6a** and **5a** in a ratio of 41:59 with a total yield of 61% (Table AIII.3, entry 1) without a trace of **7a** or isomerization to 4-PEA.

Several reaction mixtures showed slight turbidity at the end of the reactions, indicating formation of a precipitate. The solid material that was isolated from the catalytic reaction using

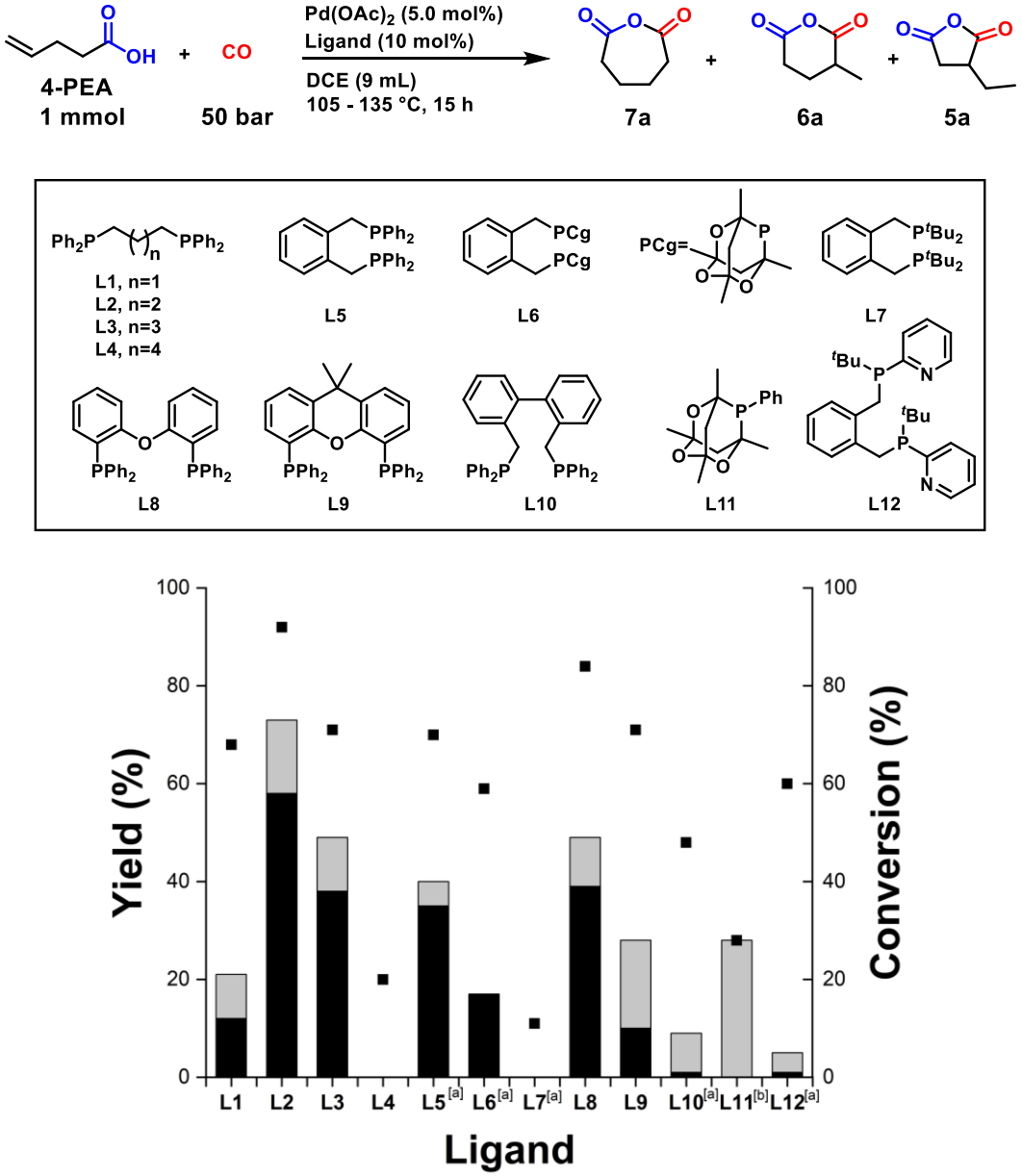


Figure 4.1. Conversion of PEA, yield of and selectivity for cyclic anhydrides for catalytic systems comprising different phosphine ligands in cyclocarbonylation of 4-PEA. Reaction conditions: 4-PEA (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), ligand (0.10 mmol), CO (50 bar), DCE (9 mL), 15 h. Yield % of cyclic anhydrides (left y-axis) indicating regioselectivity (**7a**, black bar; **6a**, grey bar) and conversion % (■, right y-axis) determined by GC using undecane as internal standard. Temperature of 105 °C used for **L1** to **L4** and **L11**. Temperature of 120 °C used for **L5** to **L7**, **L9** and **L11**. Temperature of 135 °C used for **L8**. [a] 0.075 mmol ligand used instead of 0.10 mmol. [b] 0.20 mmol ligand used instead of 0.10 mmol.

L2 appeared to be soluble in methanol and the major constituent of this precipitate was identified as adipic acid (~8% yield, quantified with ^{1}H NMR) with unidentified impurities. In addition to adipic acid, reaction mixtures also showed formation of 4-PEAn and in several cases, significant loss in mass balance.

Use of different palladium salts. The use of different palladium salts in the catalytic system containing **L2** as ligand resulted in large differences in yields and regioselectivity of the reaction (Table AIII.2, entries 1 to 3). Whereas with $Pd(OAc)_2$ a total yield of 73% cyclic anhydrides was obtained with **7a**:**6a** selectivity of 79:21, a reaction with $Pd(TFA)_2$ resulted in a yield of 70% cyclic anhydrides with a selectivity for **7a**:**6a**:**5a** of 12:55:33. A catalytic system with $PdCl_2$ did not yield any cyclic product, which may be attributed to strong coordination of chloride anions to the metal center. Observing the difference in regioselectivity on varying the counter ion, we then studied the influence of various additives on the outcome of our catalytic reaction based on the anion generated by the additive and its coordinating ability using the catalytic system $Pd(OAc)_2$/**L2**.

Influence of additives. For stimulating isomerization, *p*-toluenesulfonic acid ($HOTs.H_2O$, pK_a –2.8) or methanesulfonic acid (HOMs, pK_a –1.9) are often added to palladium-based catalytic systems with bulky ligands such as **L7**, yielding terminal products of long chain unsaturated fatty acids with internal double bonds such as oleic or linoleic acid (and their derivatives) in hydroxy- or methoxycarbonylation reactions.[27–29] Typically, the acidity (pK_a) of an acid additive dictates the coordinating ability of the resulting anion and thereby the rate of β-hydrogen elimination and thus the rate of isomerization.

Using the catalytic system $Pd(OAc)_2$/**L2**, various additives were tested at 12.5 mol% and the key results are presented in Figure 4.2 (see also Table AIII.2). Because of the acidic 4-PEA substrate, we consider the standard reaction to comprise the substrate itself as additive with a pK_a of 4.9. The addition of formic acid (FA, pK_a 3.8) or 2,4,6-trimethylbenzoic acid (TBA, pK_a 3.5), resulted in formation of **7a** as the major cyclic product, although the relative selectivity for **7a** became smaller (Table AIII.2, entries 4 and 5). Addition of phenyl phosphonic acid (PPA, pK_a 1.8) led to a total anhydride yield of 76% with a selectivity of 10:56:34 for **7a**:**6a**:**5a**. Use of camphorsulfonic acid (10-CSA, pK_a 1.2) yielded a mixture of **6a** and **5a** in a ratio of 26:74, with a total yield of 85%. Catalytic systems comprising *p*-toluenesulfonic acid ($HOTs.H_2O$, pK_a –2.8) or methanesulfonic acid (HOMs, pK_a –1.9) resulted in exclusive formation of **5a** (>99% selectivity), in a yield of 69 and 83% respectively, confirming the requirement of a strong acid to enforce rapid isomerization.

We also tested the influence of addition of Lewis bases with relatively weak coordination ability. The use of alcohols (phenols, naphthol, hexafluoroisopropanol) resulted in selectivity for **7a**, but neither the total yield of cyclic anhydrides nor the overall regioselectivity improved relative to the standard reaction (Table AIII.2, entries 16 to 20).

Palladium-based catalytic systems in combination with $SnCl_2$ have been reported to catalyze hydroalkoxycarbonylation and cyclocarbonylation of alkenols to lactones.[30–32] It was stated that use of the hydrate ($SnCl_2.H_2O$) is essential for promoting formation of a palladium-hydride species. As in our reaction the presence of an excess of PEA guarantees formation of palladium-hydride species, we used anhydrous $SnCl_2$ in combination with **L2**/$Pd(OAc)_2$ in our catalytic reaction, which resulted in 92% yield of cyclic anhydrides with formation of **5a** up to 90% and 10% **6a**. We presume that the catalyst formed contains the weakly coordinating anion

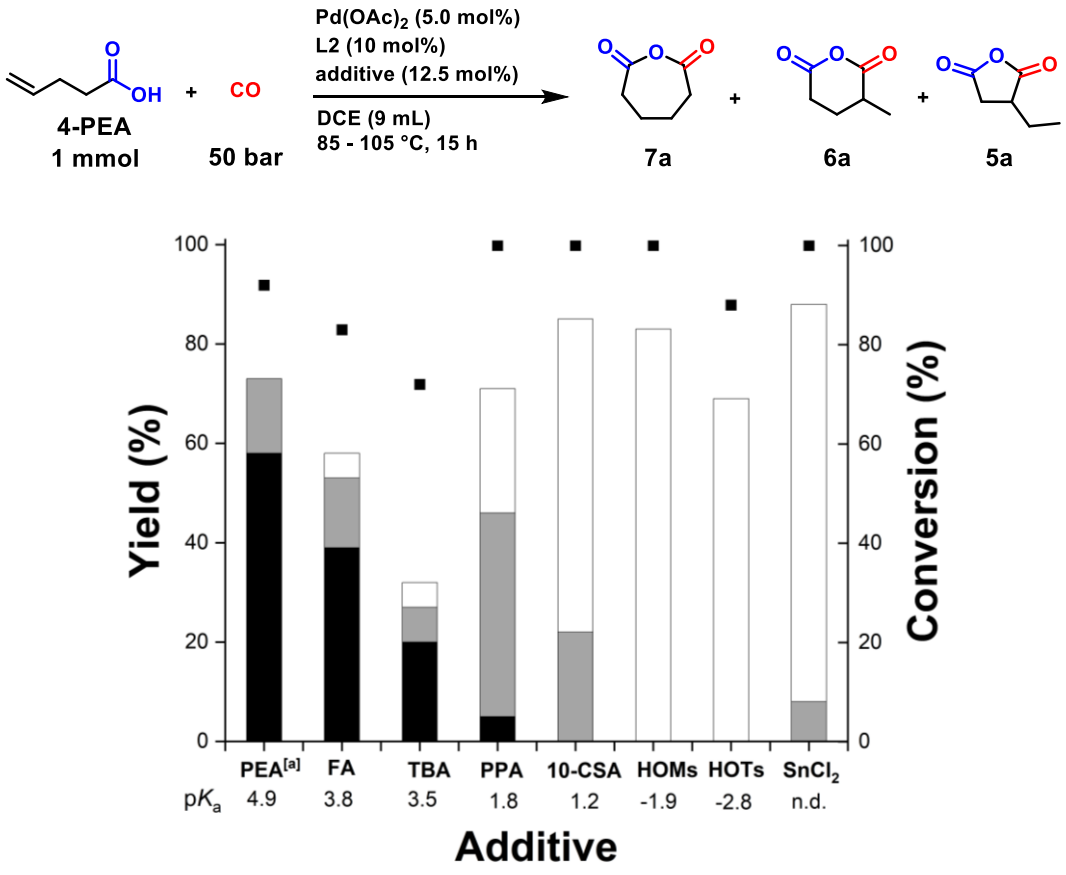


Figure 4.2. Conversion of PEA, yield of and selectivity for cyclic anhydrides for catalytic systems comprising different additives in cyclocarbonylation of 4-PEA. Reaction conditions: 4-PEA (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), **L2** (0.10 mmol), additive (0.125 mmol), CO (50 bar), 85 °C, DCE (9 mL), 15 h. Yield % of cyclic anhydrides (left y-axis), regioselectivity (**7a**, black bar; **6a**, grey bar; **5a**, white bar) and conversion % of PEA (■, right y-axis) determined by GC using undecane as internal standard. [a] Temperature of 105 °C used instead of 85 °C. Abbreviations: FA: formic acid, TBA: 2,4,6-trimethylbenzoic acid, PPA: phenylphosphonic acid, 10-CSA: camphorsulfonic acid, HOMs: methanesulfonic acid, HOTs: *p*-toluenesulfonic acid monohydrate, $SnCl_2$: tin(II) chloride, n.d.: not determined.

$[SnCl_2(PEA)]^-$, as its presence was observed in a ESI mass spectrum of a methanolic solution of $SnCl_2$ with an excess of 4-PEA (pH of the solution was found to be ~ 0 - 1; see Figure AIII.6). Unfortunately, reports of pK_a values of protonated Sn(II) anions are scarce; the pK_a of $HSn(C_2F_5)_3$ has been reported to be 0.8.[33] The very low pH of a methanolic solution of $SnCl_2$ and 4-PEA indicates that the formed $[SnCl_2(PEA)]^-$ anion is weakly to non-coordinating, and the catalytic results indicate that in terms of acidity the $SnCl_2$ additive should be ranked between 10-CSA and HOMs. The use of $SnCl_2$ with **L2**/$PdCl_2$ (with the supposed generation of $SnCl_3^-$) in our reaction resulted in complete selectivity for **5a** but in a low yield of 24% (Table AIII.2, entry 12).

*Attempts to improve selectivity for **7a***. The use of a catalytic system with isomerization activity is important in order to obtain a single product from the mixture of pentenoic acid isomers that is obtained from GVL. Additionally, a bulky ligand will be necessary to enforce isomerization to the terminal position in order obtain the desired **7a**. Although the catalytic system comprising **L2** shows relatively high activity and selectivity for **7a** in the absence of acids, unfortunately, the presence of strong acids resulted in formation of **5a** or **6a** due to the limited bulkiness of this ligand. We thus set out to expand our study on the effect of strong acids or weakly coordinating anions on the outcome of the reaction using other more rigid or bulky ligands. The results are provided in Table 4.1.

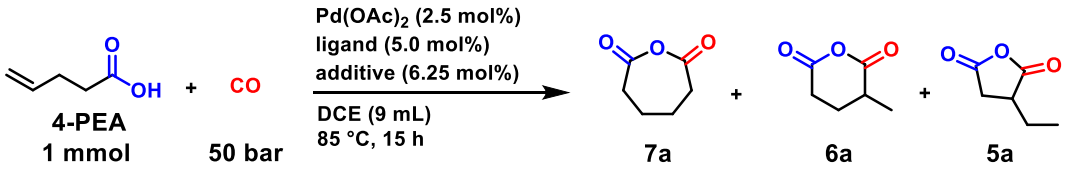
Addition of a strong acid to the catalytic system comprising the electron-donating ligand **L7** resulted in some catalytic activity, but unfortunately gave mostly **6a** and trace amounts of **7a**, albeit in very low yield (Table 4.1, entry 1). Use of the more strongly chelating ligand **L5** (as compared to **L2**) in combination with a strong acid also resulted in complete selectivity (>99%) for **5a** in a yield of 75% (Table 4.1, entry 2), while the more bulky and electron-withdrawing ligand **L6** yielded a small amount of **6a** in addition to **5a** in 94% selectivity (Table 4.1, entry 3). The use of **L6** in combination with acid in catalytic cycloamidocarbonylation of 4-pentenamide also resulted in high selectivity for the five-membered imide ring.[22] Remarkably, the ligand **L9**, with relatively electron-withdrawing phenyl groups and a large bite angle, in combination with acid maintained part of its selectivity for **7a** (Table 4.1, entry 4).

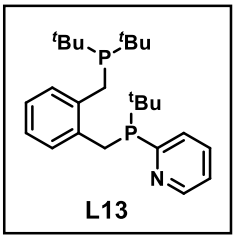
Use of the ligand **L12** in combination with HOTs in our reaction conditions selectively resulted in **6a** in a yield of 24% and traces of **7a** (Table 4.1, entry 5) while use of the more electron-donating ligand **L13** did not yield any product at all (Table 4.1, entry 6). Remarkably, the catalytic system comprising **L12** shows the same selectivity as that with **L7**, but with much higher activity (note the lower catalyst loading for **L12**). This observation strengthens our

hypothesis that ligands with relatively electron-withdrawing groups are required in order to obtain higher activity for reactions with the poorly nucleophilic carboxylate group. Using **L12** in the conditions reported for terminal hydroalkoxycarbonylation (toluene, 120 °C),[20] predominantly resulted in isomerization to internal alkenes and a very small amount of **6a** (Table AIII.2, entry 30).

Addition of $SnCl_2$ to the catalytic systems comprising the ligands **L9** or **L10** resulted in high yields of anhydrides with a selectivity for **6a** up to 81% (and 19% **5a**) from 4-PEA (Table 4.1, entry 7 and 8). This reaction was easily scaled up to 10 mmol at a catalyst loading of 0.5 mol% using **L10** as the ligand, resulting in a yield of 93% of cyclic anhydrides with 80% regioselectivity for **6a** (Table AIII.4, entry 5).

Table 4.1. Cyclocarbonylation of 4-PEA: Attempts to find an isomerizing catalyst to synthesize **7a**.



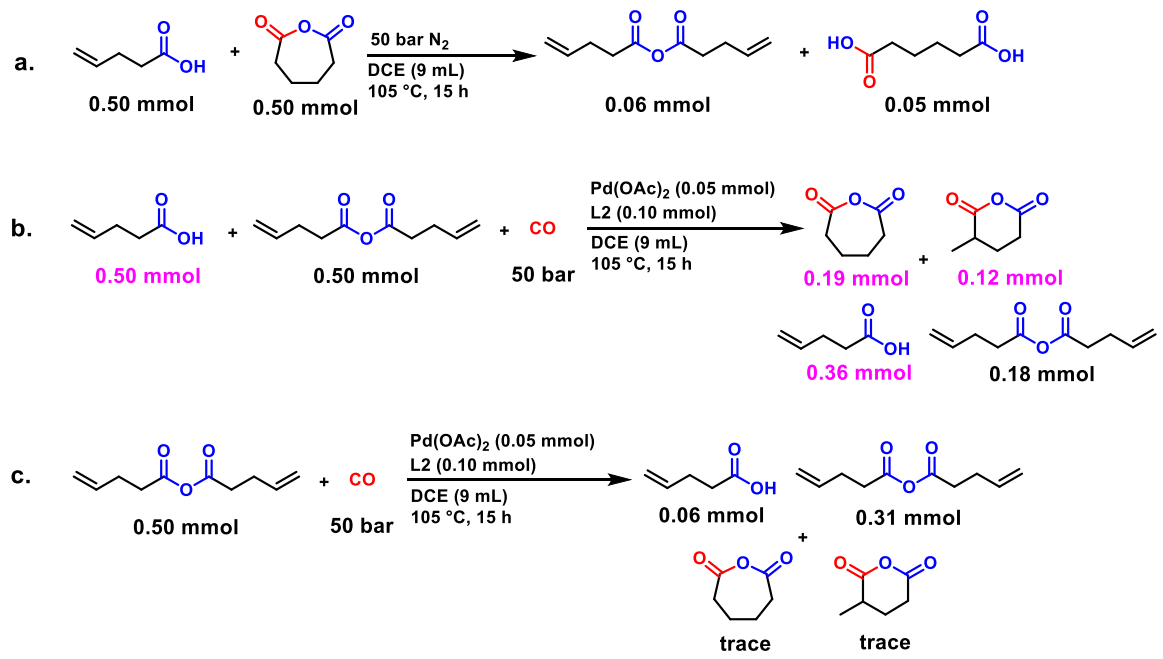


Entry	Ligand	Additive	Conversion %	Regioselectivity 7a:6a:5a	Total yield%
1[a]	**L7**	HOMs	36	trace : >99 : -	4
2[a]	**L5**	HOTs.H_2O	>99	- : - : >99	75
3[a][b]	**L6**	HOTs.H_2O	>99	- : 6 : 94	96
4	**L9**	HOTs.H_2O	>99	17:62:21	65
5[c]	**L12**	HOTs.H_2O	55	trace : >99 : -	24
6[c]	**L13**	HOTs.H_2O	22	-	-
7	**L9**	$SnCl_2$	>99	- : 81 : 19	96
8[a]	**L10**	$SnCl_2$	>99	- : 81 : 19	91

Reaction conditions: 4-PEA (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), ligand (0.050 mmol), additive (0.0625 mmol), CO (50 bar), 85°C, DCE (9 mL), 15 h. Total yield %, regioselectivity of cyclic anhydrides (**7a**, **6a**, **5a**) and conversion % of PEA determined by GC using undecane as internal standard. [a] ligand 0.0375 mmol instead of 0.050 mmol. [b] temperature 120 °C, solvent toluene. [c] $Pd(OAc)_2$ 0.010 mmol, ligand 0.015 mmol, additive 0.025 mmol.

Reaction insights. In the section 'General reaction considerations', we described the complexity of the reaction and the potential formation of side-products such as adipic acid and 4-PEAn, the anhydride of 4-PEA, whose formation are influenced by the concentration of the reactants and products formed. In most of our reaction mixtures, formation of 4-PEAn was observed and losses in mass balance indicate the formation of other products that we did not observe in the GC, or could not identify and quantify.

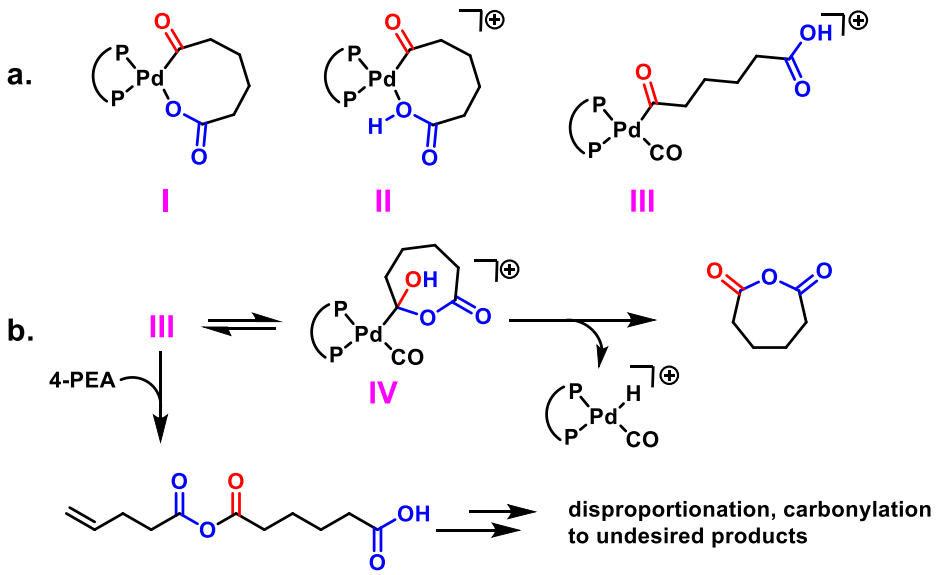
We carried out some test reactions in order to determine the fate of the desired reaction products under reaction conditions. Heating a mixture of **7a** and 4-PEA under N_2 resulted in substantial loss of **7a** and mass balance, formation of 4-PEAn along with small amounts of unknown products was observed by GC analysis (Scheme 4.3.a, Table AIII.5, Section AIII.8.1). Furthermore, a white precipitate was formed; NMR analysis in methanol-d^4 showed the major constituent of this solid to be adipic acid in approximately the same amount as 4-PEAn. Reaction of an equimolar amount of 4-PEA and 4-PEAn under catalytic conditions in presence of CO resulted in formation of **7a** and **6a**, a drastic decrease in the amount of 4-PEAn, and a larger amount of 4-PEA than would be expected based on the quantity of anhydrides formed (Scheme 4.3.b, Table AIII.6, Section AIII.8.2). The resulting reaction mixture was turbid and



Scheme 4.3. Control reactions to study 4-PEAn formation and loss of mass balance. Reaction conditions: a. 4-PEA (0.50 mmol), **7a** (0.50 mmol), DCE (9 mL), 105 °C, 15 h, 50 bar N_2. b. 4-PEA (0.50 mmol), 4-PEAn (0.50 mmol), CO (50 bar), $Pd(OAc)_2$ (0.05 mmol), **L2** (0.10 mmol), DCE (9 mL), 105 °C, 15 h. Changes in 4-PEA concentration (including products formed from 4-PEA) is highlighted in pink. c. 4-PEAn (0.50 mmol), CO (50 bar), $Pd(OAc)_2$ (0.05 mmol), **L2** (0.10 mmol), DCE (9 mL), 105 °C, 15 h. All compounds were quantified using GC analysis with undecane as internal standard.

the formation of adipic acid was confirmed by NMR. When the same reaction is performed in the absence of CO, the amount of 4-PEAn that is lost is lower (Table AIII.7, Section AIII.8.3). This suggests that the loss in mass balance observed under catalytic reactions in presence of CO is mostly due to hydrocarbonylation reactions occurring between 4-PEA and 4-PEAn, which would give rise to oligomers with the release of adipic acid. A reaction of 4-PEAn (0.50 mmol) as the substrate in catalytic conditions (Scheme 4.3.c) led to formation of traces of **7a** and **6a**, as well as 0.06 mmol of 4-PEA, which might be formed *via* the oxidative addition of 4-PEAn to Pd(0) followed by decarbonylation and β-hydrogen elimination to release 1,3-butadiene and 4-PEA (Section AIII.8.4, Scheme AIII.2).

Reaction Intermediates and Mechanism. It is safe to presume that the classical palladium-hydride pathway is operative in the catalytic cyclocarbonylation reaction described in this manuscript, proceeding *via* alkyl-palladium and acyl-palladium species in equilibrium reactions. In our standard reaction conditions, i.e. in absence of a strong acid, isomerization does not take place resulting in the exclusive formation of **7a** and **6a** when 4-PEA is used as the substrate and **6a** and **5a** from 3-PEA. This observation suggests that β-hydrogen elimination is hampered by relatively strong coordination of the carboxylate ion. Thus, in absence of an acidic additive, acyl-palladium intermediates **I** and **II** may be in equilibrium in solution (Scheme 4.4.a). Alternatively, PEA may be coordinated in **I** or **II** (either deprotonated or not) instead of the chelating carboxylate ion or carboxylic acid group, as they are of equal acidity.



Scheme 4.4. a. Various palladium-acyl species that can be formed from the carbonylation of PEA in the presence of different additives, assuming terminal regioselectivity starting from 4-PEA. b. Proposed termination step with formation of **7a** or side products; these can also occur from **I** or **II**. Structures are shown only for intermediates leading to the terminal products.

Isomerization does take place after addition of a strong acid, indicating that the equilibrium changes *via* intermediate **II** to intermediate **III**, with dissociation of the coordinating carboxylic acid group.

Finally, nucleophilic attack of the terminal carboxylate group of the substrate to the carbonyl carbon of the acyl-palladium intermediate may produce hydroxy-acyloxy-alkyl palladium intermediate **IV** (Scheme 4.4.b), which upon β-hydrogen elimination releases the product and regenerates the palladium-hydride.

4.3. Conclusion

We have herein presented the results of our study on catalytic cyclocarbonylation of 4-PEA and our endeavors to synthesize seven-, six- or five-membered cyclic anhydrides. Palladium-based catalytic systems in the absence of a strongly acidic additive are not active in isomerization and result in the formation of **7a** and **6a** when 4-PEA is used as the substrate, or in **6a** and **5a** when 3-PEA is the starting material. This means that the desired adipic anhydride **7a** may only be formed selectively starting from 4-PEA, when using the appropriate ligand. Isomerization activity is essential in order to make **7a** from a mixture of pentenoates, such as obtained from GVL.

In hydrocarboxylation of PEA, the formation of adipic acid is achieved by the use of the sterically bulky ligand **L7**. It has been computationally shown that potential chelate formation resulting in intermediates **I** and **II** favors isomerization to internal positions,[13] due to the higher stability of the smaller chelate rings. The bulky *tert*-butyl groups in **L7** hamper chelate formation and thus assist in the selectivity of the catalytic system to form the linear product adipic acid.[13] Although through the same reasoning the catalytic system comprising **L7** should selectively yield **7a**, predominantly **6a** was formed instead, but in a very low yield. Currently, it is not clear why use of **L7** leads to the formation of **6a** rather than **7a**. Possibly the kinetics of the terminating ring-closing steps determine the outcome of the reaction, as the steric bulk may prevent approach of the terminal carboxylate group of the linear acyl-palladium species.

Our results show that the use of electron-poor phosphine ligands is essential for obtaining higher catalytic rates, as exemplified by the results of **L7** and **L12** (Table 4.1). Thus, while we have demonstrated the feasibility of generating **7a** from 4-PEA, a key future challenge lies in identifying a catalytic system comprising a bulky ligand preventing chelation of the terminal carboxylate group to enable isomerization to the terminal carbon, in combination with electron-poor functional groups at phosphorus to enhance the rate of the termination reaction.

4.4. References

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5

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).

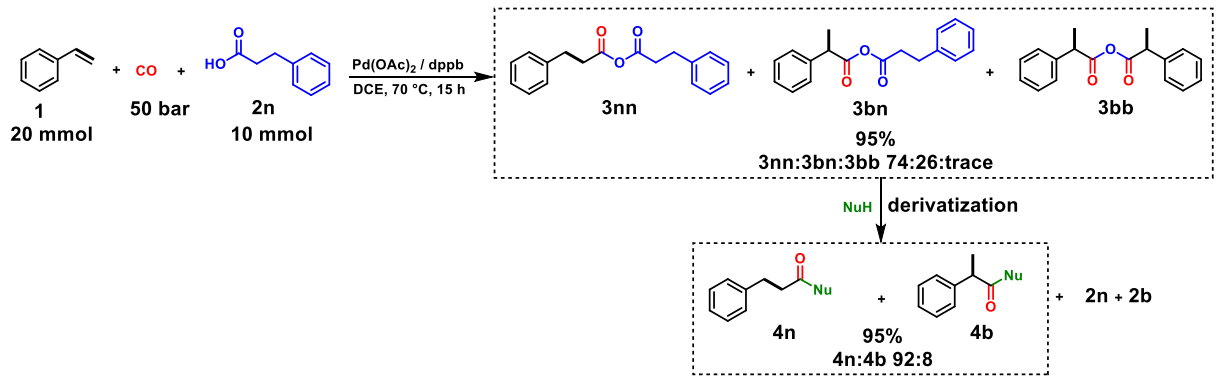
Carboxylic acid (or carboxylates) are considered to be weak nucleophiles, compared to alkoxides and water, and this low nucleophilicity may pose a challenge for their reactivity with an acyl-palladium intermediate. Only few reports describe the use of carboxylic acids as nucleophiles to synthesize acid 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.

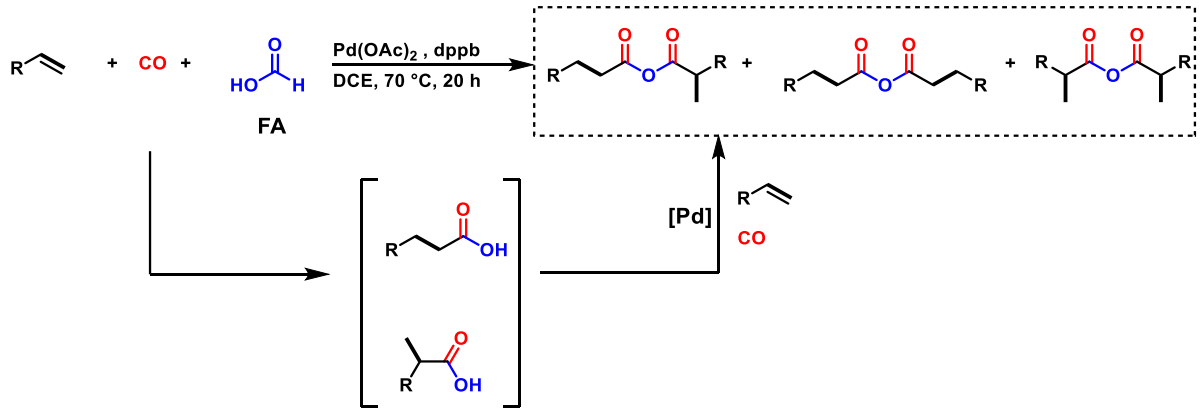
The optimized catalytic conditions were applied to a wide range of alkenes and carboxylic acids, resulting in symmetric as well as mixed anhydrides in moderate to high yields. The utility of this new catalytic procedure was demonstrated by the production of a primary amide and thioester, which are challenging 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



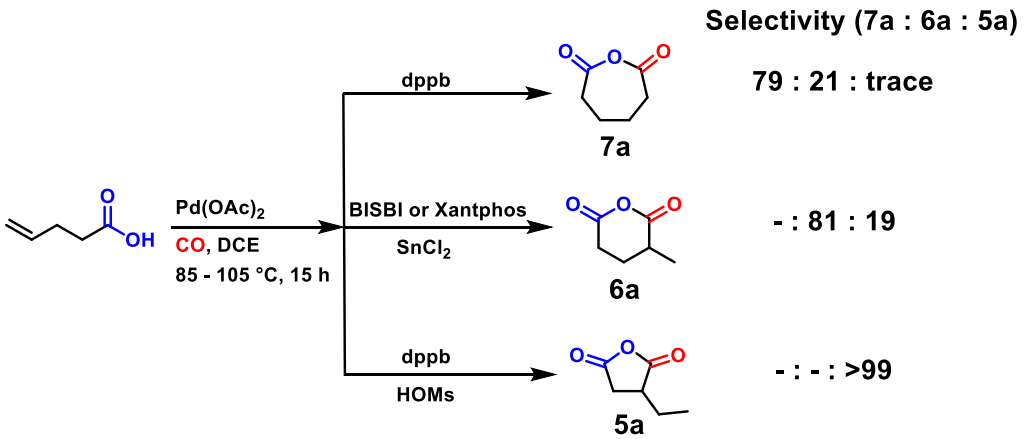
Scheme 5.2. Palladium-catalyzed synthesis of acid anhydrides from alkenes via *in situ* generated carboxylic acids.

