Palladium-catalyzed carbonylative synthesis of carboxylic acid anhydrides from Alkenes

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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

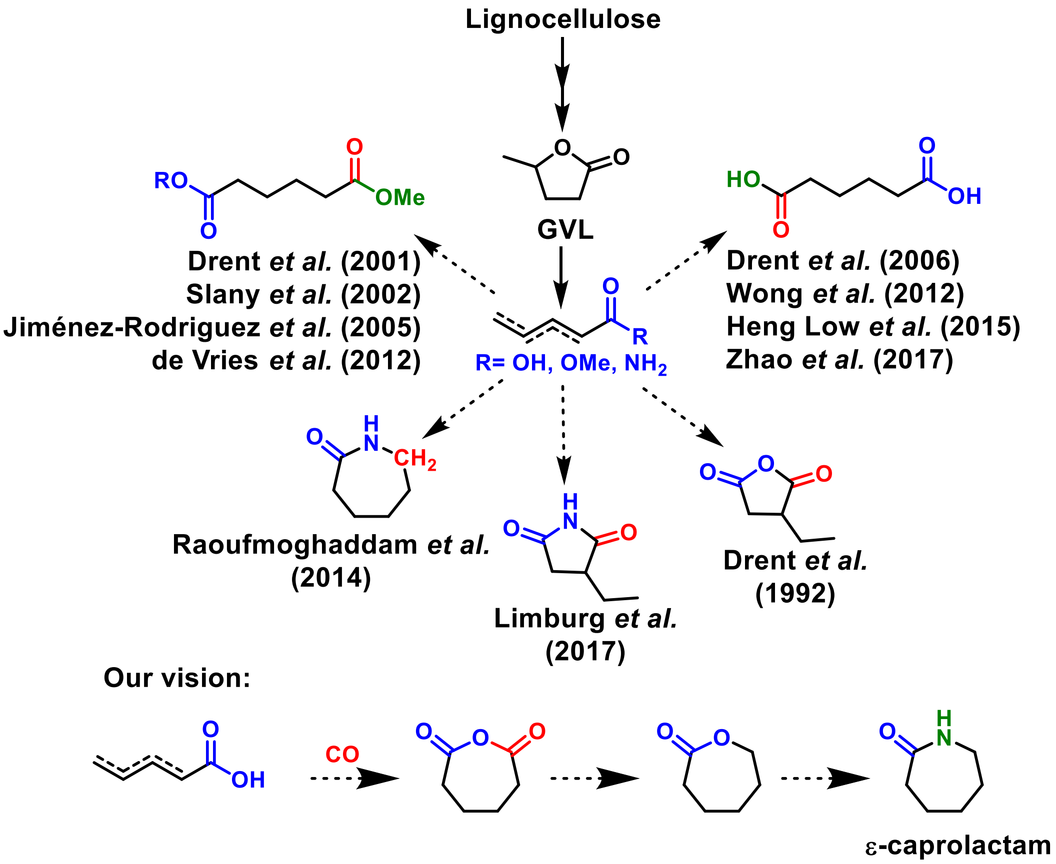
Depletion of fossil fuels has intensified the search for bio-based alternatives from renewable resources that can effectively be used for synthesis of commodity chemicals. A pivotal example in this regard is the pursuit of a sustainable route for the synthesis of adipic acid. Adipic acid is considered 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.

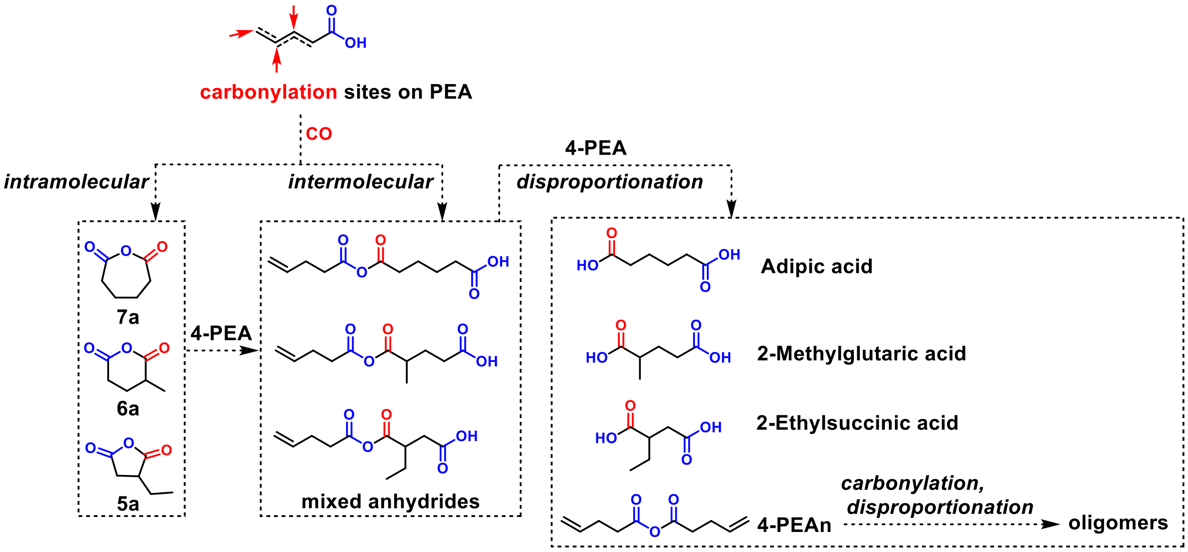


Scheme 4.1. Reported carbonylation reactions of pentenoic acid, ester or amide (ref. 10-17 and 21-23) (top) and envisioned route to synthesize ε-caprolactam from pentenoic acid (bottom).