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^tbpx) 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.

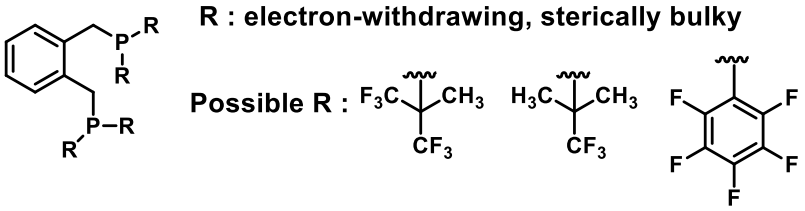


Figure 5.1. Postulated desired phosphine ligand for selective synthesis of **7a** under isomerizing conditions.

5.4. References

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Appendix I

Supporting Information for Chapter 2

Palladium-Catalyzed Synthesis of Carboxylic Acid Anhydrides from Alkenes

AI.1. General experiment details and materials

Reactions and chemicals related: All reactions and operations involving air- or moisture-sensitive compounds were performed using standard Schlenk techniques in heated and vacuum dried glassware or in N_2-filled glove box. Chemicals were purchased from Sigma-Aldrich, TCI, Acros, Brunschwig or Bio-connect and used without further purification unless otherwise stated. Anhydrous 1,2-dichloroethane (DCE) was purchased from Biosolve and dried over flame dried 4Å molecular sieves. Toluene and dichloromethane (DCM) were purchased from Honeywell and dispensed *via* Pure Solv solvent dispenser by Innovative Technologies. Solvents were freeze-pump-thawed (FPT) before all catalytic reactions. All ligands except 1,2-bis(diphenylphosphanylmethyl)benzene were purchased from Sigma-Aldrich and Strem Chemicals. 1,2-bis(diphenylphosphanylmethyl)benzene was synthesized in-house.

a. Autoclaves: 100 mL stainless steel (316) autoclaves equipped with temperature probe and pressure adapter were used. For heating and stirring, an H.E.L. Polyblock PB4 was used.

b. NMR Spectroscopy: ^{1}H NMR and ^{13}C NMR were recorded on Bruker Avance 400 (operating at 400 MHz for ^{1}H, 101 MHz for ^{13}C) NMR spectrometer. ^{19}F and ^{31}P NMR spectra were referenced against $CFCl_3$ and 85% H_3PO_4 (external references) Multiplets were assigned as s (singlet), d (doublet), t (triplet), , q (quartet), p (quintet), dd (doublet of doublet), ddt (doublet of doublet of triplet) and m (multiplet). All measurements were carried out at room temperature. NMR yields were calculated using dibromomethane as internal standard.

c. GC Analysis: Gas chromatography (GC) was measured on Shimadzu GC-2010, equipped with DB-5MS UI column (length 60 m, diameter: 0.250 mm, film thickness: 1.0 µm), coupled to Flame Ionization Detector (FID). Gas chromatography-mass spectrometry (GC-MS) was measured on Agilent Technologies 7820A equipped with DB-5MS UI column (length 30 m, diameter: 0.250 mm, film thickness: 1.0 µm) column and coupled to mass detector MSD 5975. Helium was used as the mobile phase.

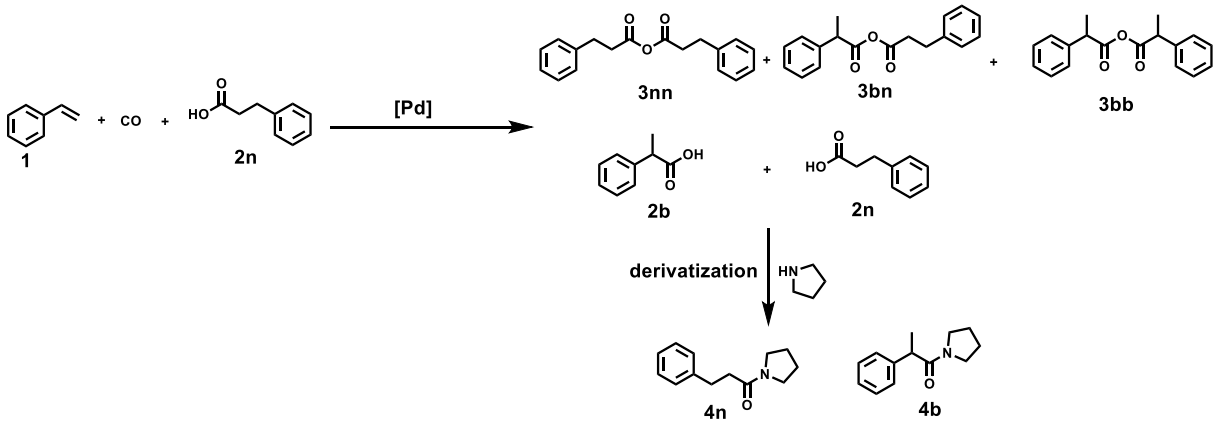
d. UPLC Analysis: Ultra Pressure Liquid Chromatography (UPLC) was measured using Waters ACQUITY UPLC equipped with a ACQUITY UPLC® BEH C18 1.7µm, 2.1 × 50 mm column and coupled to TUV detector.

e. HRMS: High resolution mass spectra (HRMS) were recorded on Q-Exactive HF Orbitrap (Thermo Scientific) equipped with an electrospray ion source (ESI) in positive mode, injection of 2 µL of a 1 µM solution *via* Ultimate 3000 nano UPLC (Dionex) system, with an external calibration (Thermo Scientific). Parameters used: Source voltage of 3.5 kV, capillary temperature 275 °C, no sheath gas, Resolution = 240.000 at m/z=400. Mass range

m/z=160-2000 or until a maximum of 6000. Eluents used: ACN:H_2O (1:1 v/v) supplemented with 0.1% formic acid. The data are given as mass units per charge (m/z).

AI.2. General reaction scheme, methods of analysis and calculations

AI.2.1. General reaction scheme showing reactants, all possible products of catalysis and products obtained on derivatization



Scheme AI.1. Overall reaction scheme showing substrates and products.

AI.2.2. Methods of analysis of substrates and products

a. GC : **1**, **4n**, **4b**

b. UPLC : **2n** + **2b** (total carboxylic acid; **2**) ; **3nn** + **3bn** + **3bb** (total anhydride; **3**)

c. NMR : **3nn**, **3bn**, **3bb**

AI.2.3. Calculations

a. Mass Balance:

The Mass Balance was calculated in terms of "number of phenyl groups" present in the reaction mixture after catalysis as follows:

$$\frac{phenyls\ of\ \mathbf{1}\ + phenyls\ of\ \mathbf{2} + \ phenyls\ of\ \mathbf{3}}{total\ initial\ phenyls} \times 100$$

Where,

Phenyls of **1** = mmol of **1** unreacted ; determined by GC

Phenyls of **2** = mmol of (**2n**+**2b**) ; determined by UPLC

Phenyls of **3** = 2 × mmol of **3**; determined by UPLC

Total initial phenyls = mmol of (**1**+**2n**) introduced in the reaction

An error margin of ±10% is considered to be acceptable for the mass balance.

b. Total Anhydride Yield %:

The total anhydride yield % was calculated as follows:

$$\frac{mmol\ of\ \mathbf{3}}{mmol\ of\ limiting\ substrate} \times 100$$

Where,

Limiting substrate can be either **1** or **2n** based on the equivalents used

mmol of **3** was determined by UPLC

c. Regioselectivity:

3nn:**3bn:3bb** was calculated as follows:

$$\frac{\boldsymbol{3nn}\ or\ \boldsymbol{3bn}\ or\ \boldsymbol{3bb}}{Total\ anhydride\ yield} \times 100$$

Where,

mmol of **3nn**, **3bn**, **3bb** were determined by NMR using dibromomethane as internal standard

4n:**4b** was calculated as follows:

$$\frac{\boldsymbol{4n}\ or\ \boldsymbol{4b}}{\boldsymbol{4n} + \boldsymbol{4b}} \times 100$$

Where,

mmol of **4n**, **4b** were determined by GC

d. Conversion %

Conversion % with respect to styrene (**1**) was calculated as follows:

$$\left[1 - \frac{\mathbf{1}\ unreacted}{initial\ \mathbf{1}\ charged}\right] \times 100$$

Where,

mmol of **1** was determined by GC

An error margin of ±5% is considered to be acceptable for the conversion.

e. Concentrations mentioned in mol% are always given with respect to the limiting reagent in cases where one of the reagents is used in excess.

AI.3. General catalytic procedure (GP) and analysis

Palladium acetate (0.05 mmol; 11.2 mg), 1,4-bis(diphenylphosphanyl)butane, dppb, (0.10 mmol; 42.7 mg) and 3−phenylpropionic acid (**2n**, 10.0 mmol; 1.50 g) were weighed into a clean and dried glass liner containing an oven−dried stirring bar. The glass liner was fitted inside a 100 mL stainless steel Parr autoclave and the autoclave was closed. The autoclave was connected to a Schlenk line and subjected to five cycles of evacuation and refilling with nitrogen gas. The required volume of degassed and dried solvent (6.0 mL) was added using standard Schlenk techniques and the mixture was stirred for one hour to allow for catalyst formation. Then the required volume of degassed and dried styrene (**1**, 10.5 mmol; 1.2 mL) was added using standard Schlenk procedures and the autoclave was closed and disconnected from the Schlenk line. The autoclave was transferred to a HEL PB4 polyblock and connected to the gas lines. The lines connecting the autoclave was flushed with nitrogen (N_2) (3 × 30 bar). The autoclave was flushed with carbon monoxide (CO) (1 × 30 bar) and then was charged with CO to 50 bar. The autoclave was stirred at 350 rpm and heated for 15 h at the desired temperature. At the end of the reaction time, the autoclave was brought to room temperature, cooled further for 30 minutes using an ice-bath and then was slowly depressurized. After 30 minutes of thawing, the contents of the glass liner were transferred to a 10 mL volumetric flask (**A**) and the total volume was adjusted to 10 mL using dichloromethane (DCM).

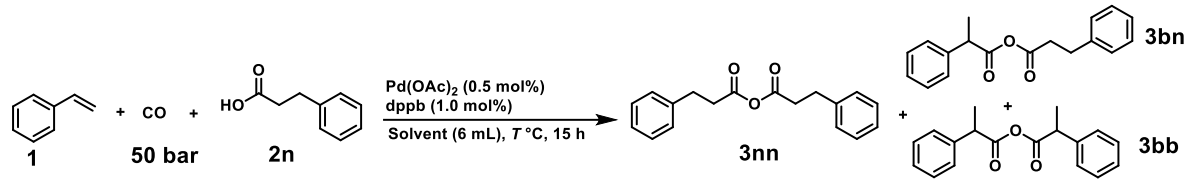
a. *GC Analysis*: 1 mL of the reaction mixture in flask **A** was transferred to a 10 mL volumetric flask (**B**), to which 0.3 mL undecane (internal standard for GC analysis) was added and was diluted up to 10 mL with DCM. The resulting solution was then analyzed using GC. The amount of styrene (**1**) present in the GC sample was determined using calibration lines with undecane as the internal standard. A 60 m × 0.250 mm ; 1.0 µm thickness DB-5MS GC column was used for analysis. 2.0 µL of each sample was injected and the following temperature program was used: injector at 350 °C, FID at 350 °C, oven at 40 °C for 3 min, increasing to 300 °C with 10 °C/min and hold at 300 °C for 10 min.
b. *UPLC Analysis*: 0.5 mL of the reaction mixture in flask **A** was transferred to a 10 mL volumetric flask (**C**) containing 20 mg benzamide (internal standard for UPLC analysis) and diluted up to 10 mL DCM. The resulting solution was then analyzed using UPLC. The amounts of phenylpropionic acid (**2**) and phenylpropionic anhydride (**3**) present in the reaction sample were determined using calibration lines with benzamide as the internal standard. The column used was an ACQUITY UPLC® BEH C18 1.7 µm, 2.1 × 50 mm column and the wavelength of the UV-Vis detector was set at 260 nm. An ACN/Milli-Q (MQ) water with 0.1% TFA gradient with a flow rate of 0.5 ml/min was used. The run was initiated with 98% solvent A (MQ water with 0.1% TFA) and 2% solvent B (ACN with 0.1% TFA) followed by a linear gradient to 100% solvent B in 5 min, staying at 100% B until 6 min and back to the initial 98% solvent A at 6.1 min. The total run time was 8.0 min. Injection volume was 2.0 µL.
c. *Derivatization Procedure*: In a capped microwave vial, 2.5 mL of the reaction mixture from flask **A** was added under N_2 to a cooled solution of pyrrolidine (0.5 mL; 6.1 mmol) and triethylamine (1.0 mL; 7.3 mmol) in DCM (1.0 mL). The reaction mixture was stirred for 5 mins in an ice-bath and then heated to 35 °C for 15 h in an aluminium block.
d. *GC Analysis after derivatization*:1 mL of the derivatization reaction mixture was transferred to a 5 mL volumetric flask (**D**), 0.3 mL undecane (internal standard for GC analysis) was added and the volume was adjusted to 5 mL with DCM. The resulting solution was then analyzed using GC. The pyrrolidine-derivatized products (**4n** and **4b**) present in the GC sample were quantified using calibration lines with undecane as the internal standard. A 60 m × 0.250 mm ; 1.0 µm thickness DB-5MS GC column was used for analysis. 2.0 µL of each sample was injected and the following temperature program was used: injector at 350 °C, FID at 350 °C, oven at 40 °C for 3 min, increasing to 300 °C with 10 °C/min and hold at 300 °C for 10 min. The resulting yield of product was further calculated for the initial 10 mmol scale hydrocarbonylation reaction.

AI.4. Results: Optimization of reaction conditions

AI.4.1. Temperature and solvent screening

a. *Procedure same as GP*

Table AI.1. Temperature and solvent screening studies for anhydride synthesis from alkenes. See Scheme AI.1 for the derivatization reaction forming **4**.



Entry	Temperature (°C)	Solvent	Conversion %[a]	Total anhydride (3) Yield (%) [b]	Yield (4) (%) and regioselectivity (4n:4b) based on derivatization[a]
1	120	Toluene	90	Trace	0
2	120	DCE	90	Trace	0
3	105	Toluene	88	Trace	0
4	105	DCE	94	Trace	0
5	105	Diglyme	73	Trace	0
6	105	Anisole	82	Trace	0
7	85	Toluene	55	42	40 (90:10)
8	85	DCE	74	38	40 (95:5)
9	85	Diglyme	47	17	18 (>99:-)
10	85	Anisole	56	37	36 (92:8)
11	70	Toluene	30	26	26 (89:11)
12	70	DCE	63	65	62 (94:6)
13	70	Diglyme	12	0	0
14	70	Anisole	19	20	20 (>99:-)
15	55	DCE	21	23	25 (>99:-)
16	40	DCE	0	0	0

Reaction conditions: **1** (10.5 mmol), **2n** (10 mmol), $Pd(OAc)_2$ (0.05 mmol), dppb (0.1 mmol), CO (50bar), *T* °C, Solvent (6 mL), 15 h. [a] Conversion% based on **1**, yield% (based on **2n**) and regioselectivity based on derivatization determined by GC using undecane as internal standard. [b] Total anhydride yield % (based on **2n**) determined by UPLC using benzamide as internal standard.

b. Mass Balance

Table AI.2. Mass Balance of the temperature and solvent screening studies for anhydride synthesis from alkenes.

Entry	Temperature (°C)	Solvent	1 (mmol) [a]	2 (mmol) [b]	3 (mmol)[b]	4 (mmol) / (4n:4b) [a]	Mass Balance %
1	120	Toluene	1.1	8.4	Trace	0	46
2	120	DCE	1.1	7.7	Trace	0	43
3	105	Toluene	1.3	10.5	Trace	0	58
4	105	DCE	0.6	10.7	Trace	0	55
5	105	Diglyme	2.8	9.7	Trace	0	61
6	105	Anisole	1.9	9.3	Trace	0	55
7	85	Toluene	4.7	5.5	4.2	4.0 (90:10)	91
8	85	DCE	2.7	7.3	3.8	4.0 (95:5)	86
9	85	Diglyme	5.6	8.4	1.7	1.8 (>99:-)	85
10	85	Anisole	4.6	6.9	3.7	3.6 (92:8)	92

11	70	Toluene	7.3	7.8	2.6	2.6 (89:11)	99
12	70	DCE	3.9	3.7	6.5	6.2 (94:6)	101
13	70	Diglyme	9.2	10.2	0	0	95
14	70	Anisole	8.5	8.1	2.0	2.0 (>99:-)	100
15	55	DCE	8.3	8.1	2.3	2.5 (>99:-)	102
16	40	DCE	10.4	9.9	0	0	99

[a] Determined by GC using undecane as internal standard. [b] Determined by UPLC using benzamide as internal standard. Total number of phenyls at the start of the reaction: **1** (1.2 mL = 10.5 mmol) + **2** (1.50 g = 10.0 mmol) = 20.5 mmol.

c. CO pressure drop graphs

Time for the reaction temperature to reach 70 °C is 1.5 h. The reaction time is 15 h (1.5 to 16.5 h).

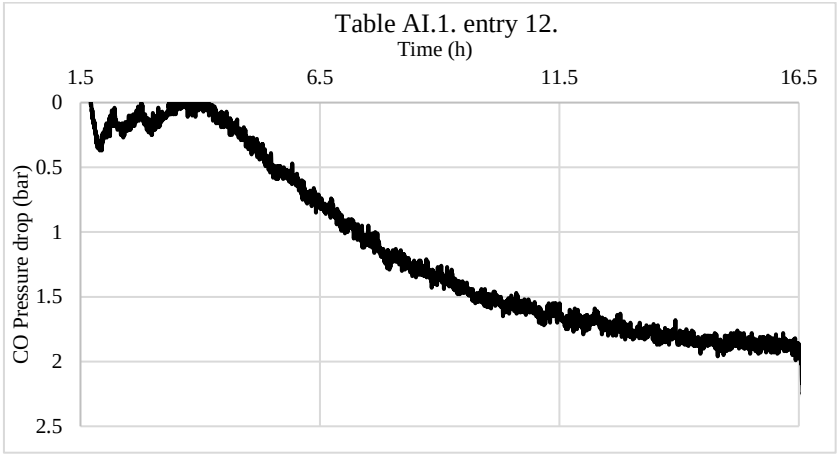
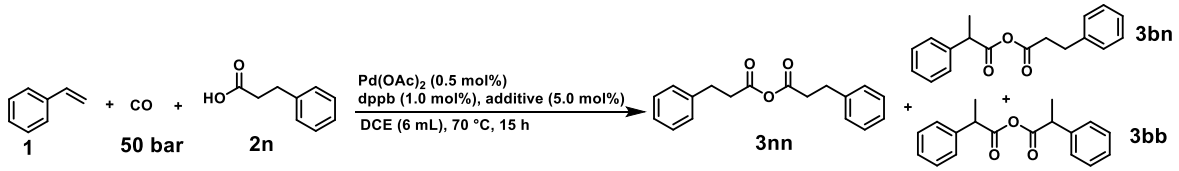


Figure AI.1. CO pressure drop for the reaction in Table AI.1. entry 12.

AI.4.2. Additive screening

a. *GP followed with a deviation*: additive (0.5 mmol) weighed in air and added along with $Pd(OAc)_2$, dppb and **2n**.

Table AI.3. Additive screening studies for anhydride synthesis from alkenes.



Entry	Additive	Total anhydride (3) Yield %[a]
1	None	65
2	$HOTs.H_2O$	0
3	Camphorsulfonic acid	0
4	2,4,6-trimethylbenzoic acid	49[b]
5	LiCl	0
6	LiOAc	60

Reaction conditions: **1** (10.5 mmol), **2n** (10 mmol), $Pd(OAc)_2$ (0.05 mmol), dppb (0.1 mmol), additive (0.5 mmol), CO (50bar), 70 °C, DCE (6 mL), 15 h. [a] Total anhydride yield % determined by UPLC using benzamide as internal standard. [b] Additional peak of mixed anhydride observed.

b. Mass Balance

Table AI.4. Additive screening studies for anhydride synthesis from alkenes.

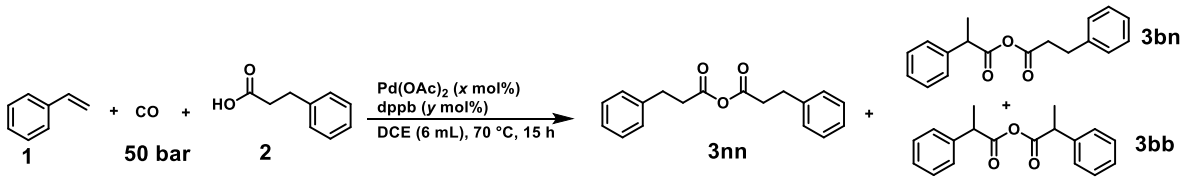
Entry	Additive	1 (mmol)[a]	2 (mmol)[b]	3 (mmol)[b]	Mass Balance %
1	None	3.9	3.7	6.5	101
2	$HOTs.H_2O$	3.7	8.7	0	61
3	Camphorsulfonic acid	5.1	9.2	0	70
4	2,4,6-trimethylbenzoic acid	2.8	5.7	4.9[c]	89
5	LiCl	9.0	10.6	0	96
6	LiOAc	3.3	5.2	6.0	100

[a] Determined by GC using undecane as internal standard. [b] Determined by UPLC using benzamide as internal standard. [c] Additional peak of mixed anhydride observed. Total number of phenyls at the start of the reaction: **1** (1.2 mL = 10.5 mmol) + **2** (1.50 g = 10.0 mmol) = 20.5 mmol.

AI.4.3. Effect of increased catalyst concentration

a. GP followed with a deviation: $Pd(OAc)_2$ (22.4 mg instead of 11.2 mg), dppb (85.4 mg instead of 42.7 mg).

Table AI.5. Catalyst loading studies for anhydride synthesis from alkenes.



Entry	Pd / L (mol%)	Total Anhydride (3) Yield %[a]	Yield % and regioselectivity (4n:4b) based on derivatization[b]
1	0.5 / 1.0	65	62 (94:6)
2	1.0 / 2.0	67	65 (94:6)

Reaction conditions: **1** (10.5 mmol), **2n** (10 mmol), $Pd(OAc)_2$ (0.05 / 0.10 mmol), dppb (0.1 / 0.2 mmol, CO (50bar), 70 °C, DCE (6 mL), 15 h. [a] Total anhydride yield % determined by UPLC using benzamide as internal standard. [b] Yield% and regioselectivity based on derivatization determined by GC using undecane as internal standard.

b. Mass balance

Table AI.6. Catalyst loading studies for anhydride synthesis from alkenes.

Entry	Pd / L (mol%)	1 (mmol) [a]	2 (mmol) [b]	3 (mmol)[b]	4 (mmol) / (4n:4b) [a]	Mass Balance %
1	0.5 / 1.0	3.9	3.7	6.5	6.2 (94:6)	101
2	1.0 / 2.0	4.0	3.6	6.7	6.5 (94:6)	102

[a] Determined by GC using undecane as internal standard. [b] Determined by UPLC using benzamide as internal standard. Total number of phenyls at the start of the reaction: 1 (1.2 mL = 10.5 mmol) + 2 (1.50 g = 10.0 mmol) = 20.5 mmol.

c. CO pressure drop graphs

Time for the reaction temperature to reach 70 °C is 1.5 h. The reaction time is 15 h (1.5 to 16.5 h)

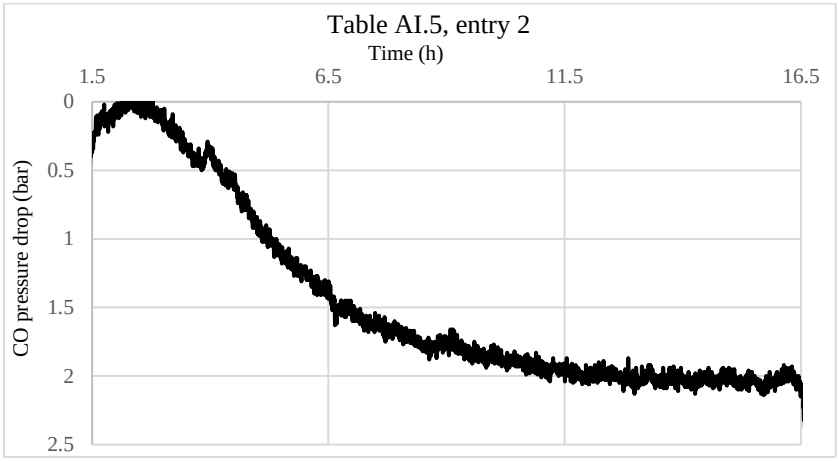


Figure AI.2. Doubling the catalyst loading (Table AI.5, entry 2) shows a quicker rate in CO consumption indicating faster reaction but the consumption of CO reaches stagnancy and no further reaction occurs.

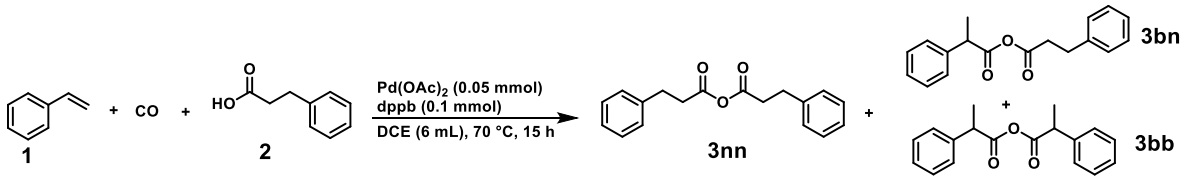
AI.4.4. Effect of substrate concentration and CO pressure

a. GP followed with a deviation in cases where equivalents of the substrates were changed:

1:2n	1	2n
10:20	1.2 mL (10.5 mmol)	3.0 g (20.0 mmol)
20:10	2.3 mL (20.2 mmol)	1.5 g (10.0 mmol)

b. 65 bar used instead of 50 bar CO wherever mentioned

Table AI.7. Varying substrate ratio for anhydride synthesis from alkenes.



Entry	CO pressure (bar)	1 : 2n (mmol)	Conversion% w.r.t 1[a]	Conversion% w.r.t 2n[b]	Total Anhydride (3) Yield %[c] (3nn:3bn)[d]	Yield % and regioselectivity (4n:4b) based on derivatization (4)[e]
1	50	10 : 10	63	63	65 (79:21)	62 (94:6)
2	50	20 : 10	50	82	95 (74:26)	95 (92:8)
3	50	10 : 20	69	38	74 (83:17)	74 (95:5)
4	50	10 : 30	71	29	74 (89:11)	75 (96:4)
5	35	20 : 10	60	66	81	76 (92:8)
6	35	10 : 20	65	27	58	60 (>99:1)
7	65	10 : 10	70	69	75 (77:23)	75 (93:7)
8	65	20 : 10	52	80	97 (74:26)	96 (93:7)
9	65	10 : 20	74	38	74 (85:15)	76 (96:4)
10	65	10 : 50	71	12	66 (89:11)	69 (96:4)

Reaction conditions: $Pd(OAc)_2$ (0.05 mmol), dppb (0.1 mmol), 70 °C, DCE (6 mL), 15 h. [a] Conversion% w.r.t **1** determined by GC using undecane as internal standard. [b] Conversion% w.r.t **2n** determined by UPLC using benzamide as internal standard (**2b** formation was calculated to be 1 to 3% in entries 1, 2, 7, 8 and 6 to 8% in entries 3, 4, 9, 10 as per NMR analysis; to calculate conversion of **2n**, we considered concentration of **2** derived from UPLC data equal to **2n** since **2b** formation is minimal). [c] Total anhydride yield (%, based on the limiting reagent) determined by UPLC using benzamide as internal standard. [d] **3nn**:**3bn** determined by NMR, **3bb** found in trace amounts in all cases. [e] Yield (%, based on the limiting reagent) and regioselectivity based on derivatization determined by GC using undecane as internal standard.

c. Mass Balance:

Table AI.8. Varying substrate ratio for anhydride synthesis from alkenes.

Entry	CO pressure (bar)	1 : 2n (mmol)	Total exact no. of phenyls	1 (mmol)[a]	2 (mmol)[b]	3 (mmol)[b]	4 (mmol) (4n:4b)[a]	Mass Balance %
1	50	10 : 10	20.5	3.9	3.7	6.5	6.2 (94:6)	101
2	50	20 : 10	30.2	10.2	1.8	9.5	9.5 (92:8)	103
3	50	10 : 20	30.5	3.3	12.5	7.8	7.8 (95:5)	103
4	50	10 : 30	40.5	3.1	21.3	7.8	7.9 (96:4)	99
5	35	20 : 10	30.2	8.0	3.4	8.1	7.6 (92:8)	91
6	35	10 : 20	30.5	3.7	14.6	6.1	6.3 (>99:1)	100
7	65	10 : 10	20.5	3.2	3.1	7.5	7.5 (93:7)	104
8	65	20 : 10	30.2	9.7	2.0	9.7	9.6 (93:7)	103
9	65	10 : 20	30.5	2.7	12.5	7.8	8.0 (96:4)	101
10	65	10 : 50	60.5	3.0	44.0	6.9	7.2 (96:4)	101

[a] Determined by GC using undecane as internal standard. [b] Determined by UPLC using benzamide as internal standard.

d. CO pressure drop graphs

Time for the reaction temperature to reach 70 °C is 1.5 h. The reaction time is 15 h (1.5 to 16.5 h).

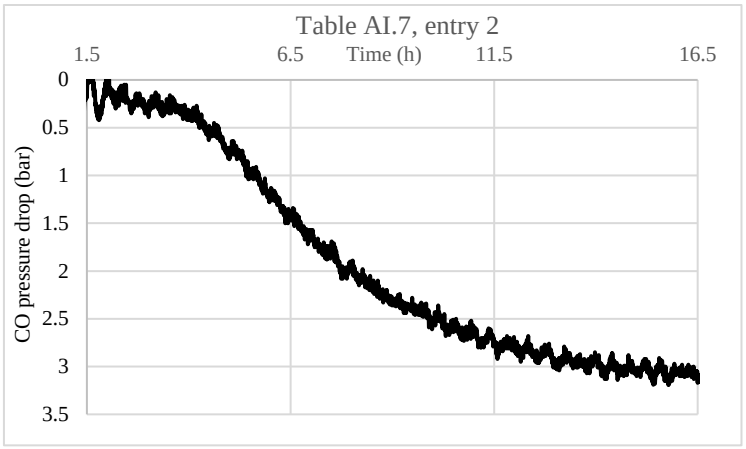


Figure AI.3. Relative CO pressure drop of Table AI.7, entry 2 when **1**:**2n** at 20:10 mmol at 50 bar CO pressure.

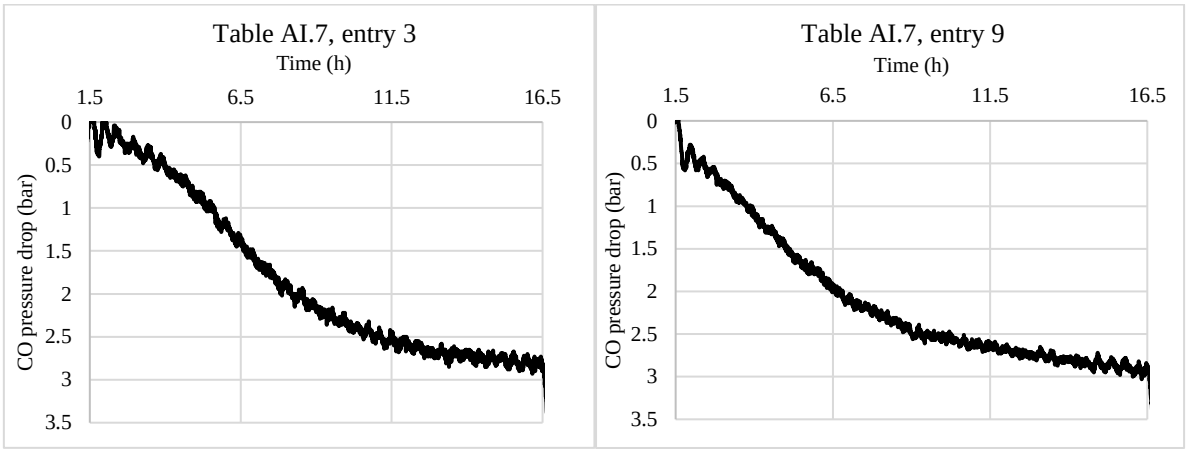


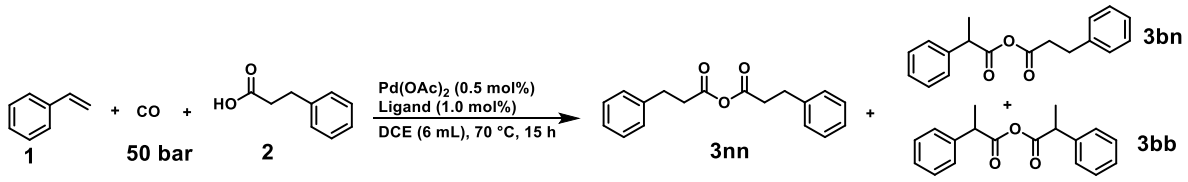
Figure AI.4. Relative CO pressure drop when **1:2n** at 10:20 mmol at 50 (left graph, Table AI.7, entry 3) and 65 bar (right graph, Table AI.7, entry 9) CO pressure.

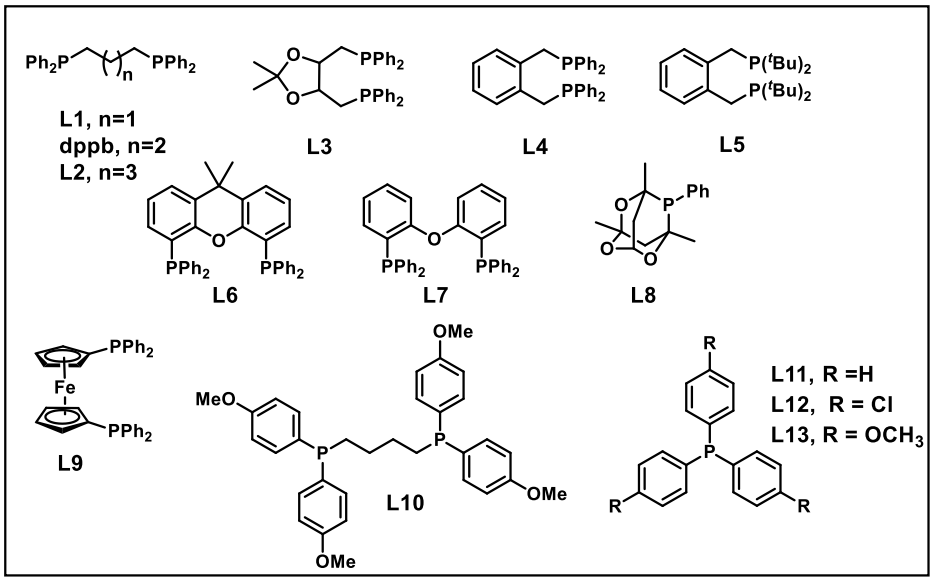
AI.4.5. Influence of ligands

a. GP followed with a deviation: Diphosphine (0.05 mmol) or monophosphine ligand (0.20 mmol) was weighed in air if air stable. Otherwise, air-sensitive ligands along with palladium acetate were weighed in a Schlenk flask in the glovebox and dissolved with DCE (6.0 mL).

b. Mass balance

Table AI.9. Influence of ligands on synthesis of anhydrides from alkenes.



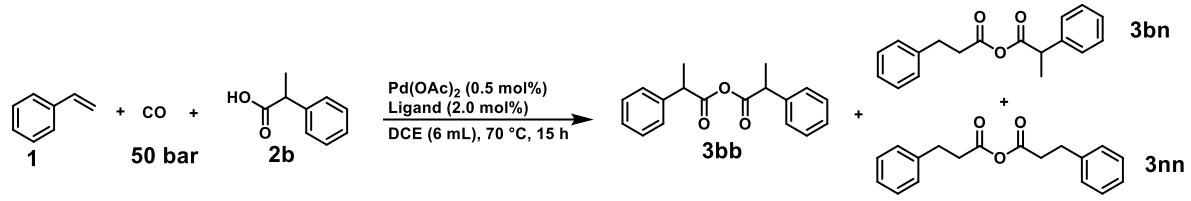


Entry	1 (mmol)[a]	2 (mmol)[b]	3 (mmol)[b]	4 (mmol) / (4n:4b)[a]	M.B. %	NMR Yield % (3)[c]			Total NMR Yield %	3nn: 3bn: 3bb
						3nn	3bn	3bb		
dppb	10.2	1.8	9.5	9.5 (92:8)	103	68	24	Trace	92	74:26: -
L1	9.6	6.2	4.0	4.0 (>99:-)	79	37	0	Trace	37	>99:-:-
L2	13.0	5.6	5.8	5.9 (93:7)	100	43	15	Trace	58	74:26: -
L3	9.5	2.1	9.1	9.2 (91:9)	99	60	29	Trace	89	67:33: -
L4[d]	13.0	8.0	3.2	3.3 (>99:1)	91	31	0	0	31	>99:-:-
L4[d][e]	6.5	7.5	2.8	2.8 (>99:1)	65	32	0	0	32	>99:-:-
L5[d]	16.5	10.5	0	0	89	0	0	0	0	-
L6	15.7	7.6	3.2	3.2 (>99:-)	99	31	0	0	31	>99:-:-
L6[e]	11.7	3.6	7.8	7.9 (94:6)	102	61	15	Trace	76	80:20: -
L7	11.3	4.1	7.0	7.1 (95:5)	97	56	12	Trace	68	82:18: -
L8	14.7	2.4[c]	6.2[c]	6.2 (80:20)	98	26	27	9	62	42:44: 14
L9	12.7	5.8	6.1	6.0 (93:7)	102	44	15	Trace	59	75:15: -
L10	9.1	4.1	6.4	6.9 (94:6)	86					

[a] Determined by GC using undecane as internal standard. [b] Determined by UPLC using benzamide as internal standard. [c] Determined by NMR analysis using dibromomethane as internal standard. [d] 0.075 mmol of ligand used instead of 0.10 mmol. [e] reaction temperature = 85 °C instead of 70 °C. Total number of phenyls at the start of the reaction: 1 (2.3 mL = 20.2 mmol) + 2 (1.5 g = 10.0 mmol) = 30.2 mmol. Abbreviation: M.B: Mass balance.

AI.4.6. Attempts to test influence of ligands on branched selectivity

Table AI.10. Influence of ligands on branched selectivity for synthesis of **3bb**.



Entry	3bb Yield%	Yield % and regioselectivity (4n:4b) based on derivatization (4)[a]
L11	-did not determine-	51 (18:82)
L12	-did not determine-	34 (12:88)
L13	-did not determine-	60 (23:76)
L8[b]	65[c]	65 (-:>99)

Reaction conditions: **1** (20.2 mmol), **2b** (10 mmol), $Pd(OAc)_2$ (0.05 mmol), **L** (0.20 mmol), CO (50bar), 70 °C, DCE (6 mL), 15 h. [a] Yield (%, based on the limiting substrate, **2b**) and regioselectivity based on derivatization determined by GC using undecane as internal standard. [b] reaction time = 20 h instead of 15 h. [c] **3bb** yield (%, based on the limiting substrate, **2b**) determined by NMR using dibromomethane as internal standard; **3nn** was not found, **3bn** was found in trace.

Table AI. 11. Mass Balance of catalytic reaction with **L8**.

Entry	1 (mmol) [a]	2b (mmol) [b]	3bb (mmol)[b][c]	4 (mmol) (4n:4b) [a]	Mass Balance %
L8[d]	14.0	4.3	6.5	6.5 (-:>99)	103

[a] Determined by GC using undecane as internal standard. [b] determined by NMR using dibromomethane as internal standard. [c] **3nn** was not found, **3bn** was found in trace. [d] reaction time= 20 h instead of 15 h.

AI.4.7. Derivatization of mixed anhydride and validation of UPLC and GC results with NMR data

a. Synthesis and derivatization of mixed anhydride: In a capped microwave vial with a stir bar, 5.0 mL $CDCl_3$ was charged to which 2-phenyl propionic acid (696 µL; 5.0 mmol) and triethylamine (732 µL; 5.5 mmol) were added. The mixture was cooled in an ice-bath and to it, 3-phenylpropionyl chloride (740 µL; 5.0 mmol) was added dropwise. After addition, the reaction mixture was stirred at room temperature overnight. 2.5 mL of the reaction mixture was added to a cooled solution of pyrrolidine (0.5 mL; 6.1 mmol) and triethylamine (1.0 mL; 7.3 mmol) in DCM (1.0 mL) under N_2. The reaction mixture was stirred for 5 mins in an ice-bath and then heated to 35 °C for 15 h. On GC analysis of the derivatization performed as described in GP, the selectivity of **4n**:**4b** was found to be 69:31.

b. Calculation applied to catalytic reaction mixtures:

Estimated **4n** selectivity: $\frac{\boldsymbol{3nn}+(0.69\times\boldsymbol{3bn})}{\boldsymbol{3nn}+\boldsymbol{3bn}}\times 100$

Estimated **4b** selectivity: $\frac{0.31\times\boldsymbol{3bn}}{\boldsymbol{3nn}+\boldsymbol{3bn}}\times 100$

Similarly, from the derivatization data, the composition of the catalytic mixture (**3nn**:**3bn**) can be estimated.

Table AI.12. Selectivity analysis based on NMR and GC data

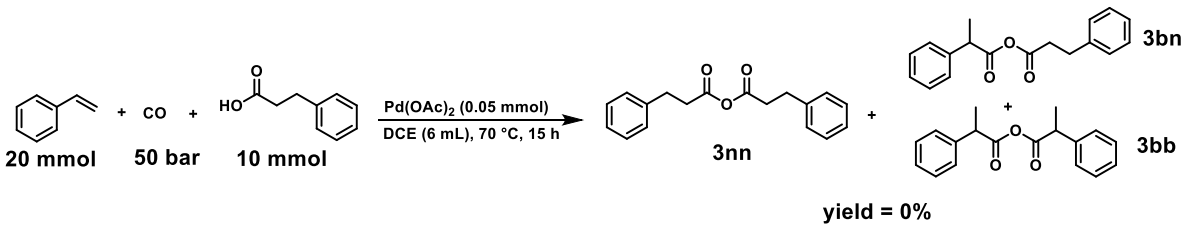
Condition	UPLC Yield%[a]	NMR Yield%[b]			3nn:3bn	Predicted selectivity on derivatization		Determined selectivity on derivatization (4n:4b)[c]
		3nn	3bn	3bb		4n	4b	
dppb	95	68	24	0	74:26	92	8	92:8
L1	40	37	0	0	>99:-	>99	-	>99:-
L2	58	43	15	0	74:26	92	8	93:7
L3	91	60	29	0	67:33	90	10	91:9
L4[d]	32	31	0	0	>99:-	>99	-	>99:-
L6[e]	78	61	15	0	80:20	94	6	94:6
L7	70	56	12	0	82:18	95	5	95:5
L9	61	44	15	0	75:25	92	8	93:7

Reaction conditions: **1** (20.2 mmol), **2n** (10 mmol), $Pd(OAc)_2$ (0.05 mmol), **L** (0.10 mmol), CO (50bar), 70 °C, DCE (6 mL), 15 h. [a] UPLC yield (%, based on **2n**) determined using benzamide as internal standard. [b] NMR yield (%, based on **2n**) determined using dibromomethane as internal standard; **3bb** found in trace amounts in all cases. [c] **4n**:**4b** based on derivatization determined by GC using undecane as internal standard. [d]] 0.075 mmol of ligand used instead of 0.10 mmol. [e] reaction temperature at 85 °C instead of 70 °C.

AI.4.8. Other control experiments and reaction considerations

AI.4.8.1. Without dppb

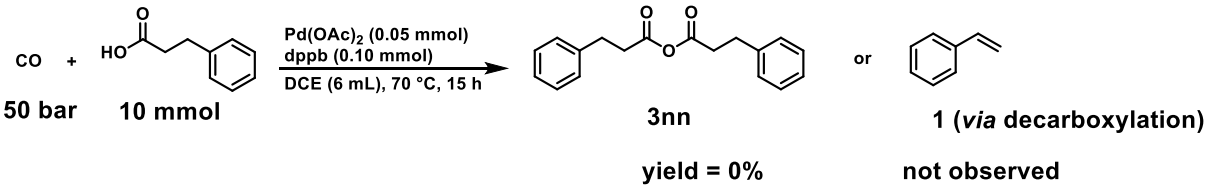
Palladium acetate (11.2 mg) and 3-phenylpropionic acid (**2n**, 1.50 g) were weighed in a clean and dried glass liner containing an oven-dried stirring bar in open air. The glass liner was fitted inside a 100 mL stainless steel Parr autoclave and the autoclave was closed. The autoclave was connected to the Schlenk line and subjected to five cycles of evacuation and refilling with nitrogen gas. Degassed and dried solvent DCE (6.0 mL, was added using standard Schlenk techniques and the mixture was stirred for one hour. After one hour, the required volume of degassed and dried styrene (**1**, 1.2 mL) was added using standard Schlenk procedures and the autoclave was closed and disconnected from the Schlenk line. The autoclave was transferred to the HEL PB4 polyblock and connected to the gas lines. The lines connecting the autoclave was flushed with N_2 (30 bar × 3). The autoclave was flushed with CO (30 bar × 1) and then, charged with CO to 50 bar. The autoclave was stirred at 350 rpm and heated for 15 h at 70 °C. At the end of the reaction, the autoclave was cooled using an ice-bath for 30 minutes and depressurized slowly. After 30 minutes of thawing, the reaction mixture is transferred to a 10 mL volumetric flask and adjusted to 10 mL using dichloromethane (DCM). The anhydride yield was determined by UPLC.



Scheme AI.2. Control reaction in absence of ligand

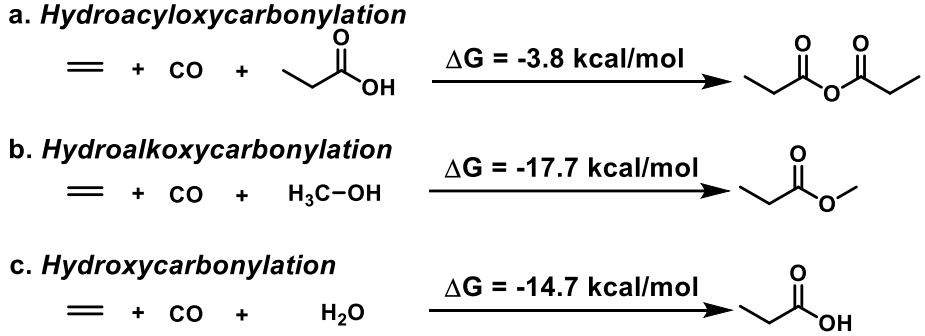
AI.4.8.2. Control reaction in absence of styrene; 2n in catalytic conditions

Palladium acetate (11.2 mg), dppb (42.7 mg) and 3-phenylpropionic acid (**2n**, 1.50 g) were weighed in a clean and dried glass liner containing an oven-dried stirring bar in open air. The glass liner was fitted inside a 100 mL stainless steel Parr autoclave and the autoclave was closed. The autoclave was connected to the Schlenk line and subjected to five cycles of evacuation and refilling with nitrogen gas. Degassed and dried solvent DCE (6.0 mL, was added using standard Schlenk techniques. The autoclave was closed and disconnected from the Schlenk line. The autoclave was transferred to the HEL PB4 polyblock and connected to the gas lines. The lines connecting the autoclave was flushed with N_2 (30 bar × 3). The autoclave was flushed with CO (30 bar × 1) and then, charged with CO to 50 bar. The autoclave was stirred at 350 rpm and heated for 15 h at 70 °C. At the end of the reaction, the autoclave was cooled using an ice-bath for 30 minutes and depressurized slowly. After 30 minutes of thawing, the reaction mixture is transferred to a 10 mL volumetric flask and adjusted to 10 mL using dichloromethane (DCM). The anhydride yield was determined by UPLC. Presence of styrene was determined by GC.

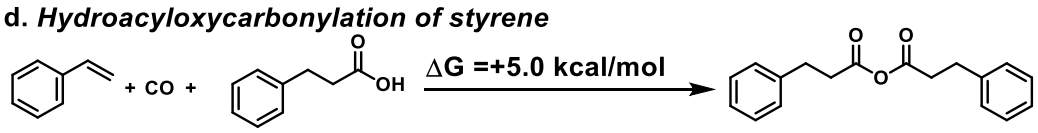


Scheme AI.3. Control reaction in absence of styrene.

AI.4.8.3. Computational calculation of Gibbs Free Energy (Δ*G*) of hydrocarbonylation reactions in gas-phase



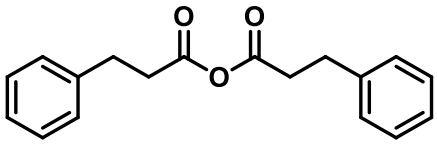
Scheme AI.4. Gibbs Free Energy (Δ*G*) in gas phase for hydrocarbonylation reactions of ethene: hydroacyloxycarbonylation, hydroalkoxycarbonylation, hydrocarboxylation.



Scheme AI.5. Gibbs Free Energy (Δ*G*) in gas phase for hydroacyloxycarbonylation reactions of styrene (**1**) with **2n**. The calculated $\Delta G_{\text{gas-phase}}$ shows the reaction to be endergonic but we do observe the reaction occurring, thus indicating a limitation in computational calculations.

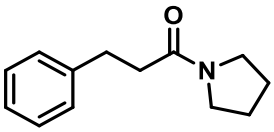
Computational details: Amsterdam Density Functional (ADF 2019.104), XC: GGA BLYP- Dispersion Grimme 3 BJDAMP, Basis set: TZ2P, Core: small

AI.5. Synthesis of standards and substrates



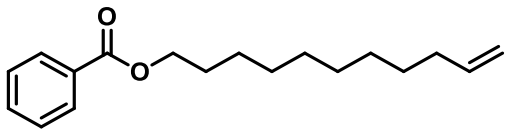
3-phenylpropionic anhydride

N,N'-Dicyclohexylcarbodiimide, DCC (2.8 g; 13.3 mmol) was dissolved in DCM (20 mL). The solution was cooled in an ice-bath and 3-phenylpropionic acid (4.0 g; 26.6 mol) was added. The solution was stirred at r.t. overnight. The reaction mixture was filtered, washed with half-saturated solution of Na_2CO_3 (2 x 10 mL) followed by water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo* to obtain a colourless oil (waxy solid at -20 °C), 2.4 g, 64% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.32-7.27 (m, 4H), 7.23 - 7.18 (m, 6H), 2.95 (t, *J* = 7.7 Hz, 4H), 2.74 (t, *J* = 7.8 Hz, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 168.51, 139.56, 128.63, 128.30, 126.55, 36.82, 30.17. The NMR spectra are in agreement with literature.[1]



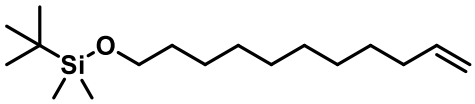
3-phenyl-1-pyrrolidin-1-yl-propane-1-one

To a cooled solution of pyrrolidine (0.5 mL, 6.0 mmol) and triethylamine (1.4 mL,10.0 mmol), 3-phenylpropionyl chloride (5.0 mmol) was added dropwise. The reaction mixture was stirred at r.t. overnight. The reaction mixture was quenched with water (2.0 mL), filtered, washed with 1N HCl (2 x 5 mL) followed by water (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The concentrate was purified by silica gel column chromatography using ethyl acetate/pentane (0 to 50%) to afford the corresponding pure product, as a yellow oil, 820 mg, 81% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.30 – 7.17 (m, 5H), 3.46 (t, *J* = 6.7 Hz, 2H), 3.29 (t, *J* = 6.6 Hz, 2H), 3.01 – 2.97 (m, 2H), 2.58 – 2.54 (m, 2H), 1.93 – 1.78 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 170.80, 141.62, 128.52, 128.50, 126.13, 46.61, 45.70, 36.85, 31.27, 26.13, 24.45. The NMR spectra are in agreement with literature.[2]



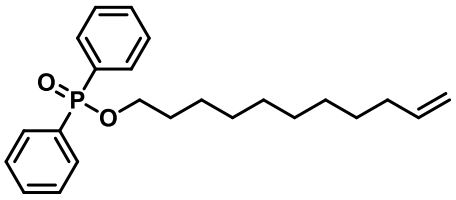
Undec-10-en-1-yl benzoate

To a solution of 10-undecen-1-ol (8.0 mL; 40 mmol), 4-dimethylaminopyridine (DMAP) (0.5 g, 4.0 mmol), and triethylamine (8.3 mL; 60 mmol) in anhydrous DCM, benzoyl chloride (5.8 mL; 50 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, and then at room temperature overnight. The reaction was quenched with water and extracted with DCM. The organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using ethyl acetate/pentane (0 to 20%) to afford the corresponding pure product, as a colourless oil, 9.9 g, 91% yield. The NMR spectra are in agreement with literature.[3] **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.06 – 8.04 (m, 2H), 7.57 – 7.54 (m, 1H), 7.46 – 7.42 (m, 2H), 5.81 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.04 - 4.89 (m, 2H), 4.31 (t, *J* = 6.7 Hz, 2H), 2.06 – 2.01 (m, 2H), 1.80 – 1.73 (m, 2H), 1.48 – 1.29 (m, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 166.77, 139.28, 132.85, 130.59, 129.59, 128.38, 114.19, 65.20, 33.86, 29.53, 29.46, 29.32, 29.16, 28.98, 28.78, 26.10.



tert-Butyldimethyl-(undec-10-en-1-yloxy)-silane

To a solution of 10-undecen-1-ol (10.0 mL; 50 mmol), 4-dimethylaminopyridine (DMAP) (0.6 g, 5.0 mmol), and triethylamine (10.4 mL; 75 mmol) in anhydrous DCM, *tert*-butyldimethylsilyl trifluoromethanesulfonate (14.4 mL; 62.5 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, and then at room temperature overnight. The reaction was quenched with water and extracted with DCM. The organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using pentane to afford the corresponding pure product, as a colourless oil, 13.2 g, 93% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.84 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.05 – 4.94 (m, 2H), 3.62 (t, *J* = 6.6 Hz, 2H), 2.09 – 2.04 (m, 2H), 1.55 – 1.52 (m, 2H), 1.42 – 1.38 (m, 2H), 1.31 (s, 10H), 0.92 (s, 9H), 0.08 (s, 6H). **^{13}C NMR** (101 MHz, CDCl3) δ: 139.33, 114.15, 63.41, 33.88, 32.94, 29.64, 29.50, 29.49, 29.19, 29.00, 26.05, 25.85, 18.45, -5.19. **HRMS**: $[M + H]^+$ calculated for $C_{17}H_{37}O_1Si_1^+$ 285.2608; Found 285.2611



Undec-10-en-1-yl diphenylphosphinate

To a solution of 10-undecen-1-ol (10.0 mL; 50 mmol), 4-dimethylaminopyridine (DMAP) (0.6 g, 5.0 mmol), and triethylamine (10.4 mL; 75 mmol) in anhydrous DCM, diphenylphosphinic chloride (11.9 mL; 62.5 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, and then at room temperature overnight. The reaction was quenched with water and extracted with DCM. The organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using ethyl acetate/pentane (0 to 50%) to afford the corresponding pure product, as a colourless oil, 16.5 g, 89% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.84 – 7.79 (m, 4H), 7.54 – 7.49 (m, 2H), 7.47 – 7.42 (m, 4H), 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.02 - 4.91 (m, 2H), 4.04 – 3.99 (m, 2H), 2.06 – 2.01 (m, 2H), 1.75 – 1.68 (m, 2H), 1.40 – 1.26 (m, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 139.27, 132.45, 132.14, 132.11, 131.75, 131.65, 131.08, 128.63, 128.49, 114.20, 65.10, 65.04, 33.86, 30.63, 30.57,29.48,29.43, 29.18, 29.14, 28.96, 25.66. **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 31.70. **HRMS**: $[M + H]^+$ calculated for $C_{23}H_{32}O_2P_1^+$ 371.2134; Found 371.2131.

AI.6. General procedure for substrate scope and applications

Palladium acetate (0.5 mol%), 1,4-diphenylphosphinobutane (dppb, 0.1 mol%) and carboxylic acid (if solid) were weighed in a clean and dried glass liner containing an oven-dried stirring bar in open air. The glass liner was fitted inside a 100 mL stainless steel Parr autoclave and the autoclave was closed. The autoclave was connected to the Schlenk line and subjected to five cycles of evacuation and refilling with nitrogen gas. Degassed and dried DCE (6.0 mL) and/or required volume of degassed liquid carboxylic acid was charged by standard Schlenk techniques and the mixture was stirred for one hour. After one hour, the required volume of degassed and dried alkene was added using standard Schlenk procedures and the autoclave was closed and disconnected from the Schlenk line. The autoclave was transferred to the HEL PB4 polyblock and connected to the gas lines. The lines connecting the autoclave was flushed with

N_2 (30 bar × 3). The autoclave was flushed with CO (30 bar × 1) and then, charged with CO to the 50 bar. The autoclave was stirred at 350 rpm and heated for a specified time at reaction temperature of 70 °C. At the end of the reaction, the autoclave was cooled using an ice-bath for 30 minutes and depressurized slowly. After 30 minutes of thawing, the reaction mixture is transferred to a 10 mL volumetric flask and adjusted to 10 mL using dichloromethane (DCM). The reaction mixture was subjected to one of the derivatization procedures as described below and the corresponding derivatized (linear) product was isolated. The scale and yield% mentioned are with respect to the carboxylic acid substrate.

a. Derivatization with pyrrolidine: To a cooled solution of pyrrolidine (0.5 mL; 6.1 mmol) and triethylamine (1.0 mL; 7.3 mmol) in DCM (1.0 mL), 2.5 mL reaction mixture was charged under N_2. The reaction mixture was stirred for 5 mins in an ice-bath and then heated to 35 °C for 15 h. The reaction mixture was subjected to column chromatography using ethyl acetate/pentane mixture (20 to 50%).

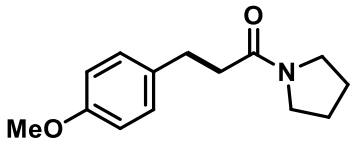
b. Derivatization with aniline: To a cooled solution of aniline (0.5 mL; 5.5 mmol), 4-dimethylaminopyridine, DMAP (3 mg) and triethylamine (1.0 mL; 7.3 mmol) in DCM (0.5 mL), 2.5 mL reaction mixture was charged under N_2. The reaction mixture was stirred for 5 mins in an ice-bath and then heated to 50 °C for 15 h. The reaction mixture was subjected to column chromatography using ethyl acetate/pentane mixture (0 to 20%).

c. Derivatization with benzyl alcohol: To a cooled solution of benzyl alcohol (0.5 mL; 4.63 mmol), 4-dimethylaminopyridine, DMAP (3 mg) and triethylamine (1.0 mL; 7.3 mmol) in DCM (0.5 mL), 2.5 mL reaction mixture was charged under N_2. The reaction mixture was stirred for 5 mins in an ice-bath and then heated to 50 °C for 15 h. The reaction mixture was subjected to column chromatography using diethyl ether/pentane mixture (50%).

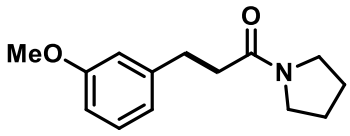
d. Derivatization with ammonia: To a cooled solution of 2.5 mL reaction mixture was added 7 N ammonia in methanol (0.1 mL; 11.9 mmol). The reaction mixture was left to thaw to room temperature overnight (15 h). The reaction mixture was subjected to column chromatography using methanol/DCM (2.5 to 10%).

e. Derivatization with benzyl mercaptan: Catalytic reaction mixture (2.5 mL) was added under N_2 to a cooled solution of benzyl mercaptan (0.3 mL; 2.75 mmol) and triethylamine (0.4 mL; 3.0 mmol) in DCM (0.5 mL),. The reaction mixture was stirred for 5 mins in an ice-bath and then heated to 35 °C for 15 h. The reaction mixture was subjected to column chromatography using diethyl ether/pentane mixture (0 to 1%).

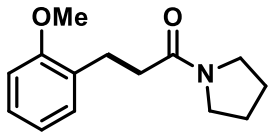
AI.7. Experimental data characterization of products (substrate scope and applications)



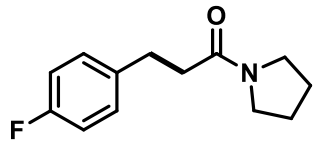
Followed procedure **AI.6a**. Colourless oil, 517 mg, 89% (2.5 mmol scale derivatization). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.15 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H), 3.46 (t, J = 6.7 Hz, 2H), 3.29 (t, J = 6.6 Hz, 2H), 2.95 – 2.91 (m, 2H), 2.55 – 2.51 (m, 2H), 1.90 – 1.80 (m , 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 170.91, 157.99, 133.67, 129.45, 113.88, 55.33, 46.62, 45.68, 37.11, 30.37, 26.14. NMR spectra are in agreement with the literature.[4]



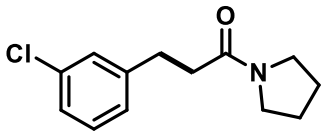
Followed procedure **AI.6a**. Yellow oil, 441 mg, 76% (2.5 mmol scale derivatization). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.20 (t, J = 7.8 Hz, 1H), 6.83 – 6.73 (m, 3H), 3.79 (s, 3H), 3.47 (t, J = 6.8 Hz, 2H), 3.30 (t, J = 6.6 Hz, 2H), 2.98 – 2.94 (m, 2H), 2.58 – 2.54 (m, 2H), 1.93 – 1.79 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 170.78, 159.72, 143.27, 129.48, 120.86, 114.20, 111.45, 55.23, 46.62, 45.73, 36.76, 31.32, 24.46. **HRMS**: $[M + H]^+$ calculated for $C_{14}H_{20}NO_2^+$ 234.1489; Found 234.1488.



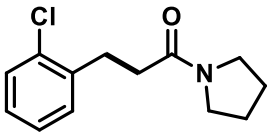
Followed procedure **AI.6a**. Pale yellow solid, 544 mg, 93% (2.5 mmol scale derivatization). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 – 7.18 (m, 2H), 6.90 – 6.83 (m, 2H), 3.83 (s, 3H), 3.46 (t, *J* = 6.7 Hz, 2H), 3.33 (t, *J* = 6.6 Hz, 2H), 2.99 – 2.95 (m, 2H), 2.55 – 2.51 (m, 2H), 1.92 – 1.79 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.46, 157.54, 130.27, 129.83, 127.47, 120.55, 110.22, 55.27, 46.56, 45.63, 35.14, 26.40, 26.17, 24.49. **HRMS**: $[M + H]^+$ calculated for $C_{14}H_{20}NO_2^+$ 234.1489; Found 234.1488.



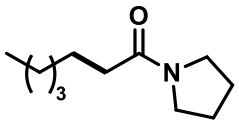
Followed procedure **AI.6a**. Pale yellow solid, 522 mg, 94% (2.5 mmol scale derivatization). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.20 - 7.17 (m, 5.4 Hz, 2H), 6.99 – 6.94 (m, 2H), 3.46 (t, *J* = 6.8 Hz, 2H), 3.30 (t, *J* = 6.7 Hz, 2H), 2.98 – 2.94 (m, 2H), 2.55 – 2.52 (m, 2H), 1.91 – 1.81 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 170.53, 162.60, 160.18, 137.20, 137.17, 129.92, 129.84, 115.26, 115.05, 46.57, 45.67, 36.76, 30.32, 26.08, 24.40. **^{19}F NMR** (377 MHz, $CDCl_3$) δ: -117.64. **HRMS**: $[M + H]^+$ calculated for $C_{13}H_{17}FNO^+$ 222.1289; Found 222.1288.



Followed procedure **AI.6a**. colourless oil, 447 mg, 75% (2.5 mmol scale derivatization). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.23 – 7.16 (m, 3H), 7.13 – 7.10 (m, 1H), 3.47 (t, *J* = 6.8 Hz, 2H), 3.31 (t, *J* = 6.7 Hz, 2H), 2.99 – 2.95 (m, 2H), 2.57 – 2.53 (m, 2H), 1.94 – 1.80 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 170.33, 143.68, 134.17, 129.75, 128.61, 126.83, 126.32, 46.63, 45.76, 36.38, 30.82, 26.13, 24.45. **HRMS**: $[M + H]^+$ calculated for $C_{13}H_{17}ClNO^+$ 238.0993; Found 238.0991.

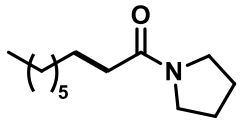


Followed procedure **AI.6a**. yellow oil, 366 mg, 62% (2.5 mmol scale derivatization). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.35 – 7.29 (m, 2H), 7.21 – 7.13 (m, 2H), 3.46 (t, *J* = 6.8 Hz, 2H), 3.32 (t, *J* = 6.7 Hz, 2H), 3.12 – 3.08 (m, 2H), 2.60 – 2.56 (m, 2H), 1.93 – 1.79 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.56, 139.08, 133.94, 131.01, 129.49, 127.73, 126.98, 46.61, 45.72, 34.72, 29.37, 26.13, 24.45. HRMS: $[M + H]^+$ calculated for $C_{13}H_{17}ClNO^+$ 238.0993; Found 238.0993.

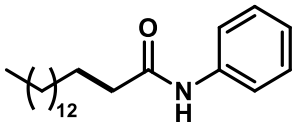


Followed procedure **AI.6a**. colourless oil, 424 mg, 92% (2.5 mmol scale derivatization). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.46 (t, *J* = 6.8 Hz, 2H), 3.41 (t, *J* = 6.9 Hz, 2H), 2.27 – 2.23 (m, 2H), 1.98 – 1.91 (m, 2H), 1.88 – 1.81 (m, 2H), 1.68 – 1.61 (m, 2H),

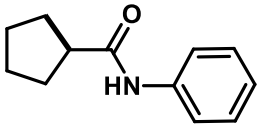
1.37 – 1.25 (m, 6H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.94, 46.67, 45.62, 34.93, 31.72, 29.28, 26.19, 24.98, 24.48, 22.61, 14.13. NMR spectra are in agreement with the literature.[5]



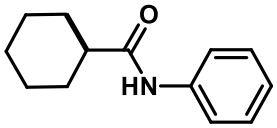
Followed procedure **AI.6a**. colourless oil, 345 mg, 65% (496 mg, 94% obtained when catalysis reaction time was 24 h) (2.5 mmol scale derivatization). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.46 (t, *J* = 6.9 Hz, 2H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.27 – 2.23 (m, 2H), 1.98 – 1.91 (m, 2H), 1.88 – 1.81 (m, 2H), 1.68 – 1.61 (m, 2H), 1.35 – 1.23 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.95, 46.67, 45.62, 34.94, 31.91, 29.62, 29.49, 29.25, 26.20, 25.02, 24.48, 22.71, 14.16. NMR spectra are in agreement with the literature.[6]



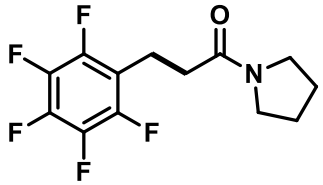
Followed procedure **AI.6b**. White solid, 191 mg, 46% (1.25 mmol scale derivatization). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 – 7.53 (m, 2H), 7.37 – 7.33 (m, 2H), 7.15 – 7.11 (m, 1H), 2.38 (t, *J* = 7.6 Hz, 2H), 1.79 – 1.72 (m, 2H), 1.29 – 1.41 (m, 24H), 0.91 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.41, 137.99, 129.06, 124.23, 119.77, 37.96, 31.99, 29.76, 29.74, 29.72, 29.68, 29.55, 29.45, 29.43, 29.34, 25.69, 22.76, 14.20. NMR spectra are in agreement with the literature.[7]



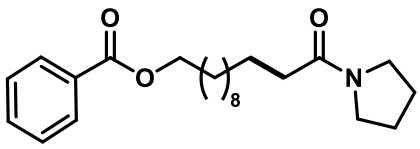
Followed procedure **AI.6b**. White solid, 372 mg, 78% (2.5 mmol scale derivatization). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.52 (m, 2H), 7.32 – 7.26 (m, 2H), 7.10 - 7.06 (m, 1H), 2.68 (p, *J* = 8.1 Hz, 1H), 1.98 – 1.84 (m, 4H), 1.83 – 1.73 (m, 2H), 1.66 – 1.55 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 174.74, 138.24, 129.01, 124.08, 119.76, 46.93, 30.60, 26.08. NMR spectra are in agreement with the literature.[8]



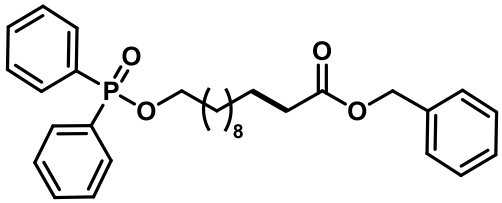
Followed procedure **AI.6b**. White solid, 181 mg, 36% (2.5 mmol scale derivatization). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.54 – 7.52 (m, 2H), 7.33 – 7.26 (m, 2H), 7.10 – 7.07 (m, 1H), 2.27 – 2.19 (m, 1H), 1.96 – 1.93 (m, 2H), 1.84 – 1.81 (m, 2H), 1.71– 1.68 (m, 1H), 1.59 – 1.49 (m, 2H), 1.34 – 1.22 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 174.52, 138.18, 129.02, 124.13, 119.83, 46.61, 29.72, 25.73. NMR spectra are in agreement with the literature.[8]



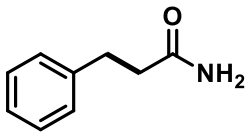
Followed procedure **AI.6a**. White solid, 105 mg, 29% (1.25 mmol scale derivatization). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.47 (t, *J* = 6.9 Hz, 2H), 3.37 (t, *J* = 6.8 Hz, 2H), 3.08 – 3.04 (m, 2H), 2.57 – 2.53 (m, 2H), 2.00 – 1.93 (m, 2H), 1.90 – 1.83 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 169.21, 46.48, 45.81, 33.61, 26.14, 24.42,17.91. **^{19}F NMR** (377 MHz, $CDCl_3$) δ: -143.85, -157.85, 163.03. **HRMS**: $[M + H]^+$ calculated for $C_{13}H_{13}F_5NO^+$ 294.0912; Found 294.0910.



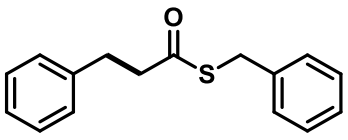
Followed procedure **AI.6a**. Colourless oil at r.t. and solidifies at -20 °C, 158 mg, 34% (338 mg, 73% when reaction performed at 2.0 mol% catalyst loading) (1.25 mmol scale derivatization). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.06 – 8.03 (m, 2H), 7.58 – 7.53 (m, 1H), 7.46 – 7.42 (m, 2H), 4.31 (t, *J* = 6.7 Hz, 2H), 3.46 (t, *J* = 6.9 Hz, 2H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.27 – 2.23 (m, 2H), 1.98 – 1.91 (m, 2H), 1.88 – 1.80 (m, 2H), 1.80-1.73 (m, 2H), 1.68 – 1.60 (m, 2H), 1.47 – 1.42 (m, 2H), 1.37 - 1.25 (m, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.92, 166.77, 132.85, 130.58, 129.59, 128.38, 65.21, 46.67, 45.63, 34.93, 29.61, 29.59, 29.57, 29.55, 29.52, 29.34, 28.78, 26.20, 26.10, 25.02, 24.49. **HRMS**: $[M + H]^+$ calculated for $C_{23}H_{36}NO_3^+$ 374.2689; Found 374.2686.



Followed procedure **AI.6c**. Colourless oil, 231 mg, 37% (*mixture with 9% branched product*; 1.25 mmol scale derivatization). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 4H), 7.54 – 7.49 (m, 2H), 7.47 – 7.42 (m, 4H), 7.37 – 7.29 (m, 5H), 5.11 (s, 2H), 4.02 (q, *J* = 6.7 Hz, 2H), 2.48 (q, *J* = 6.7 Hz, 0.11H; *belongs to branched product*), 2.35 (t, *J* = 7.5 Hz, 2H), 1.75 – 1.68 (m, 2H), 1.68 – 1.60 (m, 2H), 1.41 – 1.34 (m, 2H), 1.31 – 1.24 (m, 12H), 1.16 (d, *J* = 6.9 Hz, 0.36H; *belongs to branched product*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (*mixture with branched product*): 176.81, 173.78, 136.18, 132.44, 132.15, 132.12, 131.75, 131.65, 131.07, 128.63, 128.60, 128.57, 128.50, 128.23, 128.11, 66.13, 65.11, 65.05, 39.61, 34.39, 33.85, 30.64, 30.57, 29.77, 29.52, 29.51, 29.43, 29.45, 29.29, 29.20, 29.18,27.23, 25.67, 25.01,17.13. **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 31.13. **HRMS**: $[M + H]^+$ calculated for $C_{31}H_{40}O_4P^+$ 507.2659; Found 507.2657.



Followed procedure **AI.6d**. White solid, 316 mg, 85% (2.5 mmol scale derivatization). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.37 – 7.26 (m, 3H), 7.22 – 7.18 (m, 3H), 5.93 (br s, 1H), 5.50 (br s, 1H), 2.96 (t, *J* = 7.8 Hz, 2H), 2.52 (t, *J* = 8 Hz, 2H). δ: 3.61(q, *J* = 7.2 Hz, 0.13H), 1.51 (d, *J* = 7.2 Hz, 0.40 H) belong to the branched amide. **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 174.99, 140.72, 128.65, 128.38, 126.38, 37.60, 31.44. δ: 177.10, 141.27, 129.05, 127.67, 127.46, 46.67, 18.38 belong to the branched amide. NMR spectra are in agreement with the literature.[9]



Followed procedure **AI.6e**. Colourless oil, 595 mg, 93% (2.5 mmol scale derivatization). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.31 – 7.27 (m, 4H), 7.26 – 7.15 (m, 6H), 4.12 (s, 2H), 3.01 – 2.97 (m, 2H), 2.90 – 2.85 (m, 2H). δ: 3.90 (q, *J* =7.1 Hz, 0.13H), 1.54 (d, *J* =7.1 Hz, 0.39H) belong to the branched thioester. **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 197.95, 140.03, 137.63, 128.89, 128.70, 128.62, 128.40, 127.33, 126.44, 45.31, 33.26, 31.49. δ: 200.63, 139.76, 137.40, 128.76, 128.66, 128.05, 127.58,127.29, 54.11, 33.57, 18.48 belong to the branched thioester. NMR spectra are in agreement with the literature.[10]

AI.8. Examples of typical GC, UPLC chromatograms and NMR spectra

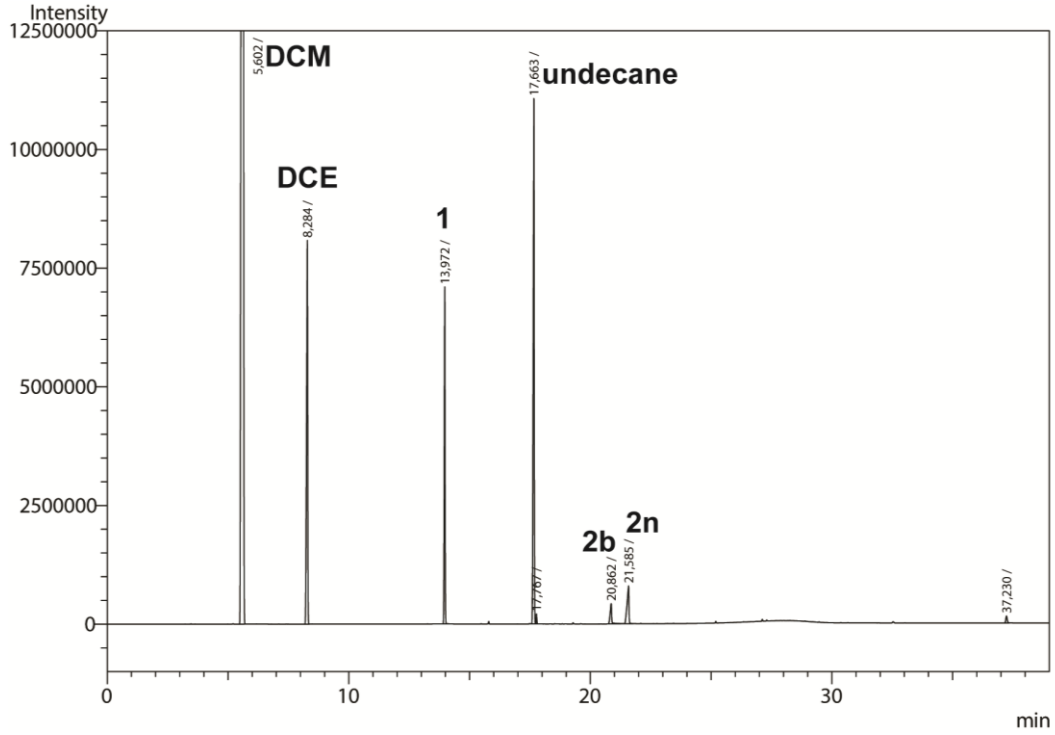


Figure AI.5. Typical GC-FID chromatogram of catalytic reaction mixture (example shown is of Table AI.7, entry 2).

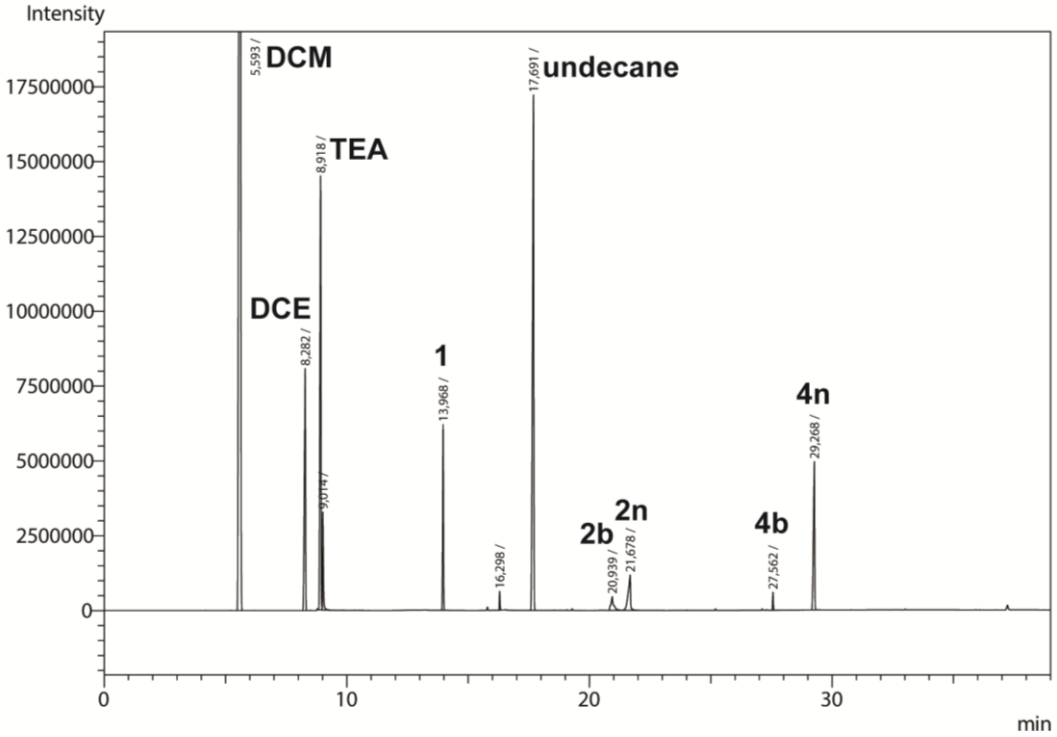


Figure AI.6. Typical GC-FID chromatogram of pyrrolidine derivatized catalytic reaction mixture (example shown is of Table AI.7, entry 2).

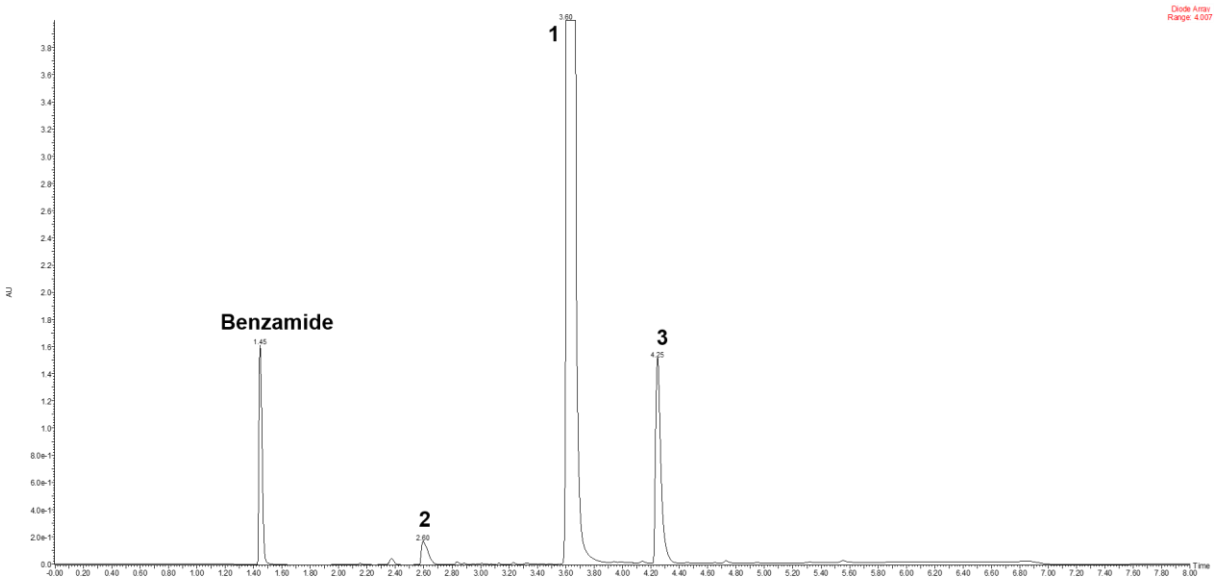


Figure AI.7. Typical UPLC chromatogram of catalytic reaction mixture (example shown is of Table AI.7, entry 2).

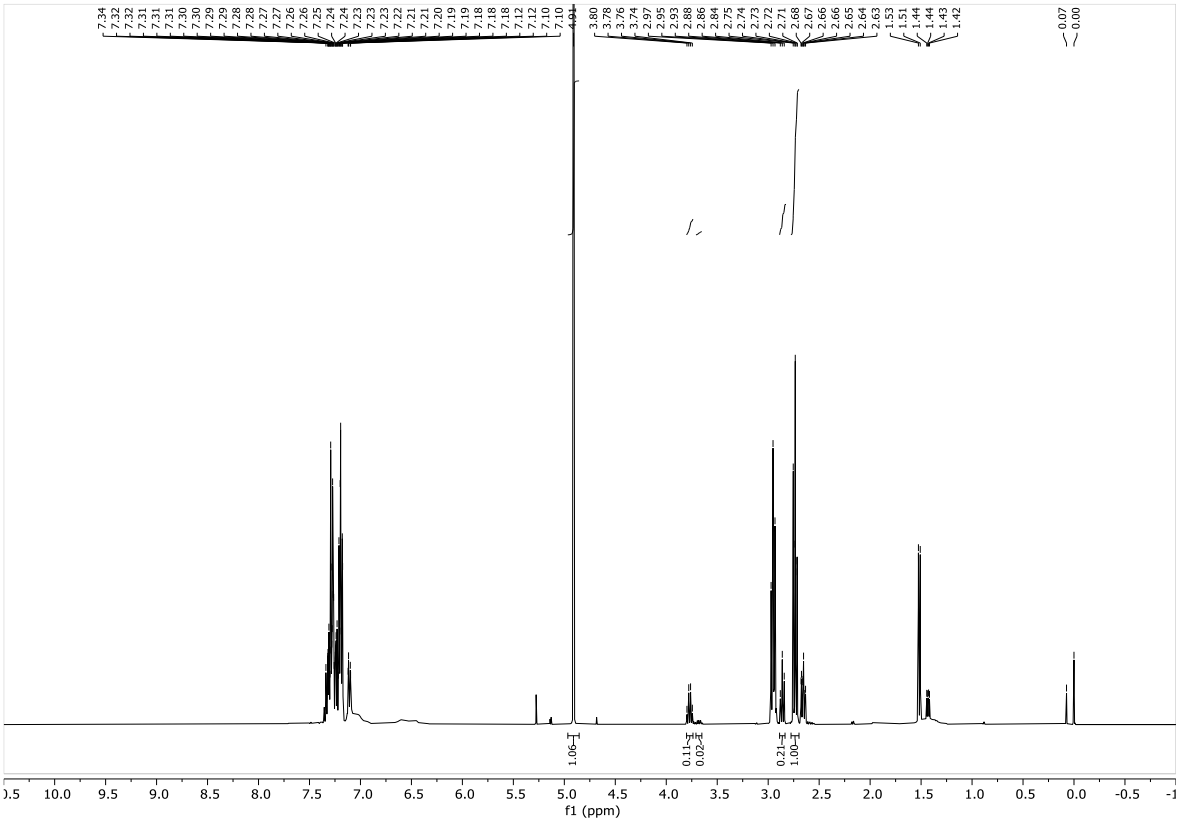


Figure AI.8. Typical NMR spectrum of catalytic reaction mixture (example shown is of Table AI.7, entry 2).

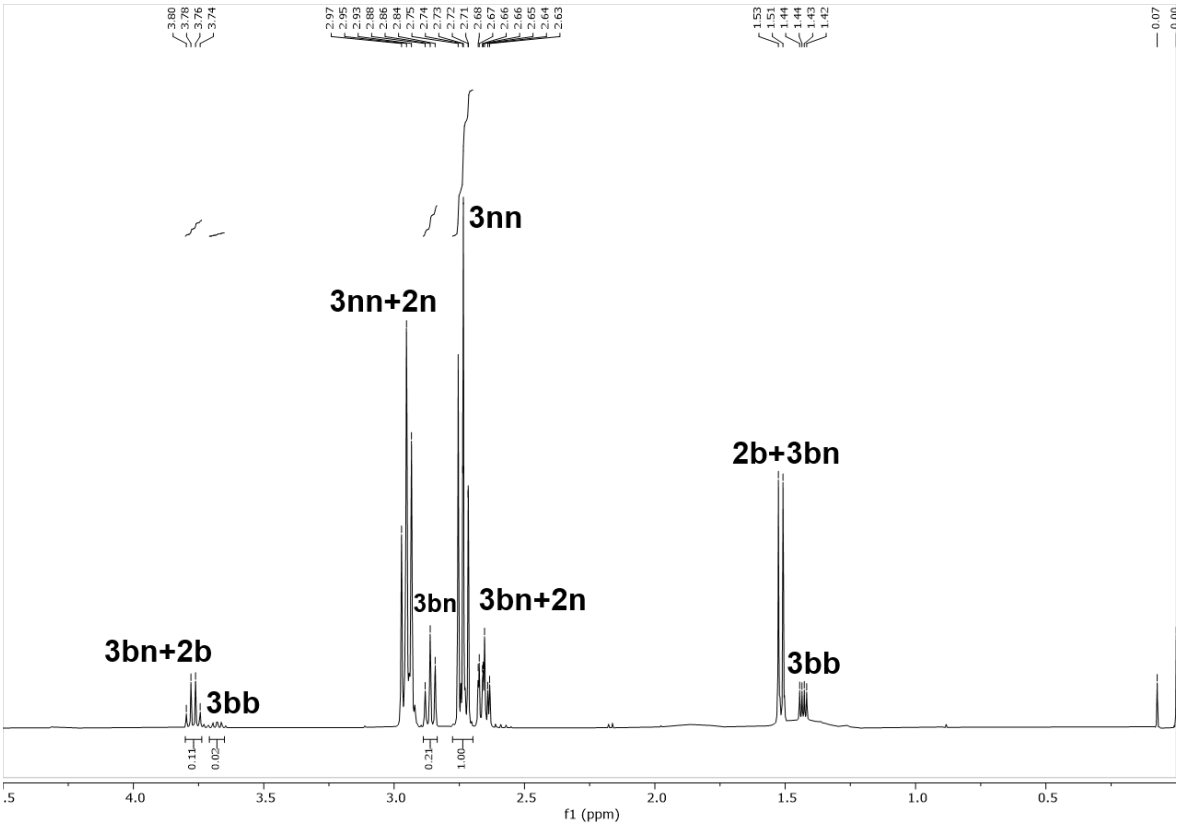


Figure AI.9. Typical NMR spectrum of catalytic reaction mixture, highlighting the important peaks to determine selectivity (example shown is of Table AI.7, entry 2).

AI.9. Computational calculations: Cartesian coordinates (in Å) and total energies ($G_{gas\text{-}phase}$)

Carbon Monoxide **CO** (-342.41 kcal mol^{-1})

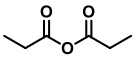
C	0.000000	0.000000	-0.568201
O	0.000000	0.000000	0.568201

Ethene ═ (-693.43 kcal mol^{-1})

C	-0.666527	0.000000	0.000000
C	0.666527	0.000000	0.000000
H	-1.238837	-0.925831	0.000000
H	-1.238837	0.925831	0.000000
H	1.238837	-0.925831	0.000000
H	1.238837	0.925831	0.000000

Propionic acid  (-1367.06 kcal mol^{-1})

C	-4.056625	-1.260868	-0.820949
C	-2.789528	-0.399554	-0.806764
C	-1.556965	-1.154524	-0.340822
O	-1.509072	-2.319199	-0.000214
O	-0.445232	-0.340061	-0.345535
H	-2.567342	0.007064	-1.802850
H	-3.938745	-2.120197	-1.488545
H	-4.911575	-0.668497	-1.163669
H	-4.279180	-1.646898	0.178792
H	-2.904320	0.475504	-0.152571
H	0.300068	-0.896065	-0.035531

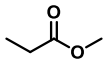
Propionic anhydride 
(-2406.66 kcal mol^{-1})

C	-3.111105	-3.451606	1.458275
C	-2.419276	-2.104488	1.434626
O	-2.898599	-1.041957	1.141188
O	-1.049218	-2.267191	1.764184
C	-0.342129	-1.219016	2.407207
O	-0.863395	-0.454078	3.173965
C	1.120599	-1.279946	2.019188
C	2.000040	-0.315108	2.821568
C	-4.543705	-3.405702	0.916359
H	-3.086784	-3.798837	2.501587
H	-2.484517	-4.159767	0.900163

H	1.168941	-1.066512	0.941318
H	1.452120	-2.321279	2.125795
H	3.040806	-0.388436	2.489242
H	1.960457	-0.546363	3.891026
H	1.664557	0.718461	2.692911
H	-4.557103	-3.078081	-0.128256
H	-5.156945	-2.705497	1.491673
H	-5.000697	-4.399121	0.974008

Methanol H_3C-OH (-655.44 kcal mol^{-1})

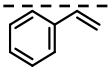
C	-4.882061	0.081262	0.000000
O	-3.439857	0.061455	0.000000
H	-5.300227	-0.400142	0.896496
H	-5.300227	-0.400142	-0.896496
H	-5.175718	1.134844	0.000000
H	-3.148729	-0.865737	0.000000

Methyl propionate 
(-1709.19 kcal mol^{-1})

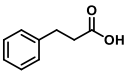
C	-4.056150	-1.259738	-0.821178
C	-2.787629	-0.399879	-0.806350
C	-1.555009	-1.160341	-0.339008
O	-1.519704	-2.327576	0.000129
O	-0.455349	-0.341778	-0.347822
C	0.787401	-0.968285	0.084055
H	-3.939239	-2.119444	-1.488610
H	-4.910849	-0.666648	-1.163930
H	-4.279413	-1.646360	0.178278
H	-2.904104	0.474476	-0.151831
H	-2.567178	0.006142	-1.802849
H	1.542633	-0.184240	0.015030
H	1.036458	-1.808680	-0.570700
H	0.692987	-1.329691	1.112372

Water H_2O (-316.23 kcal mol^{-1})

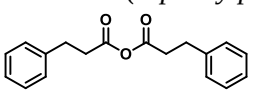
O	0.000000	0.000000	-0.284442
H	0.000000	-0.768786	0.311309
H	0.000000	0.768786	0.311309

Styrene  (-2170.80 kcal mol^{-1})

C	-0.62249869	-0.09049250	-0.12754874
C	0.68942543	0.03695300	0.12308939
H	0.55889121	-1.61910024	-2.11362469
H	-1.32281042	0.42905890	0.52891998
H	1.45293862	-0.44673773	-0.48151834
H	1.04099697	0.63961620	0.95569476
C	-1.25820443	-0.86297546	-1.20669054
C	-2.66377192	-0.87019538	-1.30263108
C	-3.31782321	-1.58666252	-2.30758357
C	-2.57721007	-2.31449560	-3.24292754
C	-1.17775919	-2.31824539	-3.16195689
C	-0.52679093	-1.60305244	-2.15899556
H	-3.24499453	-0.30484046	-0.57651060
H	-4.40413160	-1.57593207	-2.36011639
H	-3.08128940	-2.87380252	-4.02736873
H	-0.59466506	-2.88254934	-3.88640084

2n *(3-phenylpropionic acid)* 
(-2836.44 kcal mol^{-1})

C	-3.82582751	-1.26799962	-1.43026021
C	-3.02337421	-0.85983009	-0.17962084
C	-1.52650729	-0.80151002	-0.42211564
O	-0.95541171	-1.03362284	-1.46860317
O	-0.85302606	-0.44029169	0.72373950
H	-3.34626971	0.12316137	0.18854499
H	-3.61346680	-0.55787845	-2.23725936
H	-5.32293078	-3.39123197	-0.57242699
H	-3.47603146	-2.24760606	-1.77451857
H	-3.20707465	-1.55737619	0.64841430
H	0.09823200	-0.42445925	0.48712236
C	-5.31265841	-1.31111539	-1.14502525
C	-6.10545848	-0.16261631	-1.29361259
C	-7.47023014	-0.18827214	-0.99129012
C	-8.06521252	-1.36827243	-0.53281239
C	-7.28632899	-2.52031033	-0.38219325
C	-5.92192413	-2.48903326	-0.68593153
H	-5.65046025	0.75774026	-1.65642269
H	-8.06949836	0.71061659	-1.11808356
H	-9.12721370	-1.39133005	-0.30034259
H	-7.74183745	-3.44419879	-0.03267349

3nn *(3-phenylpropionic anhydride)*
 (-5344.69 kcal mol^{-1})

C	-3.11120411	-3.42601805	1.39514806
C	-2.39669679	-2.09508075	1.30878248

O	-2.83957789	-1.05205967	0.90754797	C	5.62191201	-1.47320361	2.79247453
O	-1.05109442	-2.25162816	1.72894030	C	6.15914341	-0.74746769	1.72423872
C	-0.35696470	-1.16402748	2.31906850	C	5.34575920	0.14429152	1.01725294
O	-0.90144486	-0.32615218	2.98712180	C	4.00422693	0.30540558	1.37636022
C	1.12105831	-1.28546120	2.01925972	H	3.86966160	-1.87197301	3.98420125
C	1.98729337	-0.27725492	2.79958059	H	6.24881335	-2.16380805	3.35214493
C	-4.50838453	-3.41204843	0.74437653	H	7.20366774	-0.87166257	1.44862484
H	-3.18027624	-3.69013885	2.46027840	H	5.75690684	0.71799785	0.18962865
H	-2.47020896	-4.19436470	0.94429644	C	-5.19188476	-4.75706602	0.87697663
H	1.24576836	-1.14918112	0.93536487	C	-5.99346729	-5.04735331	1.99168108
H	1.43284702	-2.31810751	2.22184086	C	-6.58884890	-6.30375920	2.13940352
H	3.37838713	1.00613209	0.82601503	C	-6.38996996	-7.29279605	1.17049521
H	1.83934311	-0.43644849	3.87395753	C	-5.59494206	-7.01493116	0.05366083
H	1.63722053	0.73727750	2.58033404	C	-5.00199901	-5.75690975	-0.08936175
H	-4.40652526	-3.14045889	-0.31271982	H	-6.15756438	-4.27998068	2.74650651
H	-5.11225197	-2.62818844	1.21416292	H	-7.21123472	-6.50869491	3.00758081
H	-4.38952942	-5.54541444	-0.96450836	H	-6.85489454	-8.26943612	1.28196535
C	3.45284598	-0.41856901	2.44469487	H	-5.44049989	-7.77572809	-0.70824692
C	4.27962741	-1.30852625	3.14741627				

AI.10. References

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Appendix II

Supporting Information for Chapter 3

Palladium-Catalyzed Synthesis of Symmetric Carboxylic Acid Anhydrides from Alkenes with *in situ* Generated Carboxylic Acids

AII.1. General experiment details and materials

Reactions and chemicals related: All reactions and operations involving air- or moisture-sensitive compounds were performed using standard Schlenk techniques in heated and vacuum dried glassware or in N_2-filled glove box. Chemicals were purchased from Sigma-Aldrich, TCI, Acros, Brunschwig or Bio-connect and used without further purification unless otherwise stated. Anhydrous 1,2-dichloroethane (DCE) was purchased from Biosolve and dried over flame dried 4Å molecular sieves. Toluene and dichloromethane (DCM) were purchased from Honeywell and dispensed *via* Pure Solv solvent dispenser by Innovative Technologies. Solvents were freeze-pump-thawed (FPT) before all catalytic reactions. All ligands except 1,2-diphenylphosphinomethyl benzene were purchased from Sigma-Aldrich and Strem Chemicals. 1,2-diphenylphosphinomethyl benzene was synthesized in-house.

a. Autoclaves: 100 mL stainless steel (316) autoclaves equipped with temperature probe and pressure adapter were used. For heating and stirring, an H.E.L. Polyblock PB4 was used.

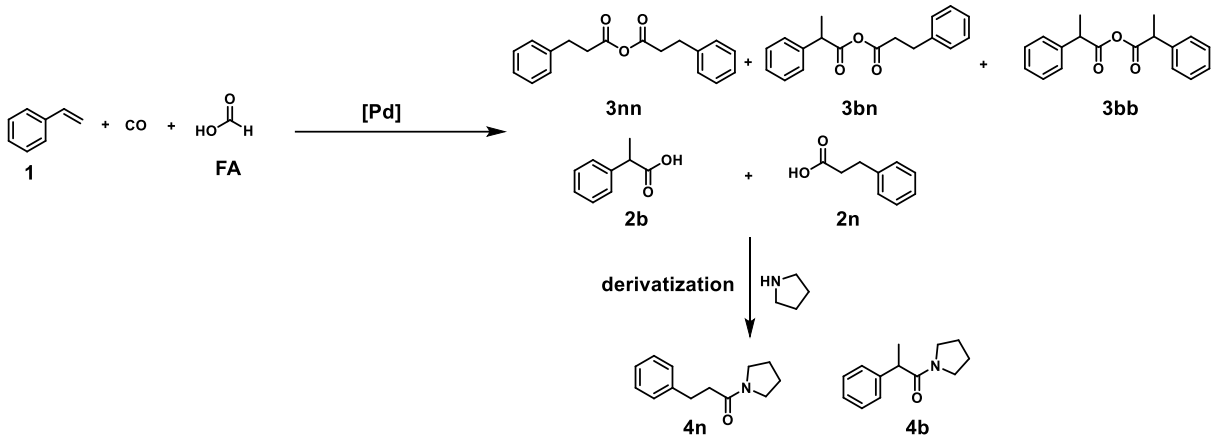
b. NMR Spectroscopy: ^{1}H NMR and ^{13}C NMR were recorded on Bruker Avance 400 (operating at 400 MHz for ^{1}H, 101 MHz for ^{13}C) NMR spectrometer. ^{19}F and ^{31}P NMR spectra were referenced against $CFCl_3$ and 85% H_3PO_4 (external references). Multiplets were assigned as s (singlet), d (doublet), t (triplet), , q (quartet), p (quintet), dd (doublet of doublet), ddt (doublet of doublet of triplet) and m (multiplet). All measurements were carried out at room temperature. NMR yields were calculated using dibromomethane as internal standard.

c. GC Analysis: Gas chromatography (GC) was measured on Shimadzu GC-2010, equipped with DB-5MS UI column (length 60 m, diameter: 0.250 mm, film thickness: 1.0 µm), coupled to Flame Ionization Detector (FID). Gas chromatography-mass spectrometry (GC-MS) was measured on Agilent Technologies 7820A equipped with DB-5MS UI column (length 30 m, diameter: 0.250 mm, film thickness: 1.0 µm) column and coupled to mass detector MSD 5975. Helium was used as the mobile phase.

d. HRMS: High resolution mass spectra (HRMS) were recorded on Q-Exactive HF Orbitrap (Thermo Scientific) equipped with an electrospray ion source (ESI) in positive mode, injection of 2 µL of a 1 µM solution *via* Ultimate 3000 nano UPLC (Dionex) system, with an external calibration (Thermo Scientific). Parameters used: Source voltage of 3.5 kV, capillary temperature 275 °C, no sheath gas, Resolution = 240.000 at m/z=400. Mass range m/z=160-2000 or until a maximum of 6000. Eluents used: ACN:H_2O (1:1 v/v) supplemented with 0.1% formic acid. The data are given as mass units per charge (m/z).

AII.2. General reaction scheme, methods of analysis and calculations

AII.2.1. General reaction scheme showing reactants, all possible products of catalysis and products obtained on derivatization



Scheme AII.1. Overall reaction scheme showing substrates and products.

AII.2.2. Methods of analysis of substrates and products

a. GC : **1**, **4n**, **4b**

b. NMR : **2n**, **2b**, **3nn**, **3bn**, **3bb**

AII.2.3. Calculations

a. Mass Balance:

The Mass Balance was calculated in terms of "number of phenyl groups" present in the reaction mixture after catalysis as follows:

$$\frac{phenyls\ of\ \mathbf{1}\ + phenyls\ of\ \mathbf{2} + \ phenyls\ of\ \mathbf{3}}{total\ initial\ phenyls} \times 100$$

Where,

Phenyls of **1** = mmol of **1** unreacted ; determined by GC

Phenyls of **2** = mmol of (**2n**+**2b**) ; determined by NMR

Phenyls of **3** = 2 × mmol of **3**; determined by NMR

Total initial phenyls = mmol of **1** introduced in the reaction

An error margin of ±10% is considered to be acceptable for the mass balance.

b. Total Anhydride Yield %:

The total anhydride yield % was calculated as follows:

$$\frac{mmol\ of\ \mathbf{3}}{mmol\ of\ limiting\ reagent} \times 100$$

Where,

mmol of **3** (**3nn** + **3bn** + **3bb**) was determined by NMR

c. Regioselectivity:

3nn:**3bn:3bb** was calculated as follows:

$$\frac{\boldsymbol{3nn}\ or\ \boldsymbol{3bn}\ or\ \boldsymbol{3bb}}{Total\ anhydride\ yield} \times 100$$

Where,

mmol of **3nn**, **3bn**, **3bb** were determined by NMR using dibromomethane as internal standard

4n:**4b** was calculated as follows:

$$\frac{\boldsymbol{4n}\ or\ \boldsymbol{4b}}{\boldsymbol{4n}+\boldsymbol{4b}} \times 100$$

Where,

mmol of **4n**, **4b** were determined by GC

d. Conversion %

Conversion % with respect to styrene (**1**) was calculated as follows:

$$\left[1-\frac{\mathbf{1}\ unreacted}{initial\ \mathbf{1}\ charged}\right] \times 100$$

Where,

mmol of **1** was determined by GC

An error margin of ±5% is considered to be acceptable for the conversion.

e. Concentrations mentioned in mol% are always given with respect to the limiting reagent in cases where one of the reagents is used in excess.

AII.3. General catalytic procedure (GP) and analysis

Palladium acetate (0.05 mmol; 11.2 mg) and 1,4-bis(diphenylphosphanyl)butane, dppb, (0.10 mmol; 42.7 mg) were weighed into a clean and dried glass liner containing an oven−dried stirring bar. The glass liner was fitted inside a 100 mL stainless steel Parr autoclave and the autoclave was closed. The autoclave was connected to a Schlenk line and subjected to five cycles of evacuation and refilling with nitrogen gas. A freeze-pump-thawed solution of formic acid in dried 1,2-dichloroethane (DCE) was added using standard Schlenk techniques and the mixture was stirred for 30 mins. Then the required volume of degassed and dried styrene (**1**) was added using standard Schlenk procedures and the autoclave was closed and disconnected from the Schlenk line. The autoclave was transferred to a HEL PB4 polyblock and connected to the gas lines. The lines connecting the autoclave was flushed with nitrogen (N_2) (3 × 30 bar). The autoclave was flushed with carbon monoxide (CO) (1 × 30 bar) and then was charged with CO to 50 bar. The autoclave was stirred at 350 rpm and heated for 15 h at the desired temperature. At the end of the reaction time, the autoclave was brought to room temperature, cooled further for 30 minutes using an ice-bath and then was slowly depressurized. After 30 minutes of thawing, the contents of the glass liner were transferred to a 10 mL volumetric flask (**A**) and the total volume was adjusted to 10 mL using dichloromethane (DCM).

a. GC Analysis: 1 mL of the reaction mixture in flask **A** was transferred to a 10 mL volumetric flask (**B**), to which 0.3 mL undecane (internal standard for GC analysis) was added and was diluted up to 10 mL with DCM. The resulting solution was then analyzed using GC. The amount of styrene (**1**) present in the GC sample was determined using calibration lines with undecane as the internal standard. A 60 m × 0.250 mm ; 1.0 µm thickness DB-5MS GC column was used for analysis. 2.0 µL of each sample was injected and the following

temperature program was used: injector at 350 °C, FID at 350 °C, oven at 40 °C for 3 min, increasing to 300 °C with 10 °C/min and hold at 300 °C for 10 min.

b. NMR Analysis: NMR samples were prepared by drying 0.4 mL of the reaction mixture *in vacuo*, diluted with $CDCl_3$ and dibromomethane added as internal standard.

c. Derivatization Procedure: In a capped microwave vial, 2.5 mL of the reaction mixture from flask **A** was added under N_2 to a cooled solution of pyrrolidine (0.5 mL; 6.1 mmol) and triethylamine (1.0 mL; 7.3 mmol) in DCM (1.0 mL). The reaction mixture was stirred for 5 mins in an ice-bath and then heated to 35 °C for 15 h in an aluminium block.

d. GC Analysis after derivatization:1 mL of the derivatization reaction mixture was transferred to a 5 mL volumetric flask (**C**), 0.3 mL undecane (internal standard for GC analysis) was added and the volume was adjusted to 5 mL with DCM. The resulting solution was then analyzed using GC. The pyrrolidine-derivatized products (**4n** and **4b**) present in the GC sample were quantified using calibration lines with undecane as the internal standard. A 60 m × 0.250 mm ; 1.0 µm thickness DB-5MS GC column was used for analysis. 2.0 µL of each sample was injected and the following temperature program was used: injector at 350 °C, FID at 350 °C, oven at 40 °C for 3 min, increasing to 300 °C with 10 °C/min and hold at 300 °C for 10 min. The resulting yield of product was further calculated for the initial 10 mmol scale hydrocarbonylation reaction.

AII.4. Results of screening studies:

AII.4.1. Influence of relative substrate ratio

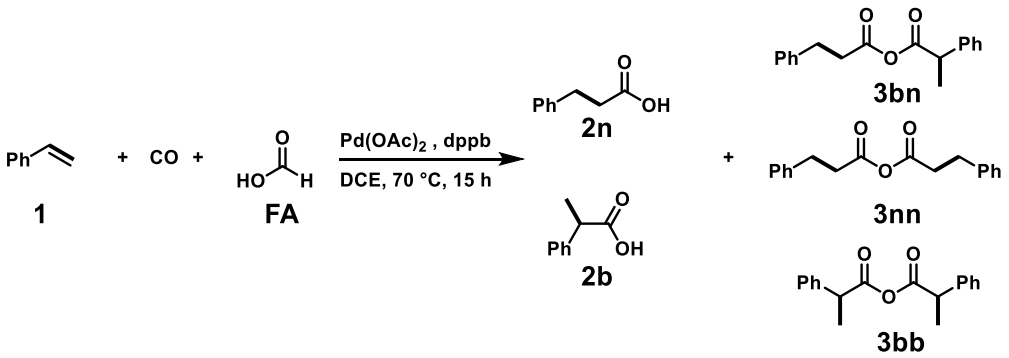
a. Procedure same as GP

b. Exact mmol of substrates used

1:FA	1	FA
5:10	572 µL (5.0 mmol)	378 µL (10.0 mmol)
5:5	572 µL (5.0 mmol)	190 µL (5.0 mmol)
10:5	1.2 mL (10.5 mmol)	190 µL (5.0 mmol)
15:5	1.7 mL (14.9 mmol)	190 µL (5.0 mmol)
30:10	3.4 mL (29.7 mmol)	378 µL (10.0 mmol)

c. Mass Balance:

Table AII.1. Mass balance: Influence of substrate ratio.



Entry	1:FA (mmol)	1[a] (mmol)	2n[b] (mmol)	2b[b] (mmol)	3nn[b] (mmol)	3bn[b] (mmol)	3bb[b] (mmol)	Yield% of 4/ (4n:4b)[a]	Mass Balance %
1	5:10	0	3.7	0.8	0	0	0	0	90
2	5:5	0	3.7	0.9	Trace	0	0	0	92
3	10:5	2.4	1.1	0.2	2.1	1.1	0.3	72 (89:11)	102
4	15:5	4.2	0.8	0.2	2.5	1.6	0.2	84 (86:14)	93
5	30:10[c]	8.0	1.5	Trace	4.7	3.5	0.6	86 (86:14)	91

Reaction conditions: **1** (x mmol), formic acid (y mmol), CO (50 bar), $Pd(OAc)_2$ (0.05 mmol), dppb (0.1 mmol), 70 °C, DCE (6 mL), 15 h. Yield% (based on limiting reagent). [a] Determined by GC analysis using undecane as internal standard. [b] Determined by NMR analysis using dibromomethane as internal standard. [c] t = 20 h instead of 15 h.

d. CO pressure drop graphs

Time for the reaction temperature to reach 70 °C is 1.5 h. The reaction time is 15 h (1.5 to 16.5 h).

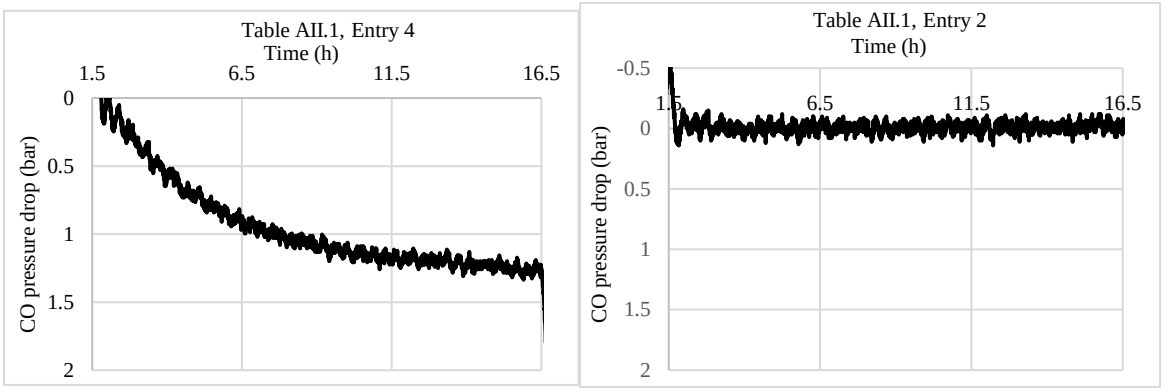


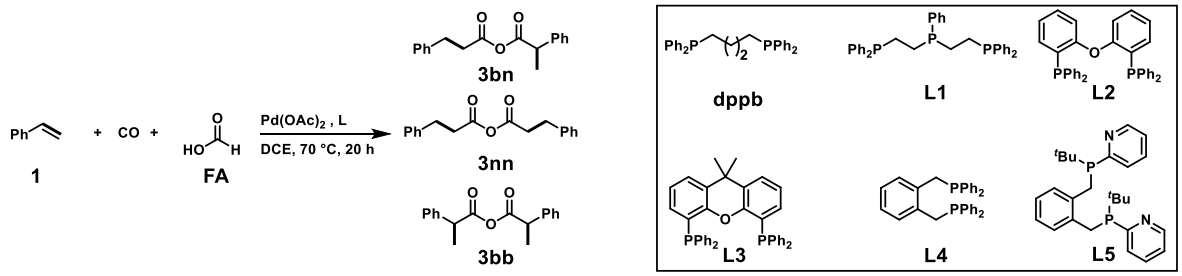
Figure AII.1. Relative CO pressure drop when **1**:FA is 15:5 mmol (left graph, Table AII.1, entry 4) and 5:5 mmol (right graph, Table AII.1, entry 2).

AII.4.2. Ligand screening

a. Procedure same as GP

b. Mass Balance:

Table AII.2. Mass Balance: Influence of ligands on synthesis of anhydrides from alkenes.



Ligand	1[a] (mmol)	2n[b] (mmol)	2b[b] (mmol)	3nn[b] (mmol)	3bn[b] (mmol)	3bb[b] (mmol)	Linearity %	Yield% of 4/ (4n:4b)[a]	Mass Balance %
dppb[c]	4.2	0.8	0.2	2.5	1.6	0.2	77	84 (86:14)	93
L1	8.3	0	0	0	0	0	-	0	56
L2	4.5	0.8	0.1	2.5	1.4	0.2	78	82 (86:14)	91
L3[d]	5.1	1.9	0.3	2.0	1.3	0.3	76	72 (86:14)	97
L4[e]	3.7	0.3	0.2	0.4	0.3	0	79	22 (73:27)	75
L5[e]	5.2	1.0	0.5	0.2	0.2	0	74		93

Reaction conditions: **1** (15 mmol), formic acid (5 mmol), CO (50 bar), $Pd(OAc)_2$ (0.05 mmol), ligand (0.1 mmol), 70 °C, DCE (6 mL), 20 h. Yield% based on FA. Linearity%: **3nn**% + (0.5×**3bn**%). [a] Determined by GC analysis using undecane as internal standard. [b] Determined by NMR analysis using dibromomethane as internal standard. [c] t = 15 h instead of 20 h. [d] 85 °C instead of 70 °C. [e] **1** (7.5 mmol), formic acid (2.5 mmol), CO (50 bar), $Pd(OAc)_2$ (0.025 mmol), ligand (0.0375 mmol), 70 °C, DCE (6 mL), 20 h.

AII.5. General procedure for substrate scope

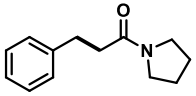
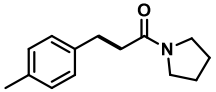
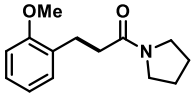
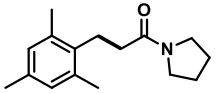
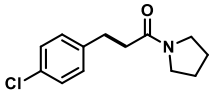
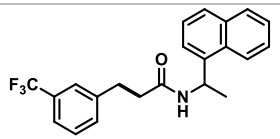
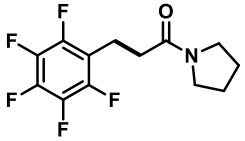
Palladium acetate (1.0 mol%) and 1,4-bis(diphenylphosphanyl)butane, dppb, (2.0 mol%) were weighed into a clean and dried glass liner containing an oven−dried stirring bar. The glass liner was fitted inside a 100 mL stainless steel Parr autoclave and the autoclave was closed. The autoclave was connected to a Schlenk line and subjected to five cycles of evacuation and refilling with nitrogen gas. A freeze-pump-thawed solution of formic acid (1.0 equiv.) in dried DCE (6.0 mL) was added using standard Schlenk techniques and the mixture was stirred for 30 mins. Then the required volume of degassed and dried alkene (3.0 equiv.) was added using standard Schlenk procedures and the autoclave was closed and disconnected from the Schlenk line. The autoclave was transferred to a HEL PB4 polyblock and connected to the gas lines. The lines connecting the autoclave was flushed with nitrogen (N_2) (3 × 30 bar). The autoclave was flushed with carbon monoxide (CO) (1 × 30 bar) and then was charged with CO to 50 bar. The autoclave was stirred at 350 rpm and heated for 20 to 36 h at 70 °C. At the end of the reaction time, the autoclave was brought to room temperature, cooled further for 30 minutes using an ice-bath and then was slowly depressurized. After 30 minutes of thawing, the contents of the glass liner were transferred to a 10 mL volumetric flask (**A**) and the total volume was adjusted to 10 mL using dichloromethane (DCM).

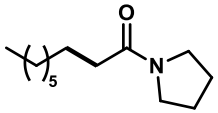
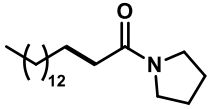
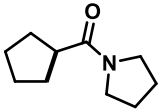
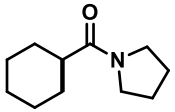
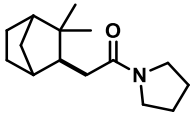
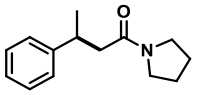
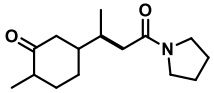
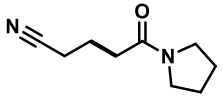
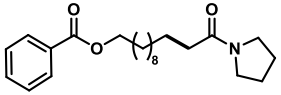
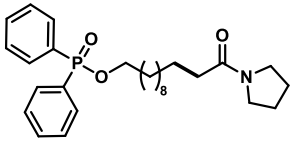
a. *Derivatization procedure with pyrrolidine*: In a capped microwave vial, 5.0 mL of the reaction mixture from flask **A** was added under N_2 to a cooled solution of pyrrolidine (0.5 mL; 6.1 mmol) and triethylamine (1.0 mL; 7.3 mmol). The reaction mixture was stirred for 5 mins in an ice-bath and then heated to 35 °C for 15 h in an aluminium block. The reaction mixture was subjected to column chromatography using ethyl acetate/pentane mixture (20 to 50%).
b. *Derivatization procedure with (1R)-(+)-1-naphthylethylamine:* In a capped microwave vial, 5.0 mL of the reaction mixture from flask **A** was added under N_2 to a cooled solution of *(1R)-(+)-1-naphthylethylamine* (222.6 mg; 1.30 mmol), DMAP (6.1 mg ; 0.05 mmol) and triethylamine (278 µL; 2.0 mmol). The reaction mixture was stirred for 5 mins in an ice-bath

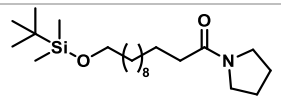
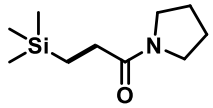
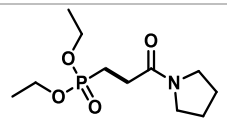
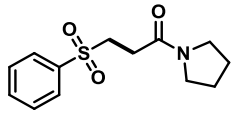
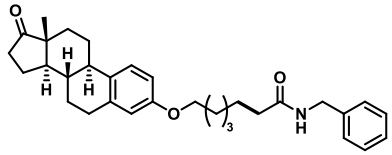
and then heated to 50 °C for 15 h in an aluminium block. The reaction mixture was subjected to column chromatography using diethyl ether/pentane mixture (20%). The reaction mixture was subjected to column chromatography using ethyl acetate/pentane mixture (0 to 30%).

c. *Derivatization procedure with benzylamine:* In a capped microwave vial, 5.0 mL of the reaction mixture from flask **A** was added under N_2 to a cooled solution of benzylamine (82 µL; 0.75 mmol), DMAP (6.1 mg ; 0.05 mmol) and triethylamine (139 µL; 1.0 mmol). The reaction mixture was stirred for 5 mins in an ice-bath and then heated to 50 °C for 15 h in an aluminium block. The reaction mixture was subjected to column chromatography using ethyl acetate/pentane mixture (0 to 30%).

Table AII.3. Substrate scope: Synthesis of symmetric acid anhydrides from alkenes.

Entry	**Structure of derivatized product**	**Scale based on FA of catalytic reaction (mmol)**	**NMR Yield% of anhydride before der^{n}.**[a]	**Regio-selectivity of anhydride formed before der^{n}.** [a] **nn:bn:bb**	**Scale of der^{n}. (mmol)**	**Isolated yield of pure linear product**	**Isolated yield % of linear product**	**Physical Properties**
4[b]		5.0	86	58:37:5	2.5	374 mg	74%	Pale yellow oil
5		5.0	90	58:37:5	2.5	434 mg	80%	Pale yellow oil
6		2.5	89	74:21:5	1.25	245 mg	84%	Pale yellow oil
7[c]		2.5	65	>99:-:-	1.25	164 mg	54%	Pale yellow oil – turns waxy on freezing
8		5.0	98	59:38:3	2.5	511 mg	86%	Off-white solid
9[d]		2.5	68	66:34:trace	1.25	270 mg	58%	White solid
10[c]		2.5	52	89:11:trace	1.25	159 mg	43%	White solid

11		5.0	>99	84:16:trace	2.5	491 mg	93%	Pale yellow oil
12		2.5	n.d	n.d.	1.25	351 mg	91%	White solid
13		5.0	77	>99	2.5	319 mg	76%	Pale yellow oil
14[e]		10.0	82	>99	2.5	365 mg	81%	White solid
15[c]		2.5	n.d.	n.d.	1.25	115 mg	39% (endo:exo 2:1)	Yellow oil turns solid on freezing
16		5.0	70	>99:trace:-	2.5	337 mg	62%	Pale yellow oil
17[c]		2.5	57	>99: -	1.25	151 mg	48%	Yellow solid (wax)
18		2.5	72	>99:-	1.25	143 mg	69%	Yellow oil
19		5.0	n.d.	n.d.	1.25	391 mg	84%	Pale yellow oil
20[c]		2.5	n.d.	n.d.	1.25	380 mg	65%	Pale yellow oil

21		5.0	n.d.	n.d.	1.25	226 mg	47%	Pale yellow oil
22		5.0	43	>99:-	2.5	171 mg	34%	Colourless oil
23		2.5	<10	-	-	-	-	Did not isolate
24		2.5	0	-	-	-	-	-
25[f]		1.0	n.d.	n.d.	0.5	181 mg	74%	White solid

Reaction conditions: Scale based on formic acid (5.0 mmol): Alkene (15.0 mmol), formic acid (5.0 mmol), CO (50 bar), $Pd(OAc)_2$ (0.05 mmol), ligand (0.1 mmol), 70 °C, DCE (6 mL), 20 h. Scale based on formic acid (2.5 mmol): Alkene (7.5 mmol), formic acid (2.5 mmol), CO (50 bar), $Pd(OAc)_2$ (0.025 mmol), ligand (0.05 mmol), 70 °C, DCE (6 mL), 20 h. Procedure AII.5a followed for derivatization of reaction mixtures unless specified. [a] Determined by NMR analysis using dibromomethane as internal standard. [b] t = 15 h instead of 20 h. [c] t = 36 h instead of 20 h. [d] Procedure AII.5b followed for derivatization. [e] Alkene (30 mmol), formic acid (10 mmol), CO (50 bar), $Pd(OAc)_2$ (0.05 mmol), ligand (0.1 mmol), 70 °C, DCE (6 mL), 24 h. [f] Alkene (2.0 mmol), formic acid (1.0 mmol), CO (50 bar), $Pd(OAc)_2$ (0.025 mmol), ligand (0.05 mmol), 70 °C, DCE (6 mL), 20 h, Procedure AII.5c followed for derivatization. Abbreviation: der^n.: derivatization, n.d.: not determined.

AII.6. Procedure of derivatizations for applications

a. Reaction with ammonia: In a capped microwave vial, 0.5 mL of the reaction mixture (maximum anhydride yield 0.25 mmol) from flask **A** was added under N_2 to a cooled solution of 7N ammonia in methanol (47.2 µL; 0.5 mmol). The reaction mixture was stirred for 5 mins in an ice-bath and then at room temperature for 15 h in an aluminium block. The reaction mixture was subjected to column chromatography using MeOH/DCM (0 to 10%).

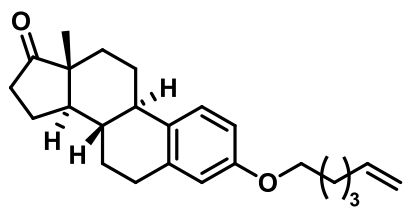
b. Reaction with β-naphthol: In a capped microwave vial, 0.5 mL of the reaction mixture (maximum anhydride yield 0.25 mmol) from flask **A** was added under N_2 to a cooled solution of β-naphthol (43.3 mg; 0.3 mmol), DMAP (3.1 mg ; 0.025 mmol) and triethylamine (69.6 µL; 0.5 mmol). The reaction mixture was stirred for 5 mins in an ice-bath and then heated to 50 °C for 15 h in an aluminium block. The reaction mixture was subjected to column chromatography using ethyl acetate/pentane mixture (0 to 20%).

c. Reaction with tert-butyl thiol: In a capped microwave vial, 0.5 mL of the reaction mixture (maximum anhydride yield 0.25 mmol) from flask **A** was added under N_2 to a cooled solution of *tert*-butyl thiol (34 µL; 0.3 mmol), DMAP (3.1 mg ; 0.025 mmol) and triethylamine (69.6 µL; 0.5 mmol). The reaction mixture was stirred for 5 mins in an ice-bath and then heated to 50 °C for 15 h in an aluminium block. The reaction mixture was subjected to column chromatography using ethyl acetate/pentane mixture (0 to 5%).

d. Friedel-Craft's acylation: In a capped microwave vial, 0.5 mL of the reaction mixture from flask **A** was taken. To the solution anisole (27.2 µL, 0.25 mmol) and $SnCl_4$ (29 uL, 0.25 mmol) were added under N_2. The mixture was stirred overnight at room temperature. The reaction mixture was subjected to column chromatography using ethyl acetate/pentane mixture (0 to 10%).

e. Suzuki coupling: 0.5 mL of the reaction mixture from flask **A** was dried *in vacuo*, the concentrate was dissolved in 0.5 mL dry toluene and transferred into a microwave vial under N_2. $Pd(PPh_3)_2Cl_2$ (2 mol%, 0.005 mmol, 3.5 mg), K_2CO_3 (103.7 mg, 0.75 mmol, 3.0 eq.) and phenylboronic acid (36.6 mg, 0.3 mmol, 1.2 eq.) were added sequentially under N_2. The mixture was stirred overnight at 80 °C. The reaction mixture was subjected to column chromatography using ethyl acetate/pentane mixture (0 to 10%).

AII.7. Synthesis of substrates



(8R,9S,13S,14S)-3-(hex-5-en-1-yloxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one,

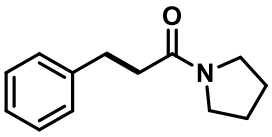
(ether derivative of estrone)

Estrone (810 mg; 3.0 mmol,) was dissolved in DMF (10 mL) and cesium carbonate (1.27 g; 3.9 mmol) was added followed by the addition of 6-bromo-1-hexene (481 µL; 3.6 mmol) and tetrabutylammonium iodide (110.8 mg; 0.3 mmol). The reaction mixture was heated to 50 °C for 16 h. The reaction was worked up using water (50 mL) and diethyl ether (50 mL), and the organic layer was washed with dilute NaOH solution, water, and brine (each 50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography using ethyl

acetate/pentane (0. to 20%) to afford the corresponding pure product, a white solid. 820 mg (78%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.19 (dd, *J* = 8.7, 1.1 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 5.88 – 5.96 (m, 1H), 5.05 – 4.95 (m, 2H), 3.94 (t, *J* = 6.5 Hz, 2H), 2.92 – 2.88 (m, 2H), 2.54 – 2.47 (m, 1H), 2.41 – 2.37 (m, 1H), 2.29– 1.94 (m, 7H), 1.82 – 1.75 (m, 2H), 1.66 – 1.41 (m, 9H), 0.91 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 221.05, 157.09, 138.59, 137.70, 131.85, 126.30, 114.70, 114.51, 112.08, 67.64, 50.39, 48.02, 43.98, 38.37, 35.89, 33.44, 31.57, 29.66, 28.77, 26.56, 25.92, 25.33, 21.59, 13.85. The NMR spectra are in agreement with the literature.[1]

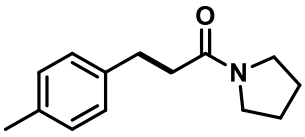
The synthesis of *undec-10-en-1-yl benzoate, tert-butyldimethyl-(undec-10-en-1-yloxy)-silane* and *undec-10-en-1-yl diphenylphosphinate* are described in AI.5 (Appendix I).

AII.8. Experimental data characterization of products (substrate scope and applications)



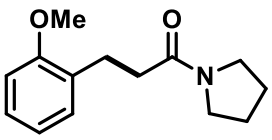
4n

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 – 7.18 (m, 5H), 3.46 (t, *J* = 6.7 Hz, 2H), 3.29 (t, *J* = 6.6 Hz, 2H), 3.01 – 2.97 (m, 2H), 2.58 – 2.54 (m, 2H), 1.90 – 1.80 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 170.73, 141.55, 128.46, 128.43, 126.06, 46.54, 45.64, 36.79, 31.21, 26.07, 24.39. NMR spectra are in agreement with the literature.[2]



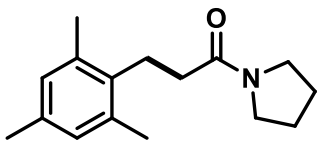
5n

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.13 – 7.08 (m, 4H), 3.46 (t, *J* = 6.7 Hz, 2H), 3.30 (t, *J* = 6.6 Hz, 2H), 2.96 – 2.92 (m, 2H), 2.56 – 2.52 (m, 2H), 2.32 (s, 3H), 1.96 – 1.79 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 170.82, 138.46, 135.53, 129.10, 128.32, 46.53, 45.62, 36.96, 30.74, 26.07, 24.40, 21.01. NMR spectra are in agreement with the literature.[3]



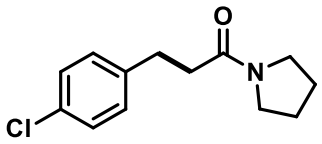
6n

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21 – 7.18 (m, 2H), 6.90 – 6.83 (m, 2H), 3.82 (s, 3H), 3.46 (t, *J* = 6.8 Hz, 2H), 3.32 (t, *J* = 6.7 Hz, 2H), 2.99 – 2.95 (m, 2H), 2.55 – 2.51 (m, 2H), 1.90 – 1.80 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.44, 157.54, 130.26, 129.82, 127.47, 120.54, 110.22, 55.26, 46.55, 45.63, 35.13, 26.40, 26.17, 24.49. **HRMS**: $[M + H]^+$ calculated for $C_{14}H_{20}NO_2^+$ 234.14886; Found 234.1487.



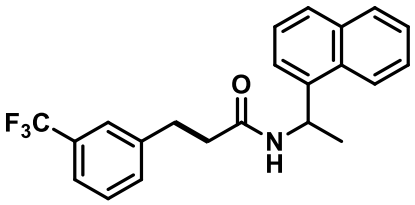
7n

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.85 (s, 2H), 3.49 (t, *J* = 6.7 Hz, 2H), 3.30 (t, *J* = 6.6 Hz, 2H), 2.99 – 2.95 (m, 2H), 2.40 – 2.36 (m, 2H), 2.30 (s, 6H), 2.25 (s, 3H), 1.93 – 1.83 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.00, 136.16, 135.40, 135.00, 128.95, 46.48, 45.70, 34.01, 26.13, 24.58, 24.40, 20.79, 19.73. **HRMS**: $[M + H]^+$ calculated for $C_{16}H_{24}NO^+$ 286.1852; Found 286.1852.



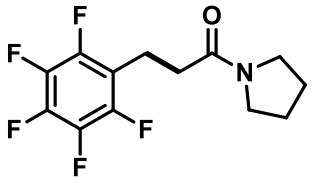
8n

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 – 7.23 (m, 2H), 7.17 – 7.15 (m, 2H), 3.46 (t, *J* = 6.8 Hz, 2H), 3.30 (t, *J* = 6.7 Hz, 2H), 2.98 – 2.94 (m, 2H), 2.55 – 2.51 (m, 2H), 1.94 – 1.79 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 170.34, 140.06, 131.79, 129.89, 128.51, 46.56, 45.68, 36.49, 30.42, 26.08, 24.40. **HRMS**: $[M + H]^+$ calculated for $C_{13}H_{17}ClNO^+$ 238.0993; Found 238.0992.



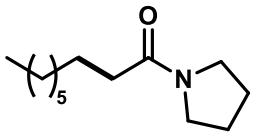
9n

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 – 8.00 (m, 1H), 7.88 – 7.83 (m, 1H), 7.81 – 7.76 (m, 1H), 7.51 – 7.49 (m, 2H), 7.45 – 7.39 (m, 4H), 7.35 – 7.30 (m, 2H), 5.93 – 5.86 (m, 1H), 5.63 – 5.61 (m, 1H), 3.09 – 2.96 (m, 2H), 2.47 – 2.42 (m, 2H), 1.59 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 170.26, 141.69, 137.95, 133.89, 131.96, 131.03, 128.89, 128.79, 128.43, 126.59, 125.90, 125.15, 125.02, 124.98, 123.31, 123.13, 123.09, 122.51, 44.61, 38.01, 31.29, 20.51. **^{19}F NMR** (377 MHz, $CDCl_3$) δ: -62.80. NMR spectra are in agreement with the literature.[4]



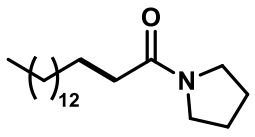
10n

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.47 (t, *J* = 6.9 Hz, 2H), 3.37 (t, *J* = 6.8 Hz, 2H), 3.08 – 3.04 (m, 2H), 2.58 – 2.54 (m, 2H), 2.00 – 1.93 (m, 2H), 1.90 – 1.83 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.19, 46.45, 45.77, 33.57, 26.10, 24.38, 17.87. **^{19}F NMR** (377 MHz, $CDCl_3$) δ: -143.61, -157.64, -162.81. **HRMS**: $[M + H]^+$ calculated for $C_{13}H_{13}F_5NO^+$ 294.0911; Found 294.0911.



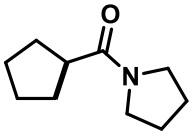
11n

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.46 (t, *J* = 6.9 Hz, 2H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.27 – 2.24 (m, 2H), 1.98 – 1.91 (m, 2H), 1.88 – 1.81 (m, 2H), 1.68 – 1.61 (m, 2H), 1.31 – 1.27 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.99, 46.65, 45.60, 34.88, 31.86, 29.56, 29.44, 29.21, 26.14, 24.98, 24.43, 22.67, 14.12. NMR spectra are in agreement with the literature.[5]



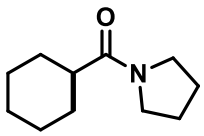
12n

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.46 (t, *J* = 6.9 Hz, 2H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.25 (t, *J* = 7.7 Hz, 2H), 1.98 – 1.83 (m, 4H), 1.67 – 1.60 (m, 2H), 1.25 (s, 25H), 0.88 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.89, 46.62, 45.57, 34.90, 31.94, 29.71, 29.68, 29.65, 29.57, 29.55, 29.49, 29.38, 26.16, 24.98, 24.44, 22.71, 14.14. **HRMS**: $[M + H]^+$ calculated for $C_{20}H_{40}NO^+$ 310.3104; Found 310.3102.



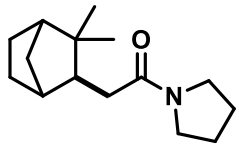
13n

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 – 3.44 m, 4H), 2.81 – 2.73 (m, 1H), 2.00 – 1.91 (m, 2H), 1.90 – 1.69 (m, 8H), 1.65 – 1.52 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.93, 46.46, 45.78, 43.10, 29.85, 26.17, 26.12, 24.36. NMR spectra are in agreement with the literature.[6]



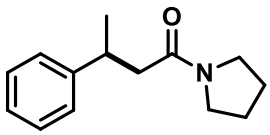
14n

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 – 3.43 (m, 4H), 2.37 – 2.29 (m, 1H), 1.98 – 1.89 (m, 2H), 1.88 – 1.62 (m, 7H), 1.58 – 1.44 (m, 2H), 1.33 – 1.19 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.78, 46.27, 45.64, 42.94, 28.90, 26.19, 25.90, 25.82, 24.30. NMR spectra are in agreement with the literature. [7]



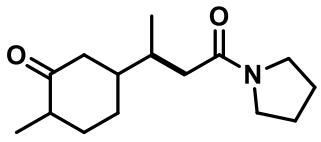
15n
Mixture of endo and exo products

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.49 – 3.39 (m, 6H), 2.35 – 2.16 (m, 4H), 2.15 – 1.97 (m, 2H), 1.95 – 1.92 (m, 3H), 1.88 – 1.81 (m, 3H), 1.81 – 1.65 (m, 7H), 1.59 – 1.49 (m, 2H), 1.37 – 1.21 (m, 5H), 1.17 – 1.15 (m, 1H), 1.10 – 1.07 (m, 1H), 1.04 (s, 1.5 H(~2H), *exo* -CH_3), 1.02 (s, 3H, *endo* -CH_3), 0.86 (s, 1.5 H(~2H), *exo* -CH_3), 0.80 (s, 3H, *endo* -CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.85, 54.55, 49.72, 49.48, 49.02, 46.68, 46.60, 46.16, 45.65, 45.63, 43.74, 42.11, 40.15, 37.06, 36.88, 36.38, 35.71, 32.22, 31.91, 29.57, 27.66, 26.18, 26.16, 25.07, 24.68, 24.42, 24.39, 24.13, 23.48, 21.62, 20.82. **HRMS**: $[M + H]^+$ calculated for $C_{15}H_{26}NO^+$ 236.2008; Found 236.2010. Note: The NMR of the derivatized products were compared with their parent carboxylic acids as reported by Kulkarni and co-workers[8] and Alper and co-workers[9] and ratio of *endo*:*exo* was determined.



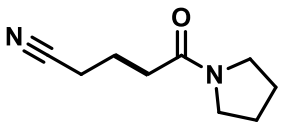
16n

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 – 7.24 (m, 4H), 7.21 – 7.17 (m, 1H), 3.48 – 3.29 (m, 4H), 3.15 – 3.09 (m, 1H), 2.56 – 2.44 (m, 2H), 1.86 – 1.74 (m, 4H), 1.35 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 170.32, 146.53, 128.38, 126.89, 126.21, 46.64, 45.54, 43.62, 36.38, 26.03, 24.34, 21.39. NMR spectra are in agreement with the literature.[10]



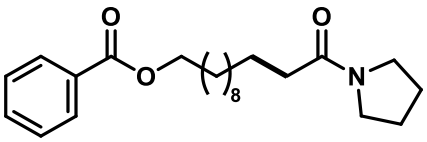
17n

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.48 – 3.39 (m, 4H), 2.40 – 2.21 (m, 3H), 2.15 – 2.05 (m, 4H), 1.99 – 1.92 (m, 2H), 1.89 – 1.84 (m, 3H), 1.77 – 1.66 (m, 2H), 1.62 – 1.44 (m, 1H), 1.39 – 1.25 (m, 1H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.97 – 0.93 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 213.46, 213.11, 170.72, 170.62, 54.19, 46.75, 46.72, 45.95, 45.71, 45.69, 45.11, 44.90, 44.75, 43.97, 39.30, 39.14, 34.90, 34.85, 34.41, 34.09, 29.83, 28.16, 26.14, 26.12, 24.38, 23.39, 16.75, 15.79, 14.35, 14.33. **HRMS**: $[M + H]^+$ calculated for $C_{15}H_{26}NO_2^+$ 252.1958; Found 252.1958. Note: The NMR of the derivatized products were compared with their parent carboxylic acids as reported by Beller and co-workers.[11]



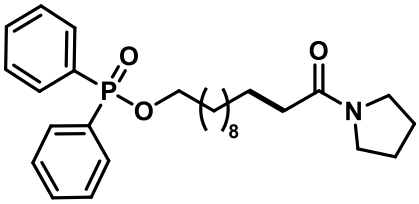
18n

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.48 – 3.41 (m, 4H), 2.53 (t, *J* = 6.9 Hz, 2H), 2.44 (t, *J* = 6.8 Hz, 2H), 2.05 – 1.91 (m, 4H), 1.89 – 1.84 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 169.40, 119.71, 46.52, 45.73, 32.25, 26.04, 24.35, 20.52, 16.68. **HRMS**: $[M + H]^+$ calculated for $C_9H_{15}N_2O^+$ 167.1178; Found 167.1179.



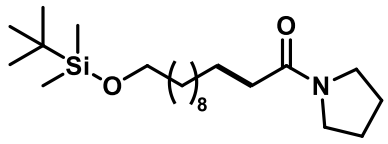
19n

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 – 8.04 (m, 2H), 7.58 – 7.53 (m, 1H), 7.46 – 7.42 (m, 2H), 4.31 (t, *J* = 6.7 Hz, 2H), 3.46 (t, *J* = 6.9 Hz, 2H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.27 – 2.23 (m, 2H), 1.98 -1.91 (m, 2H), 1.88 – 1.73 (m, 4H), 1.68 – 1.60 (m, 2H), 1.47 – 1.25 (m, 15H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.85, 166.71, 132.79, 130.52, 129.53, 128.32, 65.14, 46.61, 45.56, 34.87, 29.55, 29.53, 29.50, 29.48, 29.46, 29.28, 28.71, 26.14, 26.04, 24.96, 24.43. **HRMS**: $[M + H]^+$ calculated for $C_{23}H_{36}NO_3^+$ 374.2689; Found 374.2684, $[M + Na]^+$ calculated for $C_{23}H_{35}NO_3Na^+$ 396.2509; Found 396.2505.



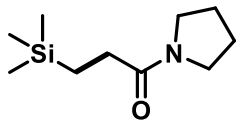
20
l:b 79:21

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 – 7.79 (m, 5H), 7.54 – 7.43 (m, 8H), 4.02 (q, *J* = 6.7 Hz, 3H), 3.46 (t, *J* = 6.9 Hz, 2H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.27 – 2.23 (m, 2H), 1.98 – 1.91 (m, 2H), 1.86 – 1.82 (m, 2H), 1.73 – 1.62 (d, *J* = 7.1 Hz, 6H), 1.30 – 1.25 (m, 18H), 1.10 (d, *J* = 6.7 Hz, 0.81 H, *branched product* -CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.95, 132.27, 132.15, 132.12, 132.09, 131.68, 131.58, 130.90, 128.58, 128.45, 65.10, 65.04, 46.64, 45.60, 34.86, 30.56, 30.49, 29.53, 29.50, 29.45, 29.13, 26.12, 25.59, 24.95, 24.42. **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 31.88. **HRMS**: $[M + H]^+$ calculated for $C_{28}H_{41}NO_3P^+$ 470.2819; Found 470.2818.



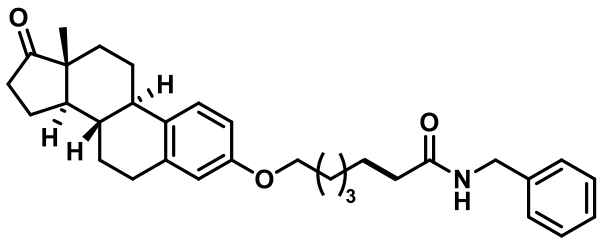
21n

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.59 (t, *J* = 6.6 Hz, 2H), 3.46 (t, *J* = 6.9 Hz, 2H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.27 – 2.23 (m, 2H), 1.98 – 1.91 (m, 2H), 1.88 – 1.79 (m, 2H), 1.68 – 1.60 (m, 2H), 1.55 – 1.47 (m, 2H), 1.30 – 1.25 (m, 16H), 0.89 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.87, 63.36, 46.61, 45.56, 34.89, 32.89, 29.63, 29.58, 29.56, 29.52, 29.48, 29.45, 26.15, 26.00, 25.80, 24.97, 24.43, 18.39, -5.25. **HRMS**: $[M + H]^+$ calculated for $C_{22}H_{46}NO_2Si^+$ 384.3292; Found 384.3291.



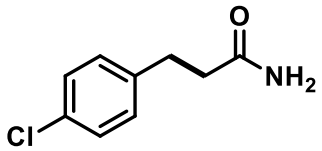
22n

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.46 (t, *J* = 6.9 Hz, 2H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.24 – 2.20 (m, 2H), 1.99 – 1.92 (m, 2H), 1.88 – 1.81 (m, 2H), 0.87 – 0.83 (m, 2H), 0.01 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 172.98, 46.48, 45.77, 29.20, 26.18, 24.42, 11.45, -1.84. **HRMS**: $[M + H]^+$ calculated for $C_{10}H_{22}NOSi^+$ 200.1465; Found 200.1466.



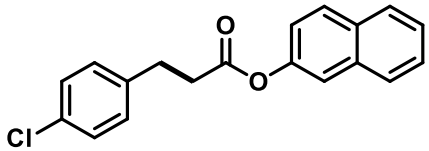
25n

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 – 7.28 (m, 4H), 7.20 – 7.17 (m, 1H), 6.71 – 6.69 (m, 1H), 6.64 – 6.63 (m, 1H), 5.72 (s, 1H), 4.44 (d, *J* = 5.7 Hz, 2H), 3.92 (t, *J* = 6.5 Hz, 2H), 2.91 – 2.87 (m, 2H), 2.54 – 2.47 (m, 1H), 2.40 – 2.37 (m, 1H), 2.24 – 1.93 (m, 7H), 1.78 – 1.51 (m, 9H), 1.49 – 1.35 (m, 5H), 1.28 – 1.17 (m, 1H), 0.90 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 221.10, 172.80, 157.06, 138.36, 137.71, 131.87, 128.73, 127.84, 127.53, 126.30, 114.51, 112.09, 67.67, 50.38, 48.03, 43.97, 43.60, 38.36, 36.66, 35.89, 31.56, 29.65, 29.14, 28.99, 26.56, 25.91, 25.80, 25.64, 21.58, 13.85. **HRMS**: $[M + H]^+$ calculated for $C_{32}H_{42}NO_3^+$ 488.3159; Found 488.3159.



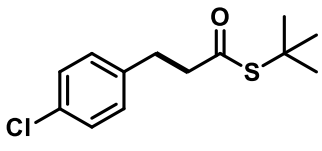
26
l:b 79:21

Followed procedure AII.6a. White solid, 32 mg, 83%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.33 – 7.31 (m, 0.50H, *branched amide phenyl H*) 7.27 – 7.24 (m, 2.7H, *2H belongs to linear amide phenyl + ~ 0.7H belongs to branched amide phenyl H*), 7.16 – 7.13 (m, 2H), 5.54 (d, *J* = 100.6 Hz, 2.5H; *2H belongs to linear amide* -NH + *0.5H belongs to branched amide* -NH), 3.58 (q, *J* = 7.2 Hz, 0.26 H, *belongs to branched amide* -CH *of tertiary* C), 2.94 (t, *J* = 7.6 Hz, 2H), 2.50 (t, *J* = 8.4 Hz, 2H), 1.50 (d, J = 7.2 Hz, 0.80 H, *belongs to branched amide* -CH_3 group present *on tertiary* C). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 174.17, 139.13, 132.05, 129.72, 128.65, 37.28, 30.61. δ (branched amide) : 176.13, 139.66, 133.22, 129.08, 128.93, 45.98, 18.48. NMR spectra are in agreement with the literature.[12]



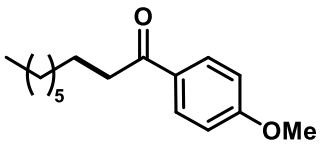
27n

Followed procedure AII.6b. White solid, 58 mg, 92%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.85 – 7.77 (m, 3H), 7.51 – 7.44 (m, 3H), 7.32 – 7.29 (m, 2H), 7.25 – 7.21 (m, 2H), 7.15 – 7.13 (m, 1H), 3.07 (t, *J* = 7.5 Hz, 2H), 2.92 (t, *J* = 7.5, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.32, 148.17, 138.56, 133.69, 132.27, 131.45, 129.84, 129.44, 128.73, 127.76, 127.63, 126.59, 125.75, 120.99, 118.45, 35.86, 30.27. **HRMS**: $[M + NH_4]^+$ calculated for $C_{19}H_{19}ClO_2N_1^+$ 328.1099; Found 328.1111.



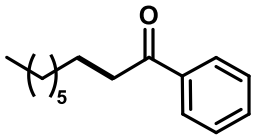
28
l:b 85:15

Followed procedure AII.6c. Colourless oil, 59 mg, 92%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.30 – 7.28 (m, 0.37 H, *branched thioester phenyl H)*, 7.26 – 7.23 (m, 2.34H, *2H belongs to linear thioester phenyl + ~ 0.34H belongs to branched thioester phenyl H*), 7.13 – 7.08 (m, 2H), 3.75 (q, *J* = 7.2 Hz, 0.18H, *belongs to branched thioester* -CH *of tertiary* C), 2.93 – 2.89 (m, 2H), 2.75 – 2.70 (m, 2H), 1.44 (s, 9H), 1.41 (s, 1.65H, *belongs to branched thioester* -CH_3 *group on tertiary* C). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (*mixture with branched thioester*): 201.25, 199.20, 138.69, 132.00, 129.75, 129.10, 128.75, 128.56, 53.84, 48.14, 45.70, 30.74, 29.77, 29.71. **GC-MS** (EI, 70 eV): m/z = 256, 200, 167, 138, 131, 125, 111, 103, 89, 77, 57.



29n

Followed procedure AII.6d. Off-white solid, 60 mg, 97%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.95 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H), 2.93 – 2.89 (m, 2H), 1.75 – 1.68 (m, 2H), 1.38 – 1.24 (m, 11H), 0.88 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 199.32, 163.29, 130.33, 130.19, 113.65, 55.45, 38.34, 31.85, 29.47, 29.46, 29.19, 24.65, 22.67, 14.12. NMR spectra are in agreement with the literature.[13]



30
l:b 92:8

Followed procedure AII.6e. Colourless oil, 46 mg, 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 – 7.93 (m, 2H), 7.59 – 7.52 (m, 1H), 7.48 – 7.44 (m, 2H), 3.45 (q, *J* = 6.8 Hz, 0.09H, *belongs to branched ketone* -CH *of tertiary* C), 2.98 – 2.94 (m, 2H), 1.77 – 1.70 (m, 2H), 1.43 – 1.18 (m, 13H), 1.19 (d, *J* = 6.9 Hz, 0.34H, *belongs to branched ketone* -CH_3 *group on tertiary* C), 0.90 – 0.86 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 200.66, 137.08, 132.87, 128.55, 128.06, 38.65, 31.85, 29.46, 29.39, 29.19, 24.39, 22.67, 14.12. δ (branched ketone) : 204.63, 132.79, 128.60, 128.24, 40.58, 33.74, 31.70, 29.71, 27.38, 22.59, 17.23, 14.07. NMR spectra are in agreement with the literature.[13]

AII.9. References

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Appendix III

Supporting Information for Chapter 4

Regioselectivity in Carbonylation of Pentenoic Acid to Synthesize Cyclic Anhydrides

AIII.1. General experiment details and materials

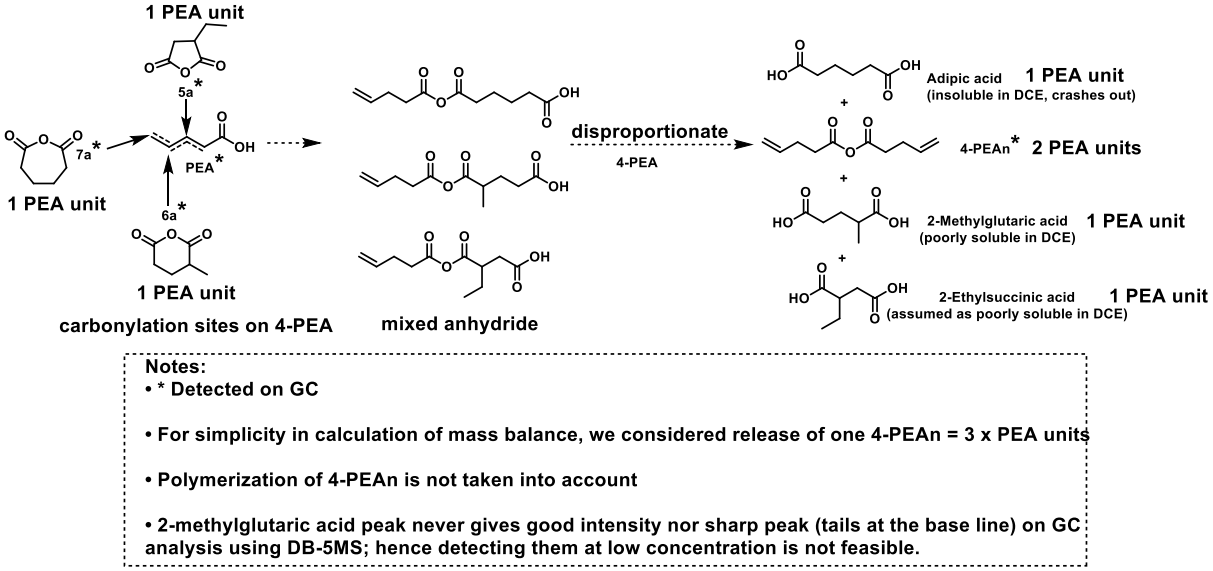
Reactions and chemicals related: All reactions and operations involving air- or moisture-sensitive compounds were performed using standard Schlenk techniques in heated and vacuum dried glassware or in N_2-filled glove box. 4-pentenoic acid and 4-pentenoic anhydride were purchased from Sigma-Aldrich and used without further purification. 2-Ethylsuccinic anhydride (**5a**) was purchased from Enamine Ltd. Anhydrous 1,2-dichloroethane (DCE) was purchased from Biosolve and dried over flame dried 4Å molecular sieves. Solvents were freeze-pump-thawed (FPT) before all catalytic reactions. All ligands were purchased from Sigma-Aldrich, Strem Chemicals and BLD pharm except 1,4-bis(*p*-chlorophenylphosphanyl)butane (**L16**),1,2-bis(diphenylphosphanylmethyl)benzene (**L5**) and o-bpax (**L6**). which were synthesized in-house. 1,2-bis((tert-butyl(pyridine-2-yl)phosphanyl)methyl)benzene (py^{t}bpx) (**L12**) was generously provided by Prof. Dr. Matthias Beller from LIKAT, Rostock, Germany.

a. Autoclaves: 75 mL stainless steel Parr autoclaves equipped with temperature probe and pressure adapter were used. For heating and stirring, Parr Multi Reactor System 5000 was used.

b. GC Analysis: Gas chromatography (GC) was measured on Shimadzu GC-2010, equipped with DB5MS (60 m) column, coupled to Flame Ionization Detector (FID). Gas chromatography-mass spectrometry (GC-MS) was measured on Agilent Technologies 7820A equipped with DB5MS (30 m) column and coupled to mass detector MSD 5975.

c. NMR Spectroscopy: ^{1}H NMR and ^{13}C NMR were recorded on Bruker Avance 400 (400MHz) NMR spectrometers. Multiplets were assigned as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), and m (multiplet). All measurements were carried out at room temperature. NMR yields were calculated using dibromomethane as internal standard.

AIII.2. General reaction scheme showing all possible products of catalysis



Scheme AIII.1. Reaction scheme depicting the possible products formed in a catalytic reaction, calculation of PEA units and compounds that can be detected and quantified by GC analysis.

AIII.2.1. Calculations

a. Mass Balance

The mass balance was calculated in terms of "number of **PEA units**" present in the reaction mixture after catalysis as follows:

$$\frac{(unreacted\ 4PEA\ and\ isomers) + (cyclic\ anhydrides) + (4PEAn\ and\ related\ disproportionation\ products)}{Initial\ 4PEA\ concentration} \times 100$$

Where,

PEA units of 4-PEA = mmol of unreacted 4-PEA

PEA units of PEA isomers = mmol of PEA isomers

PEA units of cyclic anhydrides (**7a** or **6a** or **5a**) = mmol of **7a** or **6a** or **5a**

PEA units of 4-PEAn (along with disproportionated products) = 3 × mmol of 4-PEAn

An error margin of ±10% is considered to be acceptable for the mass balance.

b. Total yield % of cyclic anhydrides

$$\frac{\boldsymbol{7a + 6a + 5a}}{initial\ mmol\ of\ 4PEA} \times 100$$

c. Regioselectivity:

7a:**6a**:**5a** was calculated as follows:

$$\frac{\boldsymbol{7a}\ or\ \boldsymbol{6a}\ or\ \boldsymbol{5a}}{\boldsymbol{7a + 6a + 5a}} \times 100$$

d. Conversion %

Conversion % with respect to PEA was calculated as follows

$$\left[1 - \frac{Unreacted\ 4PEA + isomers\ of\ PEA}{initial\ mmol\ of\ 4PEA}\right] \times 100$$

An error margin of ±5% is considered to be acceptable for the conversion.

AIII.3. General catalytic procedure (GP) and analysis

Palladium acetate (0.05 mmol; 11.2 mg), ligand (0.10 mmol) and additive (0.125 mmol) were weighed into a clean and dried glass liner, in air, containing an oven−dried stirring bar. The glass liner was fitted inside a 75 mL stainless steel Parr autoclave and the autoclave was closed. The autoclave was connected to a Schlenk line and subjected to five cycles of evacuation and refilling with nitrogen gas.

For air-sensitive phosphine ligands, palladium acetate and ligand were weighed in the glove-box and dissolved in a fixed volume of dried and degassed 1,2-dichloroethane (DCE) in a Schlenk flask. Any additive to be added was weighed separately in air into the glass liner directly. The glass liner was fitted inside a 75 mL stainless steel Parr autoclave and the autoclave was closed. The autoclave was connected to a Schlenk line and subjected to five cycles of evacuation and refilling with nitrogen gas. The catalyst solution prepared in the glove-box was added to the autoclave using standard Schlenk techniques.

Degassed solution of 4-pentenoic acid (4-PEA) (1.0 mmol; 102.2 µL) in dried DCE was added using standard Schlenk techniques The autoclave was transferred to Parr MRS5000 heating block and connected to the gas lines. The lines connecting the autoclave was flushed with nitrogen (N_2) (3 × 30 bars). The autoclave was flushed with carbon monoxide (CO) (1 × 30 bars) and subsequently charged with CO to 50 bar. The autoclave was stirred at 500 rpm and heated for 15 h at the desired temperature. At the end of the reaction time, the autoclave was brought to room temperature. The contents of the glass liner were transferred to a 10 mL volumetric flask, 0.3 mL undecane (internal standard for GC analysis) was added and the total volume was adjusted to 10 mL using DCE. The resulting solution was then analyzed using GC.

GC Analysis: Quantification of compounds: 4-PEA, **7a**, **6a**, **5a** and 4-PEAn present in the GC sample were determined using calibration lines with undecane as the internal standard. Calibration line of 4-PEA was applied for the quantification of PEA isomers. A 60 m × 0.250 mm ; 1.0 µm thickness DB-5MS GC column was used for analysis. 3.0 µL of each sample was injected and the following temperature program was used: injector at 300 °C, FID at 350 °C, oven at 50 °C for 3 min, increasing to 300 °C at 5 °C/min, then increasing to 325 °C at 15 °C/min and hold at 325 °C for 5 min.

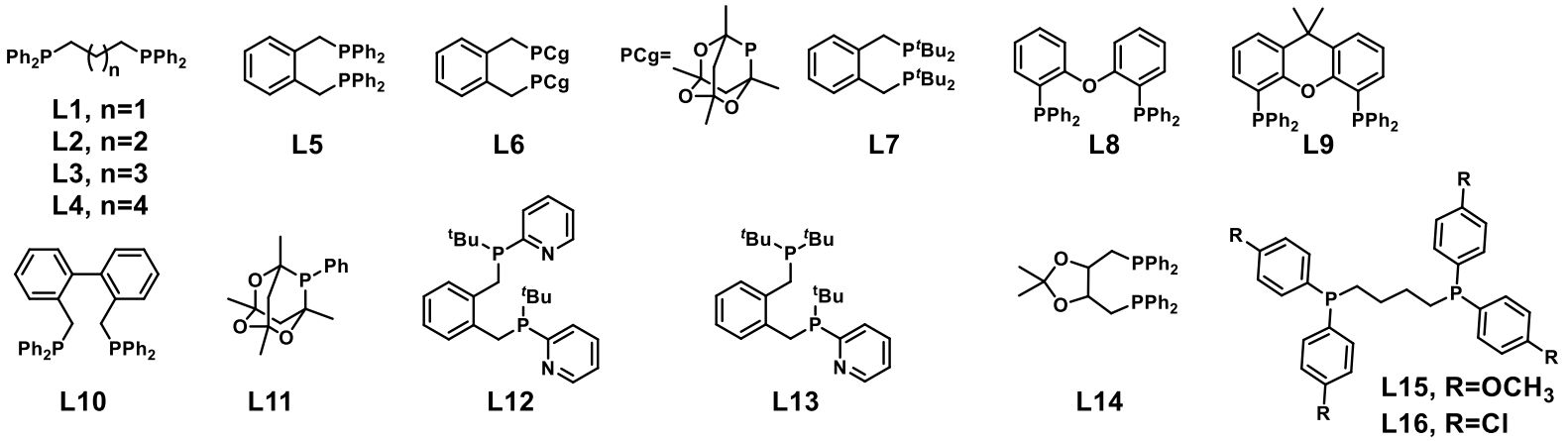
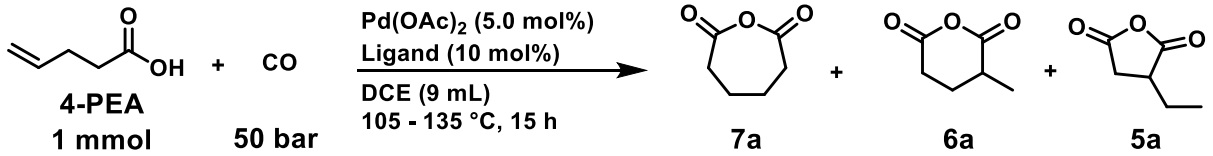


Figure AIII.1. Structures of phosphine ligands tested for cyclocarbonylation of 4-PEA.

AIII.4. Results of ligand screening

GP followed with one deviation: no additive was added

Table AIII.1. Cyclocarbonylation of 4-PEA: Study of influence of ligands on regioselectivity.



Entry	*L*	*T* (°C)	Unreacted 4-PEA mmol	PEA isomers mmol	4-PEAn mmol	7a mmol	6a mmol	5a mmol	Conversion %	Total Yield %	Selectivity 7a:6a:5a	Mass balance %
1	**L1**	105	0.29	0.03	0.07	0.12	0.09	0	68	21	57 : 43 : --	73
2[a]	**L2**	105	0.08	0	0.02	0.58	0.15	0	92	73	79: 21 : --	87
3	**L3**	105	0.24	0.05	0.03	0.38	0.11	0	71	49	78 : 22 : --	87
4	**L4**	105	0.80	0	0.05	0	0	0	20	0	--	96
5[b]	**L5**	120	0.27	0.03	0.04	0.35	0.07	0	70	42	88 : 12 : --	84

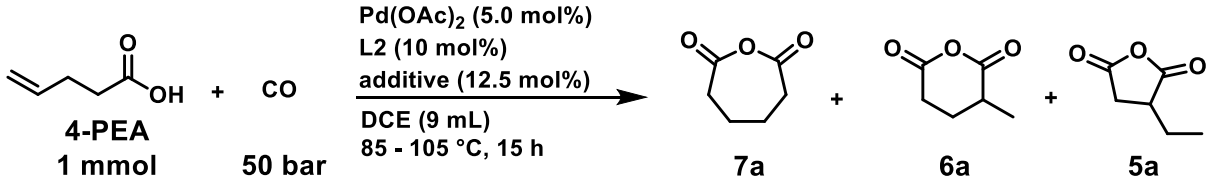
6[b]	**L6**	120	0.33	0.08	0.03	0.17	0	0	59	17	>99 : -- : --	68
7[b]	**L6**	135	0.13	0.43	0	0.06	0.02	0	44	8	75 : 25 : --	64
8[b]	**L7**	120	0.78	0.11	0	0	0	0	11	0	--	89
9	**L8**	120	0.24	0	0.04	0.31	0.09	0	76	40	78 : 22 : --	75
10	**L8**	135	0.12	0.03	0	0.39	0.10	0	85	49	79 : 21 : --	65
11	**L9**	120	0.29	0	0.04	0.10	0.18	0	71	28	36 : 64 : --	69
12[b]	**L10**	120	0.52	0	0.05	0.01	0.08	0	48	9	11 : 89 : --	76
13[c]	**L11**	105	0.24	0.48	0	0	0.28	Trace	28	28	-- : >99 : --	100
14[b]	**L12**	120	0.31	0.09	0.05	Trace	0.04	0	60	4	-- : >99 : --	59
15	**L14**	105	0.39	0	0.06	0.15	0.09	0	61	24	64 : 36 : --	81
16	**L15**	105	0.24	0.07	0.02	Trace	0.15	0.05	69	20	-- : 74 : 26	58
17	**L16**	105	0.33	0.04	0.05	0.22	0.06	0	63	28	79 : 21 : --	81

Reaction conditions: 4-PEA (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), *L* : diphosphine ligand (0.1 mmol) or monophosphine ligand (0.20 mmol), additive (0.125 mmol), CO (50 bar), *T* °C DCE (9 mL), 15 h. Quantification of compounds, conversion %, total yield % and regioselectivity were determined by GC using undecane as internal standard. [a] Adipic acid was found to be 8% (0.08 mmol) by NMR analysis; Mass Balance becomes 93%. [b] ligand 0.075 mmol used instead of 0.10 mmol. [c] ligand 0.20 mmol used instead of 0.10 mmol.

AIII.5. Influence of additives

Procedure same as GP

Table AIII.2. Cyclocarbonylation of 4-PEA: Study of additives on regioselectivity.



Entry	*L*	*T* (°C)	Additive	Unreacted 4-PEA mmol	PEA isomers mmol	4-PEAn mmol	7a mmol	6a mmol	5a mmol	Conv. %	Total Yield %	Selectivity 7a:6a:5a	Mass balance %
1[a]	**L2**	105	none	0.08	0	0.02	0.58	0.15	0	92	73	79: 21 : --	87

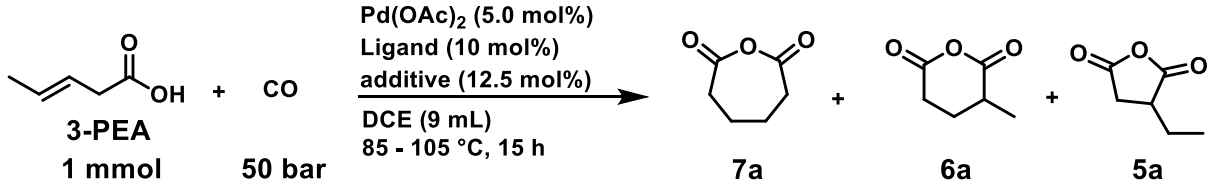
2[b]	**L2**	105	none	0	0	0	0.08	0.39	0.23	>99	70	12 : 55 : 33	70
3[c]	**L2**	105	none	0.83	0	0	0	0	0	17	0	-- : -- : --	83
4	**L2**	105	Formic acid	0.14	0.03	0.02	0.39	0.14	0.05	83	58	67 : 24 : 9	84
5	**L2**	105	2,4,6-trimethylbenzoic acid	0.28	0	0.06	0.20	0.07	0.05	72	32	61 : 23 : 16	80
6	**L2**	85	PPA	0.04	0	0	0.08	0.42	0.26	96	76	10 : 56 : 34	80
7	**L2**	85	HOTs.H_2O	0.05	0.07	0	0	0	0.69	88	69	-- : -- : >99	81
8	**L2**	85	HOMs	0	0	0	0	0	0.83	>99	83	-- : -- : >99	83
9	**L2**	85	10-CSA	0	0	0	0	0.22	0.63	>99	85	-- : 26 : 74	85
10	**L2**	85	$SnCl_2$	0	0	0	0	0.08	0.80	>99	92	-- : 10 : 90	88
11	**L2**	85	$Sn(OAc)_2$	0.13	0	0	0.49	0.09	0.15	87	73	67 : 13 : 20	86
12[c]	**L2**	85	$SnCl_2$	0	0.54	0	0	0	0.24	46	24	-- : -- : >99	78
13	**L2**	85	LiOAc	0.23	0.03	0.04	0.33	0.10	0.04	74	47	70 : 21 : 9	86
14	**L2**	85	LiCl	0.72	0	0.04	0	0.05	0	28	5	-- : >99 : --	88
15	**L2**	85	$Al(^iOPr)_3$	0.28	0	0.07	0.08	0.06	0.04	>72	18	46 : 32 : 22	67
16	**L2**	85	2,4,6-trimethylphenol	0.41	0.03	0.08	0.10	0.04	0.04	56	18	56 : 22 : 22	85
17	**L2**	85	2,6-diisopropylphenol	0.29	0	0.06	0.32	0.08	0	71	40	80 : 20 : --	88
18	**L2**	105	2,6-diisopropylphenol	0.12	0.03	0	0.48	0.12	0.04	85	64	76 : 18 : 6	79
19	**L2**	85	HFIP	0.24	0.03	0.04	0.24	0.07	0.07	73	37	63 : 18 : 18	77
20	**L2**	85	2-napthol	0.07	0.05	0	0.25	0.15	0.07	88	46	54 : 31 : 15	59
21[d]	**L5**	85	HOTs.H_2O	0	0	0	0	0	0.75	>99	75	-- : -- : >99	75
22[e]	**L6**	85	HOTs.H_2O	0	0	0	0	0.06	0.90	>99	96	-- : 6 : 94	96
23[f]	**L7**	120	HOMs	0	0.60	Trace	Trace	0.04	0	36	4	-- : >99 : --	64
24	**L8**	85	HOTs.H_2O	0	0	0	0	0	0.89	>99	89	-- : -- : >99	89
25[d]	**L9**	85	HOTs.H_2O	0	0	0	0.11	0.40	0.14	>99	65	17 : 62 : 21	65
26[d]	**L9**	85	$SnCl_2$	0	0	0	0	0.78	0.18	>99	96	-- : 81 : 19	96
27[f]	**L10**	85	HOTs.H_2O	0	0	0	0	0.47	0.21	>99	68	-- : 69 : 31	68
28[f]	**L10**	85	$SnCl_2$	0	0	0	0	0.74	0.17	>99	91	-- : 81 : 19	91
29[g]	**L12**	85	HOTs.H_2O	0.34	0.11	0	Trace	0.24	0	55	24	-- : >99 : --	69
30[h]	**L12**	120	HOTs.H_2O	0.12	0.50	0	Trace	0.06	0	38	6	-- : >99 : --	65
31[g]	**L13**	85	HOTs.H_2O	0.61	0.17	0	0	0	0	22	0	--	78

Reaction conditions: 4-PEA (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), *L* (0.1 mmol), additive (0.125 mmol), CO (50 bar), *T* °C, DCE (9 mL), 15 h. Quantification of compounds, conversion %, total yield % and regioselectivity were determined by GC using undecane as internal standard. [a] Adipic acid was found to be 8% (0.08 mmol) by NMR analysis; Mass Balance becomes 93%. [b] $Pd(TFA)_2$ instead of $Pd(OAc)_2$. [c] $PdCl_2$ instead of $Pd(OAc)_2$. [d] 4-PEA (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), *L* (0.05 mmol), additive (0.0625 mmol), CO (50 bar), *T* °C, DCE (9 mL), 15 h. [e] 4-PEA (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), *L* (0.0375 mmol), additive (0.0625 mmol), CO (50 bar), *T* °C, toluene (9 mL), 15 h. [f] 4-PEA (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), *L* (0.0375 mmol), additive (0.0625 mmol), CO (50 bar), *T* °C, DCE (9 mL), 15 h. [g] 4-PEA (1.0 mmol), $Pd(OAc)_2$ (0.01 mmol), *L* (0.015 mmol), additive (0.025 mmol), CO (50 bar), *T* °C, DCE (9 mL), 15 h. [h] 4-PEA (1.0 mmol), $Pd(OAc)_2$ (0.01 mmol), *L* (0.02 mmol), additive (0.04 mmol), CO (50 bar), *T* °C, toluene (9 mL), 15 h. Abbreviations: PPA: Phenylphosphonic acid, 10-CSA: Camphorsulfonic acid, $HOTs.H_2O$: *p*-Toluenesulfonic acid monohydrate, HOMs: Methanesulfonic acid, HFIP: 1,1,1,3,3,3-Hexafluoroisopropanol.

AIII.6. Study of certain reaction conditions on 3-PEA

GP followed with a deviation: 3-PEA used instead of 4-PEA

Table AIII.3. Cyclocarbonylation of 3-PEA: Testing of various conditions to observe regioselectivity of products.



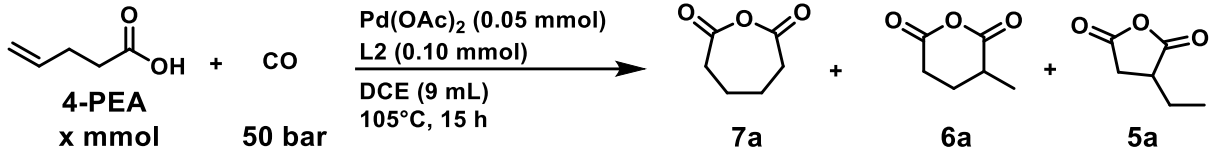
Entry	*L*	*T* (°C)	Additive	Unreacted 3-PEA mmol	PEA isomers mmol	4-PEAn	7a mmol	6a mmol	5a mmol	Conversion %	Total Yield %	Selectivity 7a:6a:5a	Mass balance%
1	**L2**	105	-	0.16	0	0	0	0.25	0.36	84	61	-- : 41 : 59	78
2[a]	**L2**	90	$HOTs.H_2O$	0.6	0	0	0	0	7.1	94	71	-- : -- : >99	77
3	**L9**	85	$HOTs.H_2O$	0	0	0	0	0.26	0.57	>99	83	-- : 31 : 69	83
4	**L9**	85	$SnCl_2$	0	0	0	0	0.34	0.56	>99	90	-- : 38 : 62	90

Reaction conditions: 3-PEA (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), *L* (0.1 mmol), additive (0.125 mmol), CO (50 bar), DCE (9 mL), *T* °C, 15 h. Quantification of compounds, conversion %, total yield % and regioselectivity were determined by GC using undecane as internal standard. [a] 3-PEA (10 mmol), $Pd(OAc)_2$ (0.08 mmol), diphosphine ligand (0.24 mmol), additive (0.80 mmol), CO (40 bar), Anisole (8 mL), 5 h.

AIII.7. Study of substrate:[Pd] ratio and dilution effect on formation of 7a, 4-PEAn and mass balance

GP followed with a deviation: mmol of 4-PEA used as mentioned in Table AIII.4

Table AIII.4. Cyclocarbonylation of 4-PEA: Study of [substrate]:[Pd] ratio and dilution factor to observe changes in **7a** selectivity and mass balance.



Entry	Scale (mmol)	Ligand	Additive	Temperature (°C)	Unreacted 4-PEA mmol	PEA isomers mmol	4-PEAn mmol	Adipic acid mmol[a]	7a mmol	6a mmol	5a mmol	Conversion %	Total Yield %	Selectivity 7a:6a:5a	Mass balance%
1	5	**L2**	-	105	0.75	0.10	0.45	0.95	0.45	0.30	Trace	83	16	63 : 37 : --	69
2	2.5	**L2**	-	105	0.45	0.10	0.13	0.40	0.78	0.25	Trace	78	45	76 : 24 : -	90
3[b]	2.5	**L2**	-	105	0.35	0.10	0.23	0.48	0.40	0.18	0.10	82	27	59 : 27 : 14	83
4	1	**L2**	-	105	0.08	0	0.02	0.08	0.58	0.15	0	92	73	79 : 21 : -	93
5[c]	10	**L10**	$SnCl_2$	85	0	0	0	0	0.4	7.4	1.5	>99	93	4 : 80 : 16	93
6	10	**L2**	$HOTs.H_2O$	90	0.6	0	0	0	0	0	5.8	94	58	-- : -- : >99	62

Reaction conditions: 4-PEA (x mmol), $Pd(OAc)_2$ (0.05 mmol), **L2** (0.10 mmol), additive (0.125 mmol), CO (50 bar), *T* °C, DCE (9 mL), 15 h. [a] determined by NMR using dibromomethane as internal standard. [b] $Pd(OAc)_2$ 0.025 mmol used instead of 0.05 mmol, **L2** 0.05 mmol used instead of 0.10 mmol. [c] **L10** 0.0625 mmol used instead of 0.10 mmol.

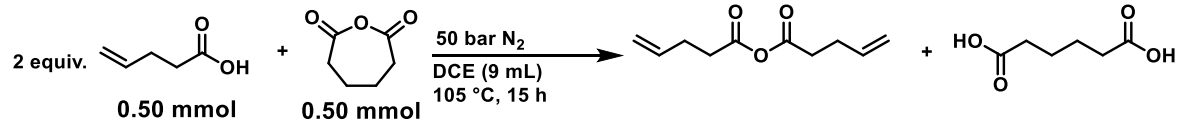
AIII.8. Control experiments for reaction insights

AIII.8.1. Reaction of 4-PEA and 7a in absence of catalyst

4-PEA (0.50 mmol; 51.2 µL) and **7a** (0.50 mmol; 64.1 mg) were weighed in a Schlenk flask, dissolved in dried DCE and transferred into an autoclave fitted with a glass liner containing an oven-dried magnetic stirring bar. The autoclave was transferred to Parr MRS5000 heating block and connected to the gas lines. The lines connecting the autoclave was flushed with N_2 (3× 30 bars). The autoclave was flushed with N_2 (1× 30 bars) and subsequently charged with N_2 to 50 bar. The autoclave was stirred at 500 rpm and heated for 15 h at 105 °C. At the end of the reaction time, the autoclave was brought to room temperature and slowly depressurized. The contents of the glass liner were transferred to a 10 mL volumetric flask. 0.3 mL undecane (internal standard for GC analysis) was added to the volumetric flask and the total volume was adjusted to 10 mL using DCE. The resulting solution was then analyzed using GC. Following observations were noted:

i. GC analysis indicated the formation of 4-PEAn majorly along with several small unknown peaks
ii. A white precipitate formed in the reaction mixture was analyzed by NMR and identified as adipic acid (9% ; 0.05 mmol).

Table AIII.5. Mass balance of reaction between 4-PEA and **7a** under N_2.



Unreacted 4-PEA (mmol)	PEA isomers (mmol)	4-PEAn (mmol)	Adipic acid (mmol)	7a (mmol)	6a (mmol)	5a (mmol)	Mass balance %
0.24	0	0.06	0.05	0.31	0	0	72

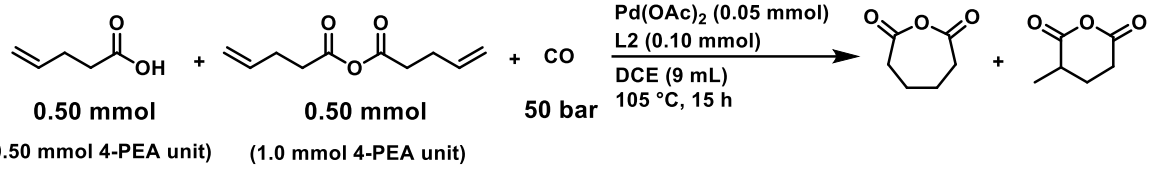
Reaction conditions: 4-PEA (0.50 mmol), **7a** (0.50 mmol), N_2 (50 bar), 105 °C, DCE (9 mL), 15 h.

AIII.8.2. Reaction of 4-PEA and 4-PEAn under catalytic conditions

Palladium acetate (0.05 mmol; 11.2 mg) and **L2** (0.10 mmol; 42.6 mg) weighed into a clean and dried glass liner, in open air, containing an oven−dried stirring bar. The glass liner was fitted inside a 75 mL stainless steel Parr autoclave and the autoclave was closed. The autoclave was connected to a Schlenk line and subjected to five cycles of evacuation and refilling with nitrogen gas. Degassed solution of 4-PEA (0.50 mmol; 51.2 µL) and 4-PEAn (0.50 mmol; 92.0 µL) in dried DCE was added using standard Schlenk techniques. The autoclave was transferred to Parr MRS5000 heating block and connected to the gas lines. The lines connecting the autoclave was flushed with N_2 (3 × 30 bars). The autoclave was flushed with CO (1 × 30 bars) and subsequently charged with CO to 50 bar. The autoclave was stirred at 500 rpm and heated for 15 h at 105 °C. At the end of the reaction time, the autoclave was brought to room temperature. The contents of the glass liner were transferred to a 10 mL volumetric flask, 0.3 mL undecane (internal standard for GC analysis) was added and the total volume was adjusted to 10 mL using DCE. The resulting solution was then analyzed using GC. Following observations were noted:

i. Reaction mixture was turbid indicating formation of adipic acid (17%; 0.09 mmol)
ii. Increase in 4-PEA concentration than expected by 0.17 mmol
iii. Decrease in 4-PEAn concentration by 0.32 mmol

Table AIII. 6. Mass balance of reaction between 4-PEA and 4-PEAn under catalytic conditions.



Unreacted 4-PEA (mmol)	PEA isomers (mmol)	4-PEAn (mmol)	Adipic acid (mmol)	7a (mmol)	6a (mmol)	5a (mmol)	Mass balance %
0.36	0	0.18	0.09	0.19	0.12	0	75

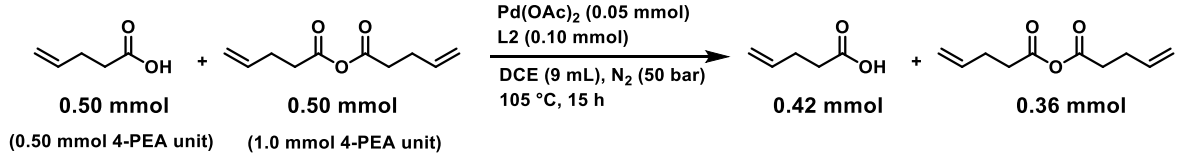
Reaction conditions: 4-PEA (0.50 mmol), 4-PEAn (0.50 mmol), $Pd(OAc)_2$ (0.05 mmol), **L2** (0.10 mmol), CO (50 bar), 105 °C, DCE (9 mL), 15 h.

AIII.8.3. Reaction of 4-PEA and 4-PEAn under catalytic conditions in absence of CO

Palladium acetate (0.05 mmol; 11.2 mg) and **L2** (0.10 mmol; 42.6 mg) weighed into a clean and dried glass liner, in open air, containing an oven−dried stirring bar. The glass liner was fitted inside a 75 mL stainless steel Parr autoclave and the autoclave was closed. The autoclave was connected to a Schlenk line and subjected to five cycles of evacuation and refilling with nitrogen gas. Degassed solution of 4-PEA (0.50 mmol; 51.2 µL) and 4-PEAn (0.50 mmol; 92.0 µL) in dried DCE was added using standard Schlenk techniques. The autoclave was transferred to Parr MRS5000 heating block and connected to the gas lines. The lines connecting the autoclave was flushed with N_2 (3 × 30 bars). The autoclave was flushed with N_2 (1 × 30 bars) and subsequently charged with N_2 to 50 bar. The autoclave was stirred at 500 rpm and heated for 15 h at 105 °C. At the end of the reaction time, the autoclave was brought to room temperature. The contents of the glass liner were transferred to a 10 mL volumetric flask, 0.3 mL undecane (internal standard for GC analysis) was added and the total volume was adjusted to 10 mL using DCE. The resulting solution was then analyzed using GC. Following observations were noted:

i. Clear reaction mixture: no formation of adipic acid
ii. Loss of 4-PEAn is lesser than in presence of CO

Table AIII.7. Mass balance of reaction between 4-PEA and 4-PEAn under catalytic conditions but in absence of CO.



Unreacted 4-PEA (mmol)	PEA isomers (mmol)	4-PEAn (mmol)	7a (mmol)	6a (mmol)	5a (mmol)	Mass balance %
0.42	0	0.36	0	0	0	76

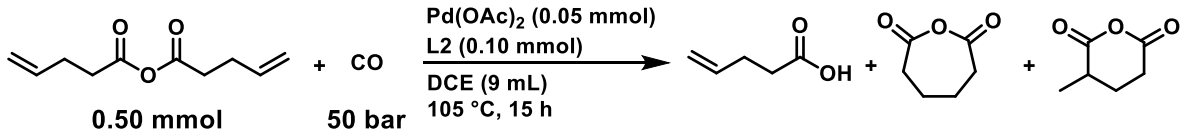
Reaction conditions: 4-PEA (0.50 mmol), 4-PEAn (0.50 mmol), $Pd(OAc)_2$ (0.05 mmol), **L2** (0.10 mmol), N_2 (50 bar), 105 °C, DCE (9 mL), 15 h.

AIII.8.4. Reaction of 4-PEAn under catalytic conditions

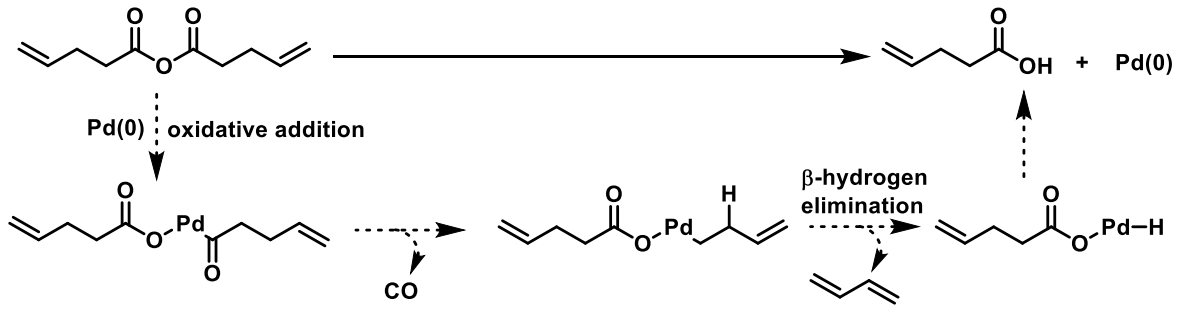
Palladium acetate (0.05 mmol; 11.2 mg) and **L2** (0.10 mmol; 42.6 mg) weighed into a clean and dried glass liner, in open air, containing an oven−dried stirring bar. The glass liner was fitted inside a 75 mL stainless steel Parr autoclave and the autoclave was closed. The autoclave was connected to a Schlenk line and subjected to five cycles of evacuation and refilling with nitrogen gas. Degassed solution of 4-PEAn (0.50 mmol; 92.0 µL) in dried DCE was added using standard Schlenk techniques. The autoclave was transferred to Parr MRS5000 heating block and connected to the gas lines. The lines connecting the autoclave was flushed with N_2 (3 × 30 bars). The autoclave was flushed with N_2 (1 × 30 bars) and subsequently charged with CO to 50 bar. The autoclave was stirred at 500 rpm and heated for 15 h at 105 °C. At the end of the reaction time, the autoclave was brought to room temperature. The contents of the glass liner were transferred to a 10 mL volumetric flask, 0.3 mL undecane (internal standard for GC analysis) was added and the total volume was adjusted to 10 mL using DCE. The resulting solution was then analyzed using GC. Following observations were noted:

i. 4-PEA formation observed along with traces of **7a** and **6a**

Table AIII. 8. Mass balance of reaction of 4-PEAn under catalytic conditions.

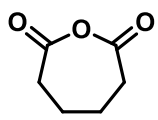


4-PEA formed (mmol)	PEA isomers (mmol)	4-PEAn (mmol)	7a (mmol)	6a (mmol)	5a (mmol)	Mass balance %
0.06	0	0.31	Trace	Trace	0	74



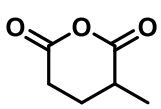
Scheme AIII.2. Possible mechanism of 4-PEA formation from 4-PEAn.

AIII.9. Synthesis of GC standards



Adipic anhydride (**7a**)

Adipic acid (2.0 g) was weighed in a 2-necked round bottom flask fitted with a reflux condenser at one end. 8.0 mL acetic anhydride was charged into the flask and the reaction mixture was refluxed overnight (~18 h). The reaction mixture was cooled to room temperature. Acetic anhydride was distilled out under vacuum to leave an oily residue. The oily residue was subjected to repeated vacuum distillations with toluene (10 mL × 3) followed by trituration with diethyl ether (10 mL) till solid appears. The suspension was filtered and the off-white precipitate collected was dried under high vacuum. The yield of the solid obtained was 1.02 g, 58% (97% purity), off-white to beige colour in appearance. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.56 – 2.48 (m, 4H), 1.82 – 1.70 (m, 4H). Peak observed at δ: 2.23 (0.22H) belongs to acetic anhydride.**^{13}C NMR** (101 MHz, $CDCl_3$) δ: 168.87, 34.73, 23.27. The NMR spectra are in agreement with the literature.[1]



2-Methylglutaric anhydride (**6a**)

2-Methylglutaric acid (2.0 g) was weighed in a 2-necked round bottom flask fitted with a reflux condenser at one end. 8.0 mL acetic anhydride was charged into the flask and the reaction mixture was refluxed overnight (~18 h). The reaction mixture was cooled to room temperature. Acetic anhydride was distilled out under vacuum to leave an oily residue. The oily residue was subjected to repeated vacuum distillations with toluene (10 mL × 3). The oil was completely solubilized in diethyl ether and cooled to -20 °C to obtain a white precipitate. The suspension was quickly filtered cold and the solid collected was immediately dried under high vacuum. The yield of the solid obtained was 594 mg, 34% and white colour in appearance. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.93 (ddd, J = 18.1, 5.1, 3.5 Hz, 1H), 2.79 – 2.61 (m, 2H), 2.07 (dddd, J = 13.8, 6.0, 5.3, 3.5 Hz, 1H), 1.79 (ddd, J = 13.8, 12.1, 5.1 Hz, 1H), 1.39 (d, J = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 169.67, 166.80, 35.80, 30.19, 24.38, 15.73. The NMR spectra are in agreement with the literature.[2]

AIII.10. Typical GC chromatograms, NMR of precipitate in attempted catalysis to synthesize 7a

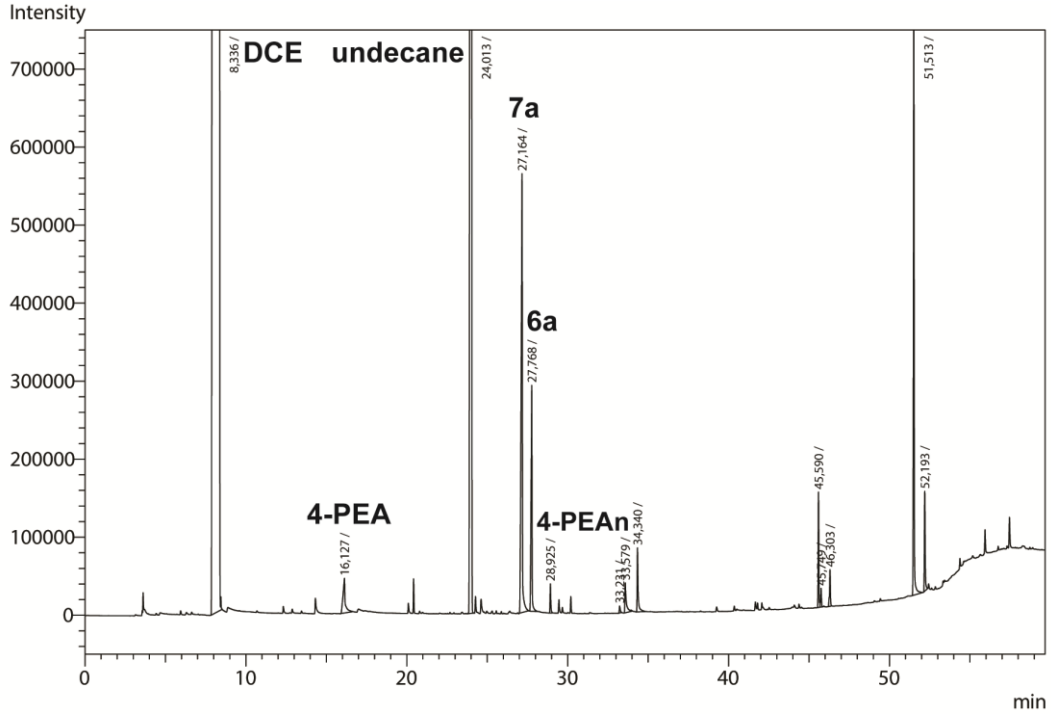


Figure AIII.2. Typical GC-FID chromatogram of catalytic reaction mixture with selectivity towards **7a** (Table AIII.1, entry 2). Peaks >30 mins could not be identified.

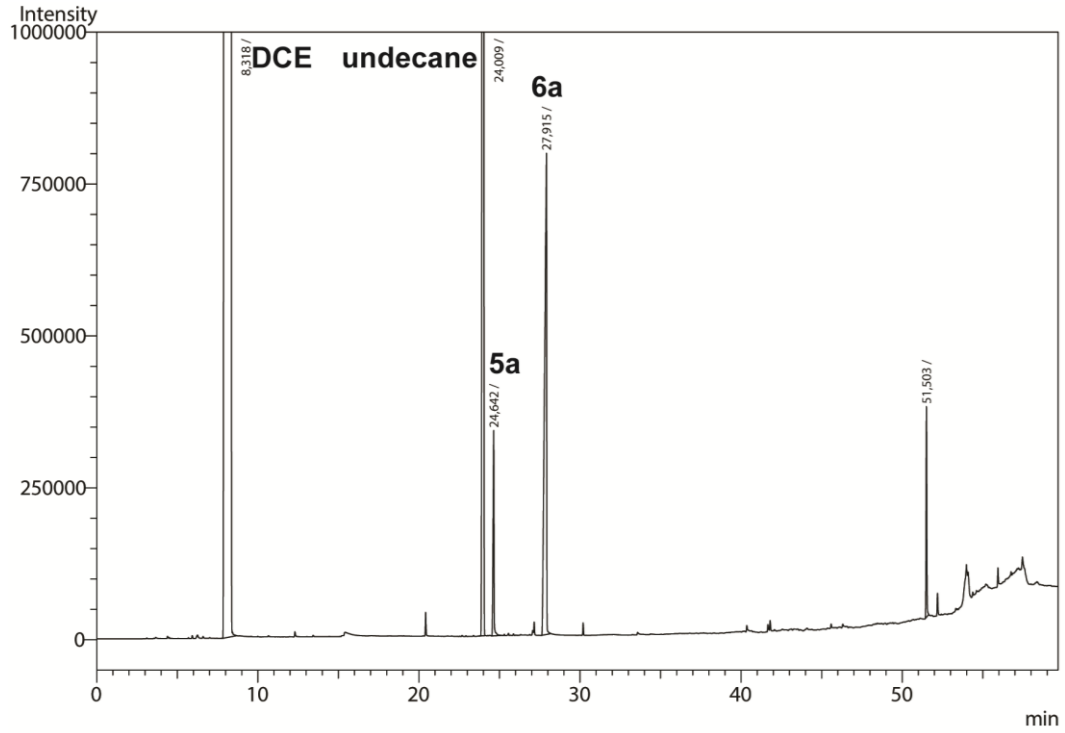


Figure AIII.3. Typical GC-FID chromatogram of catalytic reaction mixture with selectivity towards **6a** (Table AIII.2, entry 26). Peaks >30 mins could not be identified.

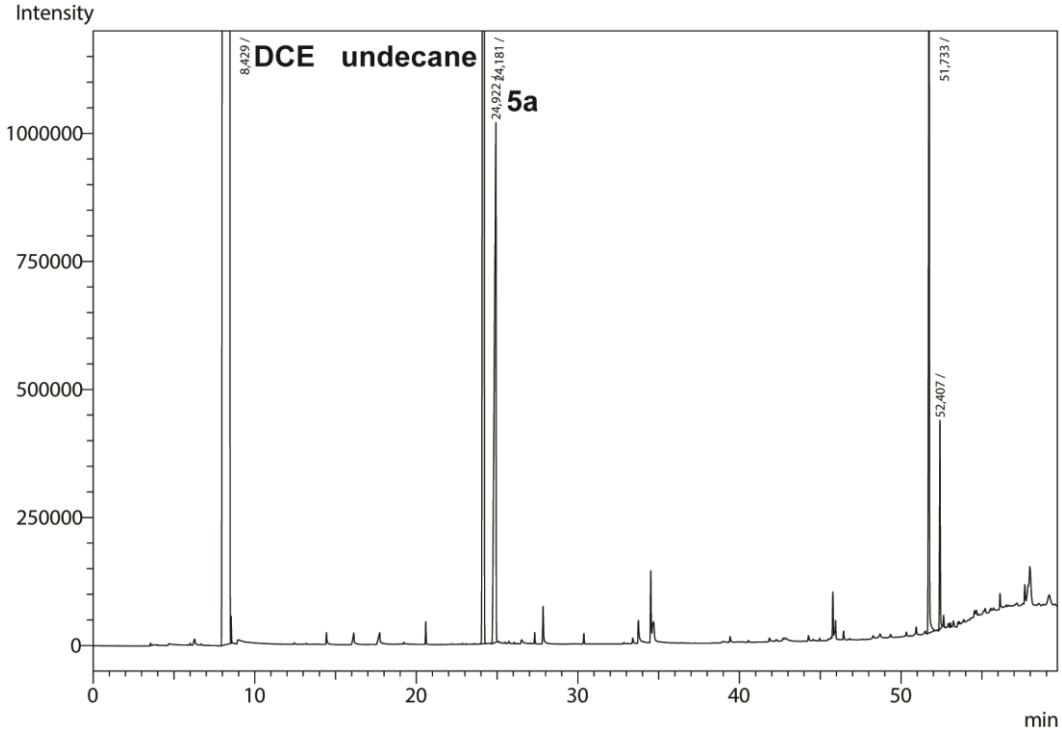


Figure AIII. 4. Typical GC-FID chromatogram of catalytic reaction mixture with selectivity towards **5a** (Table AIII.2, entry 8). Peaks >30 mins could not be identified.

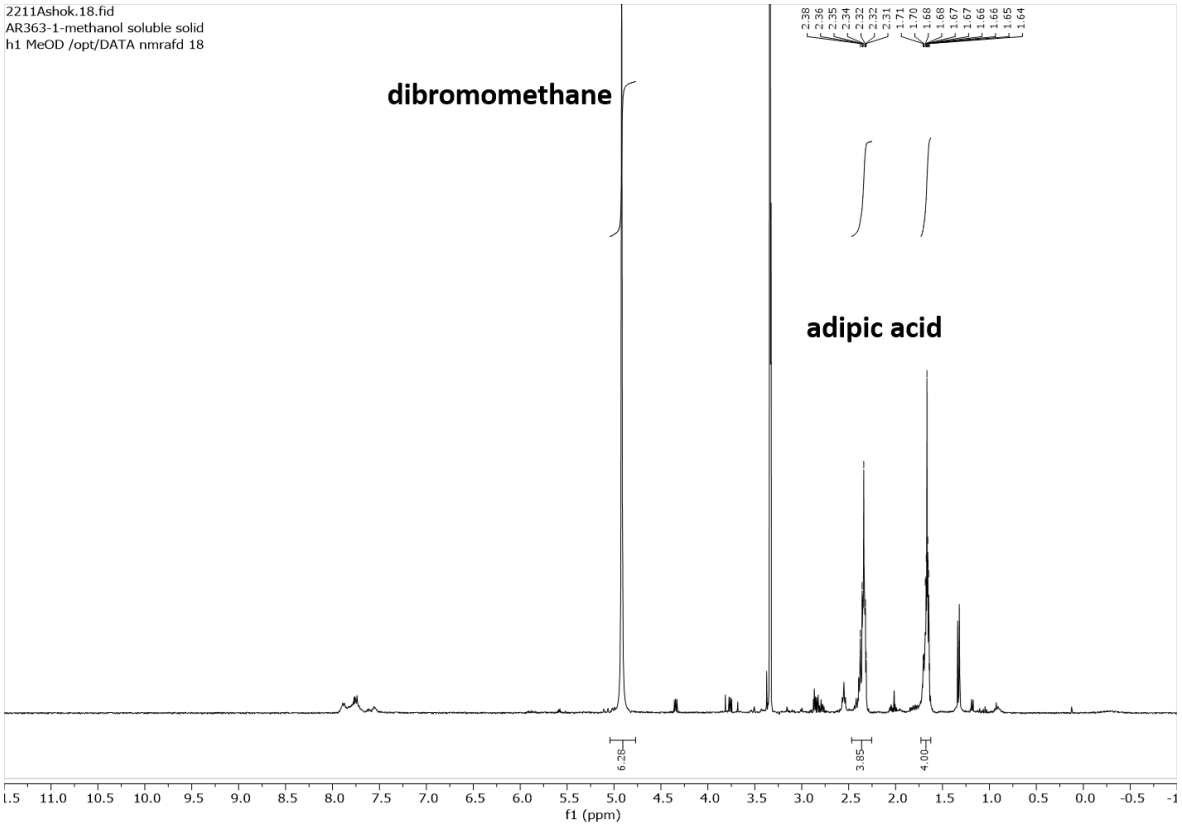


Figure AIII.5. ^{1}H NMR of precipitate formed in the catalytic reaction of Table AIII.1, entry 2.

AIII.11. ESI-MS spectra of methanolic solution of $SnCl_2$ and 4-PEA (0.125 : 1.0 mmol $SnCl_2$:4-PEA)

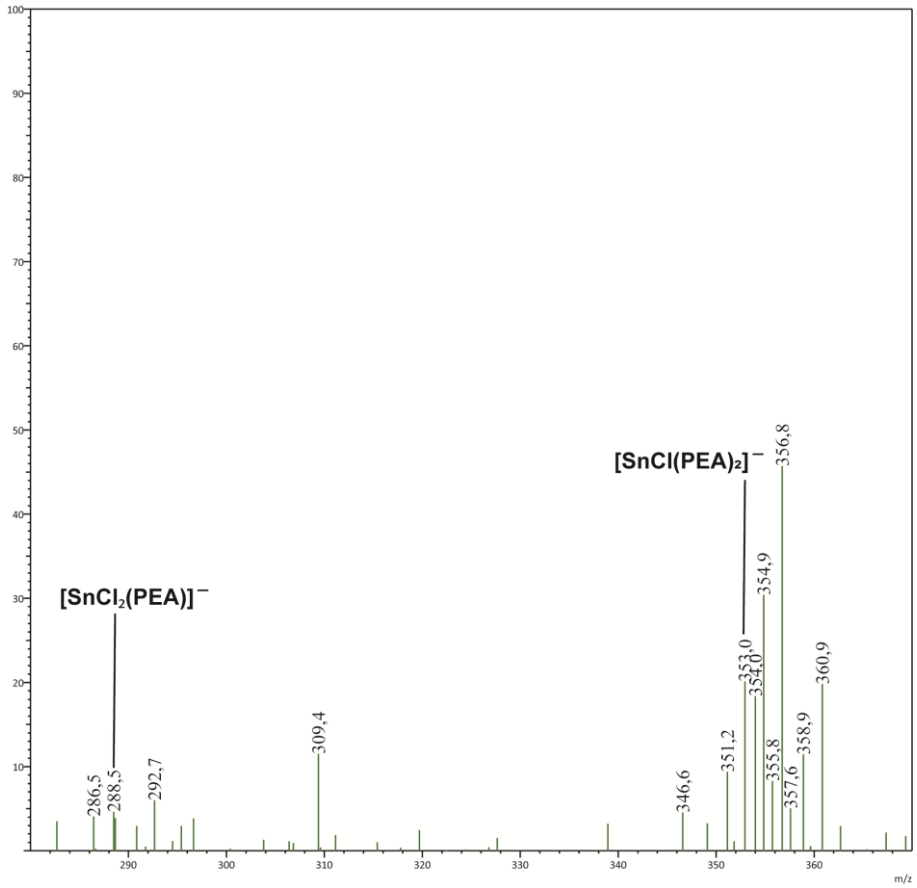


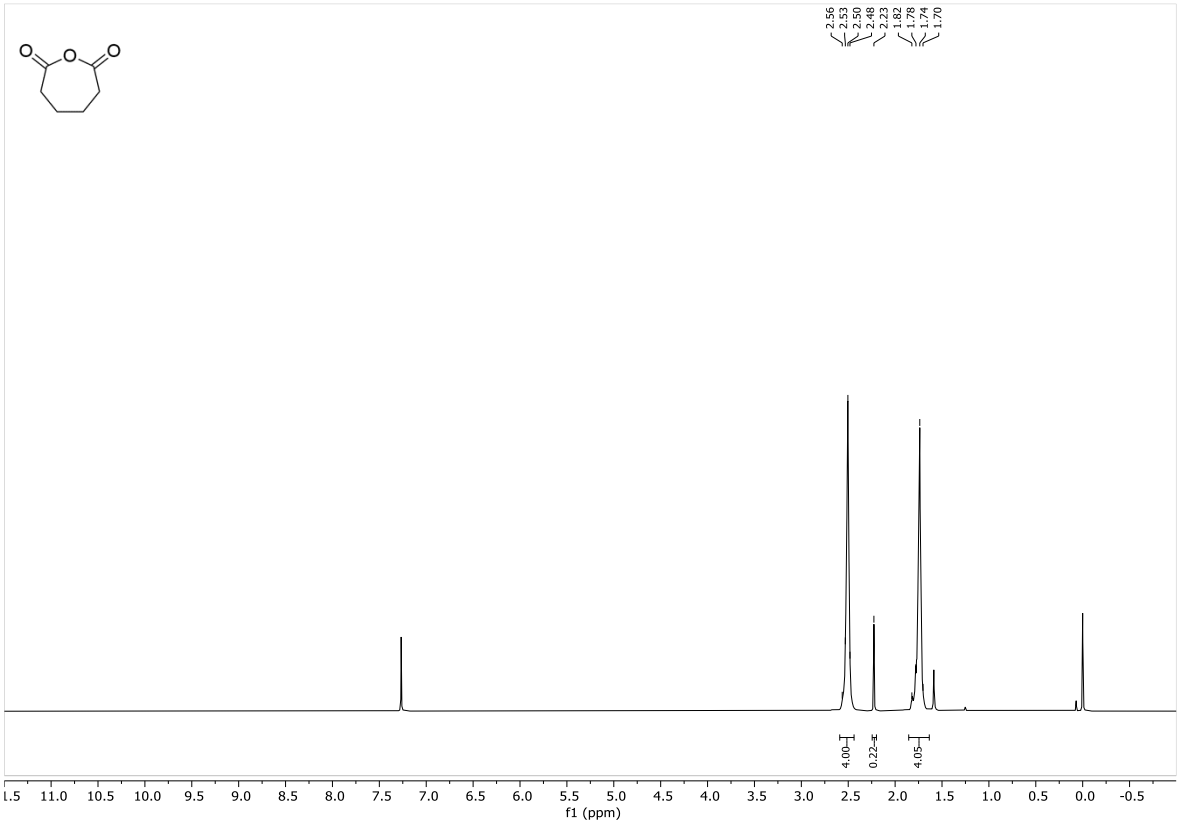
Figure AIII.6. ESI-MS (negative mode) of methanolic solution of $SnCl_2$ and 4-PEA; m/z calculated for $[SnCl_2(PEA)]^-$ is 288.9, found: 288.5; ; m/z calculated for $[SnCl(PEA)_2]^-$ is 352.96, found: 353.0.

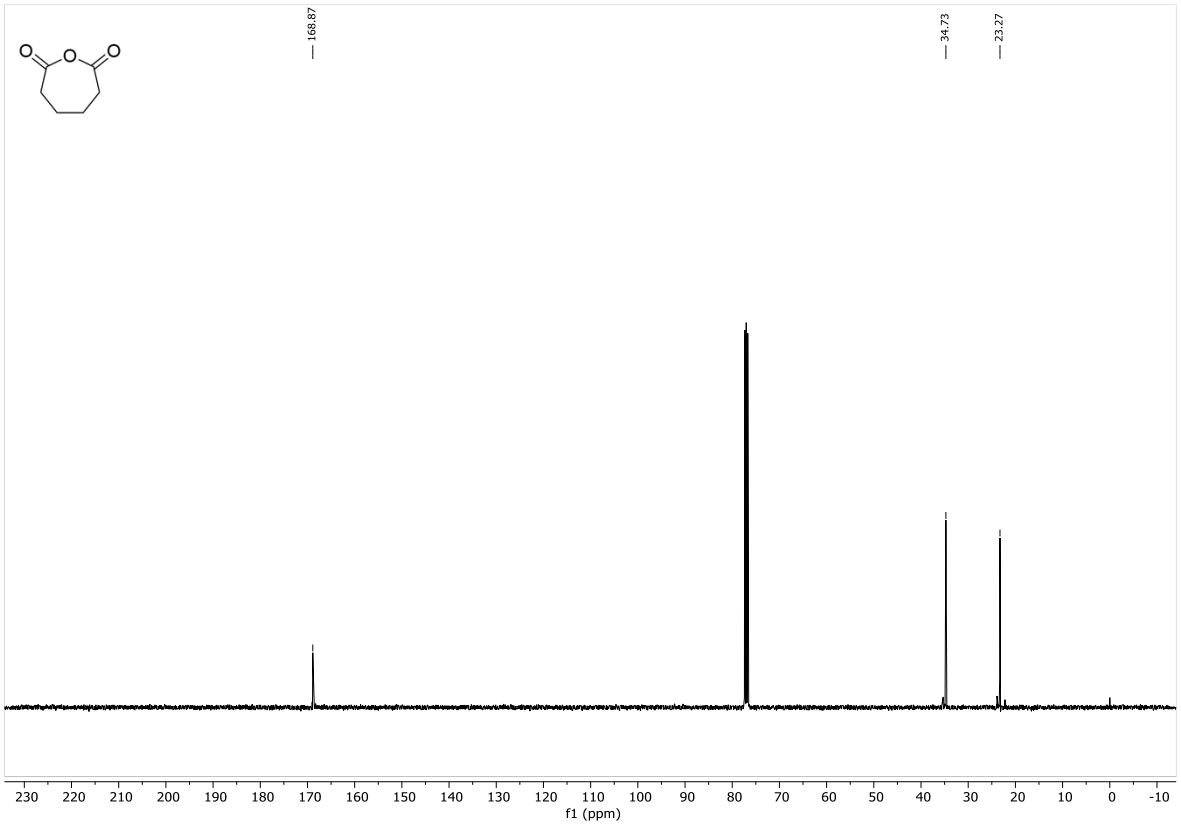
AIII.12. References

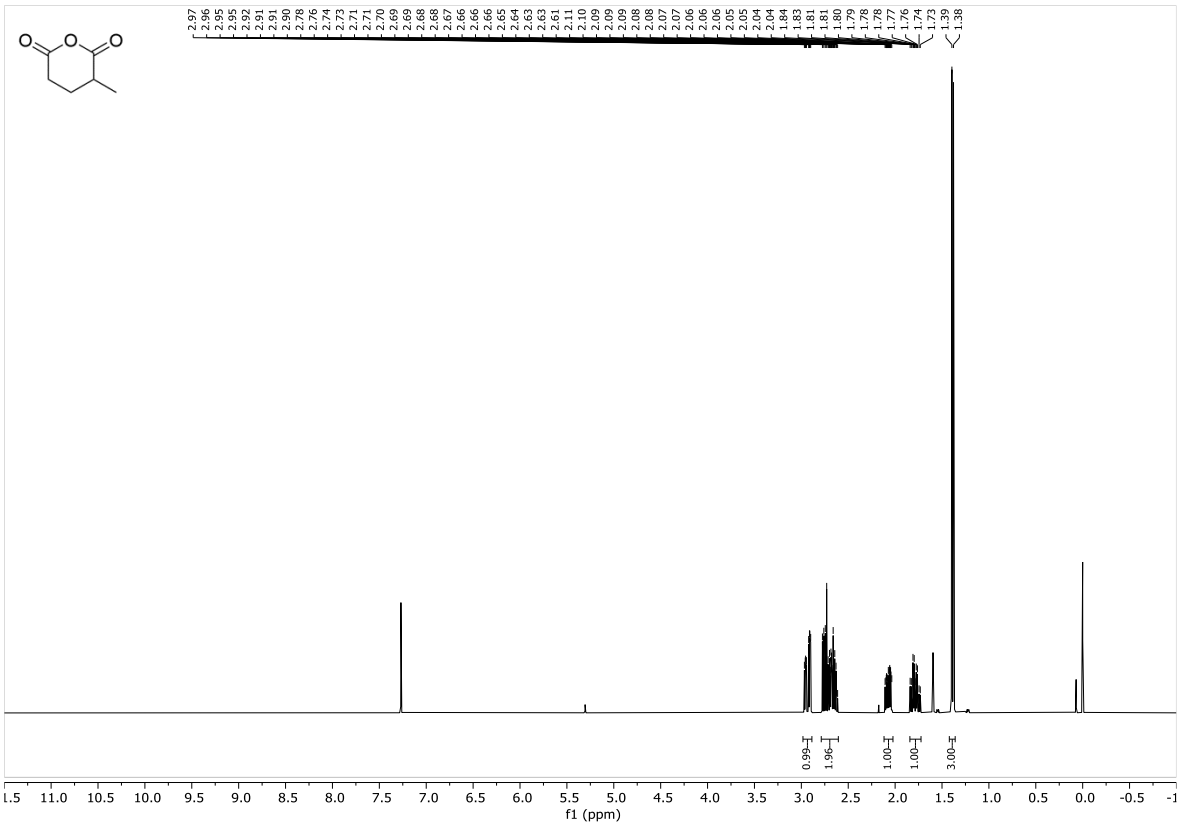
(1) Tarasenko, M.; Duderin, N.; Sharonova, T.; Baykov, S.; Shetnev, A.; Smirnov, A. V. Room-Temperature Synthesis of Pharmaceutically Important Carboxylic Acids Bearing the 1,2,4-Oxadiazole Moiety. *Tetrahedron Lett.* **2017**, *58* (37), 3672–3677.

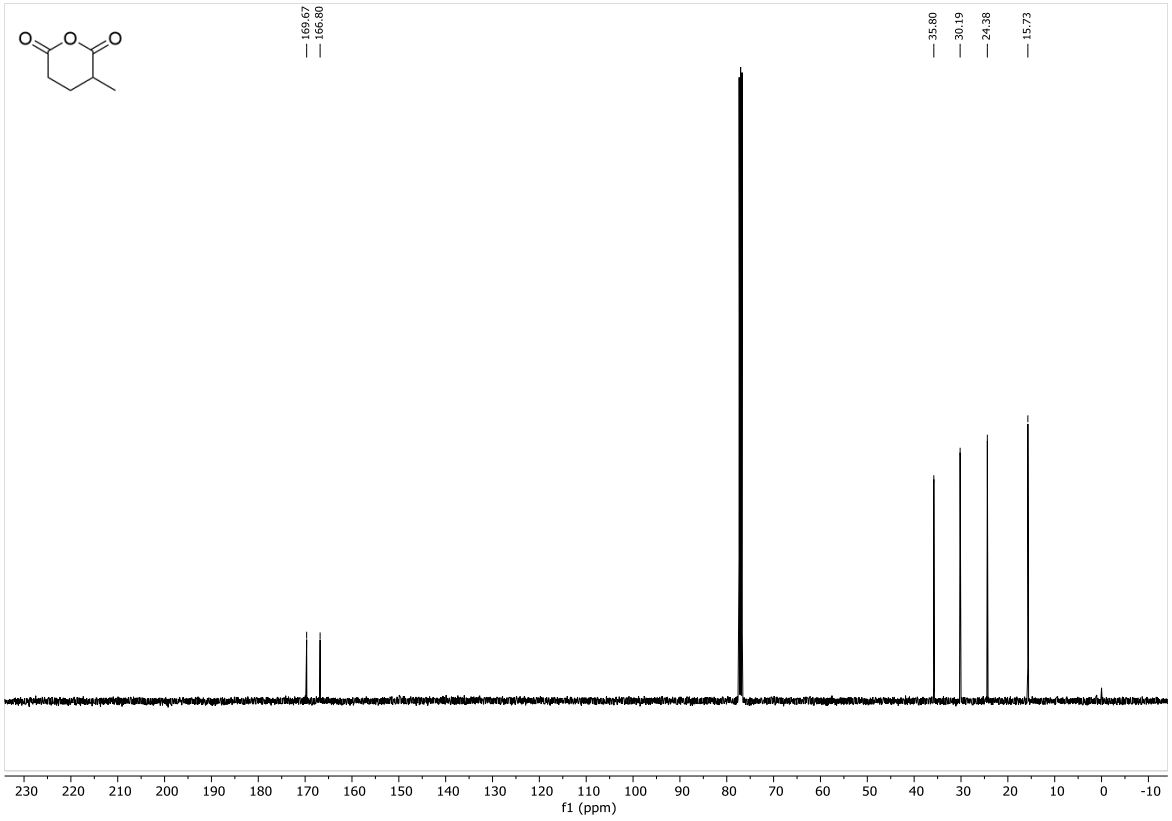
(2) Bennett, D. J.; Blake, A. J.; Cooke, P. A.; Godfrey, C. R. A.; Pickering, P. L.; Simpkins, N. S.; Walker, M. D.; Wilson, C. Stereoselectivity in Reactions of Atropisomeric Lactams and Imides. *Tetrahedron* **2004**, *60* (20), 4491–4511.

AIII.13. NMR spectra of standard compounds






2.97 2.96 2.95 2.95 2.92 2.91 2.91 2.90 2.78 2.76 2.74 2.73 2.71 2.71 2.70 2.69 2.69 2.68 2.68 2.67 2.66 2.66 2.66 2.65 2.64 2.63 2.63 2.61 2.11 2.10 2.09 2.09 2.09 2.08 2.08 2.07 2.07 2.06 2.06 2.06 2.05 2.05 2.04 2.04 2.04 1.84 1.83 1.81 1.81 1.80 1.79 1.78 1.78 1.77 1.76 1.74 1.73 1.39 1.38
0.99 1.96 1.00 1.00 3.00
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


169.67
166.80
35.80
30.19
24.38
15.73
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Samenvatting

In dit proefschrift wordt onderzoek naar de mogelijkheid en efficiëntie van een nieuw soort carbonyleringsreactie beschreven, waarbij carbonzuren als nucleofiel worden gebruikt met als uiteindelijke doel om adipinezuuranhydride te synthetiseren vanuit penteenzuren. In **Hoofdstuk 1** wordt een overzicht geschetst van palladium-gekatalyseerde hydrocarbonyleringsreacties van alkenen met verschillende nucleofielen zoals alcoholen, water, amines en thiolen, die resulteren in respectievelijk esters, carbonzuren, amides en thioesters als bruikbare, carbonyl-bevattende moleculen.

In dit hoofdstuk worden de opmerkelijke eigenschappen benadrukt van het veel gebruikte fosfineligand 1,2-bis(di-tert-butylfosfanylmethyl)benzeen (d^{t}bpx), dat voornamelijk veel toepassing vindt in hydroalkoxycarbonylering met alcoholen en water als nucleofielen om lineaire esters of carbonzuren te verkrijgen. d^{t}bpx wordt ook gebruikt in commerciële industriële processen zoals het Lucite Alpha proces voor de productie van methylmethacrylaat. De structurele eigenschappen van d^{t}bpx, met name de rigide structuur tussen de fosforatomen en de sterisch grote groepen die aan de fosforatomen vastzitten, stelt men in staat om zelfs uit interne alkenen lineaire producten te verkrijgen. De veelzijdigheid van d^{t}bpx heeft ertoe geleid dat er verschillende modificaties ontwikkeld zijn die toepassing vinden in bijvoorbeeld de selectieve synthese van adipinezuur uit 1,3-butadieen.

Voor de vorming van amides of thioesters zijn amines, ammonia of thiolen nodig als nucleofiel. Het gebruik van dit soort nucleofielen is echter niet triviaal. Er kunnen problemen ontstaan door de basiciteit van amines (wat de vorming van de benodigde palladium-hydrideintermediair verhindert) of door de sterke binding van thiolen aan metaalionen (katalysatorvergiftiging).

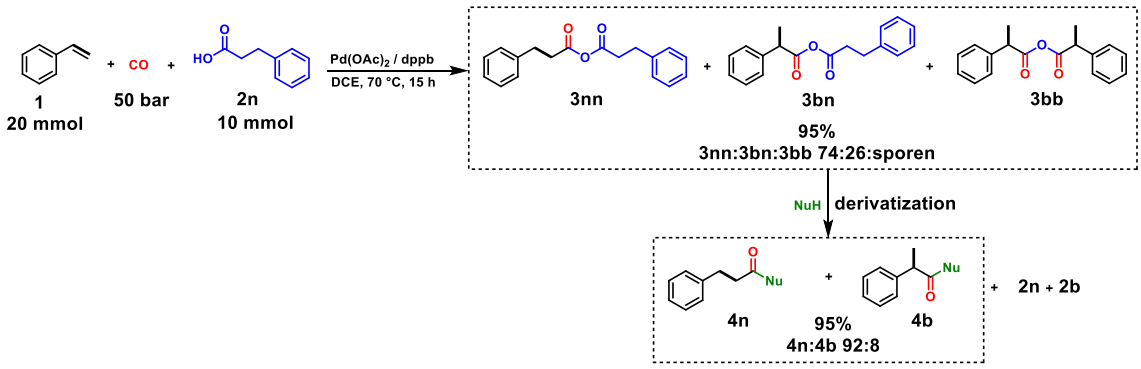
Hydrocarbonyleringsreacties van alkenen met mierenzuur of oxaalzuur zijn ook gerapporteerd. Het zuur fungeert in dit geval als nucleofiel voor het acyl-palladiumintermediair, wat resulteert in zeer labiele formaat- of oxalaat-gebaseerde zuuranhydrides. Deze ontleden naar het carbonzuur met gelijktijdige vorming van CO voor mierenzuur en CO plus CO_2 voor oxaalzuur.

Carbonzuren (of carboxylaten) worden beschouwd als zwakke nucleofielen vergeleken met alkoxides en water. Door deze verminderde nucleofiliciteit is hun reactie met het acyl-palladiumintermediair een uitdaging. Er is slechts een handvol publicaties die het gebruik van carbonzuren voor de synthese van zuuranhydrides rapporteren en het aantal verschillende substraten dat gebruikt is voor deze reactie is beperkt. Over het algemeen is de opbrengst van

de zuuranhydrides laag, met als uitzondering de vorming van propionzuuranhydride uit etheen en propionzuur. Dus, met als doel de hiervoor genoemde uitdagingen op te lossen en een synthetische methode te bewerkstelligen, wordt in dit proefschrift een studie gepresenteerd naar de carbonyleringsreactie met carbonzuren als nucleofiel (hydroacyloxycarbonylering) om zuuranhydrides te verkrijgen.

Een gemakkelijke en efficiënte katalytische methode om carbonzuuranhydrides te synthetiseren is gerapporteerd in **Hoofdstuk 2**. Er is aangetoond dat de vorming van zuuranhydrides bij temperaturen lager dan 85 °C mogelijk is met een katalytisch systeem van $Pd(OAc)_2$/dppb (dppb = 1,4-bis(difenylfosfanyl)butaan), waarbij styreen (**1**) en 3-fenylpropionzuur (**2n**) als modelsubstraat gebruikt zijn. De optimale temperatuur voor deze reactie is 70 °C met 1,2-dichloorethaan (DCE) als oplosmiddel en een druk van 50 bar CO; dit gaf de gewenste zuuranhydrides (**3**) in een opbrengst van ~65% gebruikmakend van een 1:1 molverhouding van de substraten. Temperaturen hoger dan 85 °C resulteerden in een substantieel verlies in de massabalans veroorzaakt door polymerisatie van **1**.

Pogingen om een hogere opbrengst te verkrijgen door de hoeveelheid katalysator te verhogen of door gebruik van sterke zuren als additieven waren niet succesvol. De berekende Gibbs vrije energie ($\Delta G_{gasfase}$) van de reactie gaf de indicatie dat de reactie licht endergonisch zou zijn, wat we wijten aan limiteringen van de gebruikte computationele methode. De uitkomst suggereert echter dat de reactie waarschijnlijk een evenwicht is. In lijn hiermee is de vondst dat een hogere opbrengst behaald kan worden wanneer een hogere CO druk gebruikt wordt met een 1:1 molverhouding van de substraten, of wanneer de molverhouding van de substraten aangepast wordt op een specifieke CO druk. Bovendien is de vorming van styreen gedetecteerd wanneer zuuranhydride **3** werd onderworpen aan de katalytische condities, hetgeen de reversibiliteit van de reactie bevestigt. Een totale opbrengst van zuuranhydride **3** van 95% werd verkregen wanneer een 2:1 ratio van **1**:**2n** gebruikt werd (met 50 of 65 bar CO druk; Schema 1).



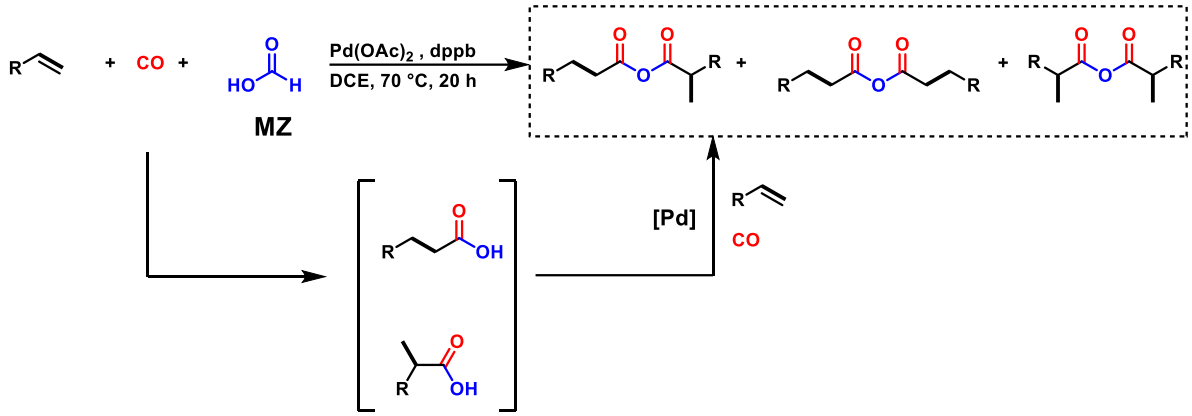
Schema 1. Palladium-gekatalyseerde synthese van zuuranhydrides vanuit alkenen en carbonzuren.

NMR-analyse van het reactiemengsel toonde de aanwezigheid aan van het lineaire-lineaire symmetrische (**3nn**) en vertakte-lineaire gemengde zuuranhydride (**3bn**) in een ratio van 74:26, met sporen van het vertakte-vertakte symmetrische zuuranhydride (**3bb**). Derivatisering van het katalytische reactiemengsel met pyrrolidine resulteerde in 95% amide **4** (92:8 **4n**:**4b**), doordat de derivatiseringsreactie bij voorkeur plaatsvindt op de lineaire acylgroep van **3bn**. Verschillende liganden zijn getest in de geoptimaliseerde katalytische reactiecondities om uit te zoeken welke eigenschappen van belang zijn voor een optimale conversie en regioselectiviteit. Het gebruik van het elektronenrijke ligand d^{t}bpx leverde helaas geen enkel product op. De reactiesnelheid leek het hoogst wanneer fenyl-gesubstitueerde liganden gebruikt werden; het gebruik van dppb resulteerde in de hoogste conversie en een lineariteit van ~80%. Het gebruik van de meer rigide xyleen-gebrugde ligand resulteerde in de hoogste selectiviteit voor de lineaire producten maar gaf helaas ook lagere reactiesnelheden.

De geoptimaliseerde katalytische condities zijn toegepast op een grote verscheidenheid aan alkenen en carbonzuren wat resulteerde in zowel symmetrische als gemengde zuuranhydrides in matige tot goede opbrengsten. De toepasbaarheid van de nieuwe katalytische reactie is gedemonstreerd met de synthese van een primair amide en thioester door middel van een *one-pot*-derivatiseringsreactie van anhydride **3** met respectievelijk ammonia en fenylmethaanthiol. Zoals in Hoofdstuk 1 al beschreven is het uitdagend om primaire amides of thioesters te verkrijgen door middel van een directe hydrocarbonyleringreactie.

In **Hoofdstuk 3** beschrijven we de resultaten van ons onderzoek naar de synthese van carbonzuuranhydrides uit alkenen door middel van *in situ* vorming van het bijbehorende C_{n+1} carbonzuur door het gebruik van mierenzuur (MZ, Schema 2). Carbonylering van een alkeen in bijzijn van FA resulteert in de vorming van een labiel formaatanhydride dat ontleedt naar het gewenste carbonzuur. Dit nieuwgevormde carbonzuur reageert vervolgens als nucleofiel in een tweede carbonyleringsreactie met het alkeen, wat uiteindelijk een zuuranhydride geeft uit twee equivalenten alkeen en één equivalent MZ.

In een reactie van styreen **1** met een 2:1 ratio van **1**:MZ werd 70% zuuranhydride **3** verkregen, gebruikmakend van het katalytische systeem uit Hoofdstuk 2. NMR-analyse liet zien dat de samenstelling van de zuuranhydrides **3nn**:**3bn**:**3bb** ongeveer 60:35:5 was, wat duidt op een lineariteit van ~80% voor de carbonyleringsreactie. Het gebruik van verschillende liganden in het katalytische systeem gaf kleine verschillen in de regioselectiviteit van de reactie. De conversie verschilde echter significant, het gebruik van dppb resulteerde in de hoogste opbrengst **3** uit de serie liganden die geëvalueerd is.



Schema 2. Palladium-gekatalyseerde synthese van zuuranhydrides uit alkenen *via in situ* gegenereerde carbonzuren.

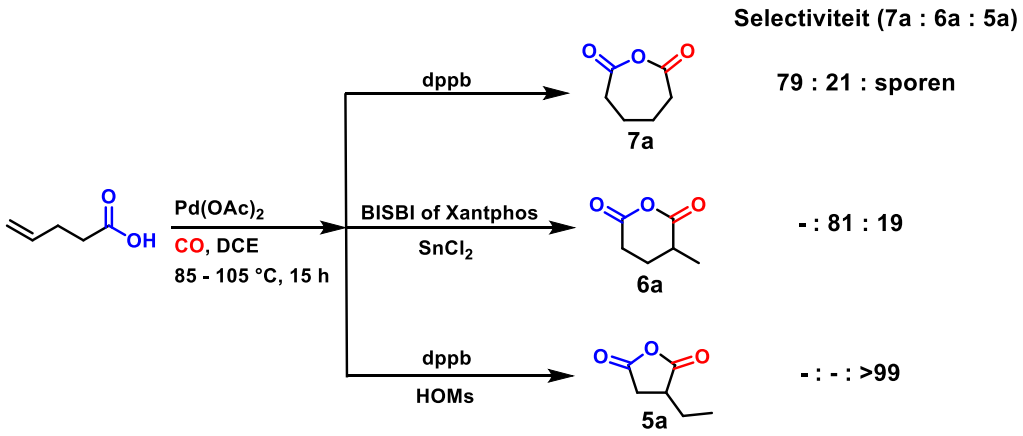
De katalytische procedure bleek toepasbaar op een grote verscheidenheid aan alkenen met verschillende functionele groepen, wat matige tot hoge opbrengsten van lineaire amides gaf na derivatisering. De toepasbaarheid van de methode is gedemonstreerd aan de hand van *one-pot*-derivatiseringsreacties van de reactiemengsels met verschillende nucleofielen wat een primair amide, een *bulky* thioester, een fenolische ester en daarnaast ook producten als ketonen na Suzuki-koppeling of Friedel-Craftsacyleringsreacties gaf.

In **Hoofdstuk 4** wordt een studie naar de synthese van cyclische zuuranhydrides uit penteenzuren (PEAs) beschreven. Cyclocarbonylering van PEA kan leiden tot de vorming van cyclische zuuranhydrides met een vijf-, zes- of zevenring (Schema 3, **5a**, **6a** of **7a**; het nummer correspondeert met de ringgrootte), afhankelijk van de regioselectiviteit van het katalytische systeem. Ongewenste intermoleculaire- en disproportioneringsreacties resulteren echter ook in de vorming van 4-penteenzuuranhydride (4-PEAn), adipinezuur en verschillende oligomeren. Een acceptabele massabalans met vrij goede opbrengsten van de gewenste cyclische producten is behaald door de reacties uit te voeren in relatief verdunde condities.

De producten **7a** en **6a** zijn verkregen in matige tot goede opbrengsten vanuit 4-PEA (4-penteenzuur) als substraat, gebruikmakend van palladium-gebaseerde katalytische systemen in afwezigheid van sterk zuur. Cyclische zuuranhydrides zijn verkregen in 73% opbrengst met een **7a**:**6a** selectiviteit van ~80:20 met $Pd(OAc)_2$/dppb als het katalytische systeem. Wanneer 3-PEA (3-penteenzuur) gebruikt werd, resulteerde dit in de vorming van **6a** en **5a** in een 41:59 verhouding, wat erop duidt dat het katalytische systeem in afwezigheid van zuur niet de isomerisatie van de dubbele band katalyseert.

Het toevoegen van sterke zuren leidt inderdaad tot isomerisatie van 4-PEA naar interne alkenen met de vorming van de kleinere ringen **5a** of **6a** in relatieve hoeveelheden die correleren met

de sterkte van het gebruikte zuur; relatief zwakke zuren geven een hogere selectiviteit naar **6a**, anderzijds geven sterkere zuren relatief meer **5a**. Aangezien isomerisatie een voorwaarde is voor de vorming van **7a** uit een mengsel van PEA-isomeren, zijn er katalytische systemen nodig met *bulky* fosfineliganden in combinatie met zuuradditieven. Helaas gaven de liganden die getest zijn allen selectiviteit voor **6a** of **5a** in plaats van **7a**, aangezien katalytische systemen met de standaard liganden d^{t}bpx en py^{t}bpx met *tert*-butylgroepen een lage activiteit vertonen in deze reactie.



Schema 3. Carbonylering van 4-penteenzuur om cyclische zuuranhydrides te verkrijgen.

Curriculum Vitae

Ashok Ramakrishnan was born on 11th September, 1991, in Kerala, India. After high school, he pursued Bachelors in Pharmacy (B.Pharm) at Mumbai University from 2009 to 2013 and graduated with distinction. He was awarded a scholarship from the Sir Ratan Tata Trust, which he received from 2011 to 2013.

Subsequently, he was admitted in one of the top institutes for pharmacy education in India – National Institute for Pharmacy Education and Research (NIPER), Mohali, where he pursued a Master's in Medicinal Chemistry (M.S. Pharm). During his master's program, Ashok conducted his thesis research under the guidance of Prof. dr. P.V. Bharatam. His thesis, entitled "Tautomerism in biologically active hydrazone derivatives and exploration of divalent N(I) character", delved into the experimental and computational study of azine-hydrazone tautomerism in amidinohydrazones. Additionally, he explored the presence of divalent N(I) character in these compounds and synthesized several amidinohydrazone derivatives to test for their anti-leishmanial activity. Ashok earned a scholarship from Bristol-Myers-Squib (BMS) during this period. He published his first research paper, "Azine or hydrazone? The dilemma in amidinohydrazones," in RSC Advances before graduating with high honors in July 2015.

Following the completion of his master's degree, Ashok ventured into industrial research with a focus on organic synthesis, a field he pursued until the end of 2018. During this period, he also worked in the peptide synthetic division of the biopharma company - Biocon Ltd., currently ranked 8th among Global Biotech Employers for 2022 by Science magazine. In January 2019, he joined the group of Prof. dr. Elisabeth Bouwman for a PhD in 'Homogenous Catalysis' in the department, 'Metals in Catalysis, Biomimetics and Inorganic Materials' (MCBIM), at the Leiden Institute of Chemistry (LIC). He supervised several practical courses for bachelor students during his PhD. Ashok followed a number of courses offered by the Holland Research School of Molecular Chemistry (HRSMC) as well as the Graduate School of Leiden University, including "Scientific Conduct", "Physical Methods in Inorganic Chemistry", "Molecular Modelling", "High Impact Writing" and "Organic Synthesis Summer School 2021". He also attended the course, 'Catalysis An Integrated Approach (CAIA)' offered by Nederlands Instituut voor Onderzoek in de Katalyse (NIOK) and passed the related exam. Further, he attended several conferences (as listed below) wherein the results reported in this thesis were presented:

2022

- Oral presentation at Chemistry As Innovating Science (CHAINS) 2022 by NWO at Veldhoven, The Netherlands
- Attended the International Symposium on Homogenous Catalysis 2022 at Lisbon, Portugal
- Poster presentation at Holland Research School of Molecular Chemistry (HRSMC) Symposium 2021 (held in March ’22) at Amsterdam, The Netherlands

2021

- Presented poster at CHAINS 2021 by NWO at Veldhoven, The Netherlands
- Presented poster at the Organic Synthesis Summer School 2021 conducted by HRSMC, The Netherlands

2020

- Presented poster at Netherlands’ Catalysis and Chemistry Conference (NCCC) 2020 at Noordwijkerhout, The Netherlands

List of Publications

1. Ramakrishnan, A.; Chourasiya, S. S.; Bharatam, P. V. Azine or Hydrazone? The Dilemma in Amidinohydrazones. *RSC Adv.* **2015**, *5* (69), 55938–55947.
2. Chourasiya, S. S.; Kathuria, D.; Nikam, S. S.; Ramakrishnan, A.; Khullar, S.; Mandal, S. K.; Chakraborti, A. K.; Bharatam, P. V. Azine-Hydrazone Tautomerism of Guanylhydrazones: Evidence for the Preference Toward the Azine Tautomer. *J. Org. Chem.* **2016**, *81* (17), 7574–7583.
3. Liu, C.; van den Bos, D.; den Hartog, B.; van der Meij, D.; Ramakrishnan, A.; Bonnet, S. Ligand Controls the Activity of Light-Driven Water Oxidation Catalyzed by Nickel(II) Porphyrin Complexes in Neutral Homogeneous Aqueous Solutions. *Angew. Chem. Int. Ed.* **2021**, *60* (24), 13463–13469.
4. 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.
5. Ramakrishnan, A.; Bouwman, E. Regioselectivity in Carbonylation of Pentenoic Acid to Synthesize Cyclic Anhydrides, *manuscript submitted.*
6. Ramakrishnan, A.; Bouwman, E. Palladium-Catalyzed Synthesis of Symmetric Carboxylic Acid Anhydrides from Alkenes with *in situ* Generated Carboxylic Acids, *manuscript in preparation.*

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First and foremost, I am immensely grateful to Prof. dr. Elisabeth Bouwman for granting me the opportunity to pursue my PhD in her group. Her unwavering encouragement I received to critically think and question every result, to present results effectively and for allowing scientific flexibility and freedom, is truly beyond measure. The countless work discussions, brainstorming sessions, and spirited scientific debates unquestionably shaped the outcome of this research and helped me complete my thesis. I would like to thank my second promotor, Dr. Dennis Hetterscheid, for his suggestions during group meetings as well as for improving this thesis. I also would like to thank Prof. dr. Sylvestre Bonnet for the scientific suggestions and feedback provided during this research.

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Ashok Ramakrishnan