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

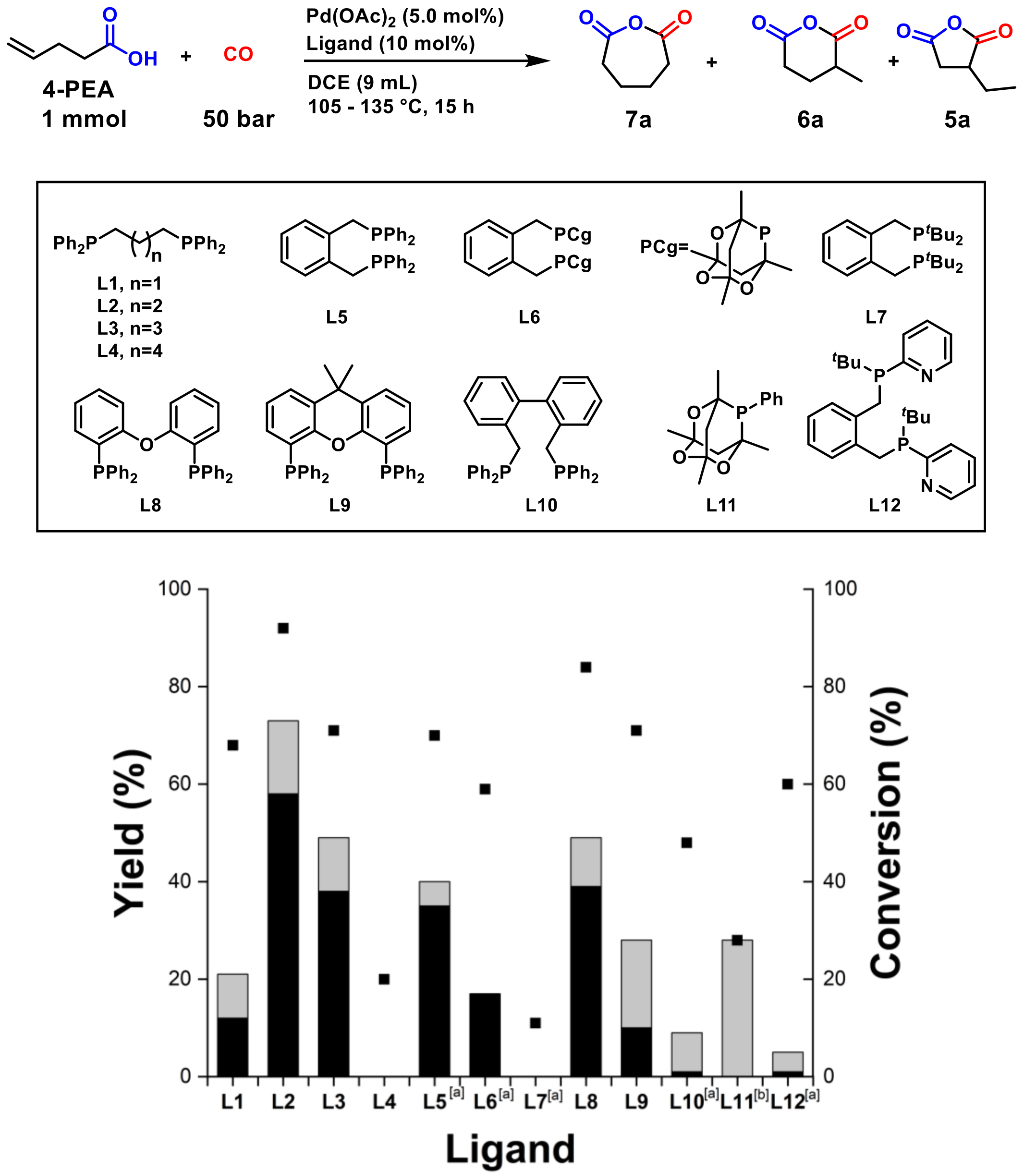


Figure 4.1. Conversion of PEA, yield of and selectivity for cyclic anhydrides for catalytic systems comprising different phosphine ligands in cyclocarbonylation of 4-PEA. Reaction conditions: 4-PEA (1.0 mmol), Pd(OAc)$_2$ (0.05 mmol), ligand (0.10 mmol), CO (50 bar), DCE (9 mL), 15 h. Yield % of cyclic 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

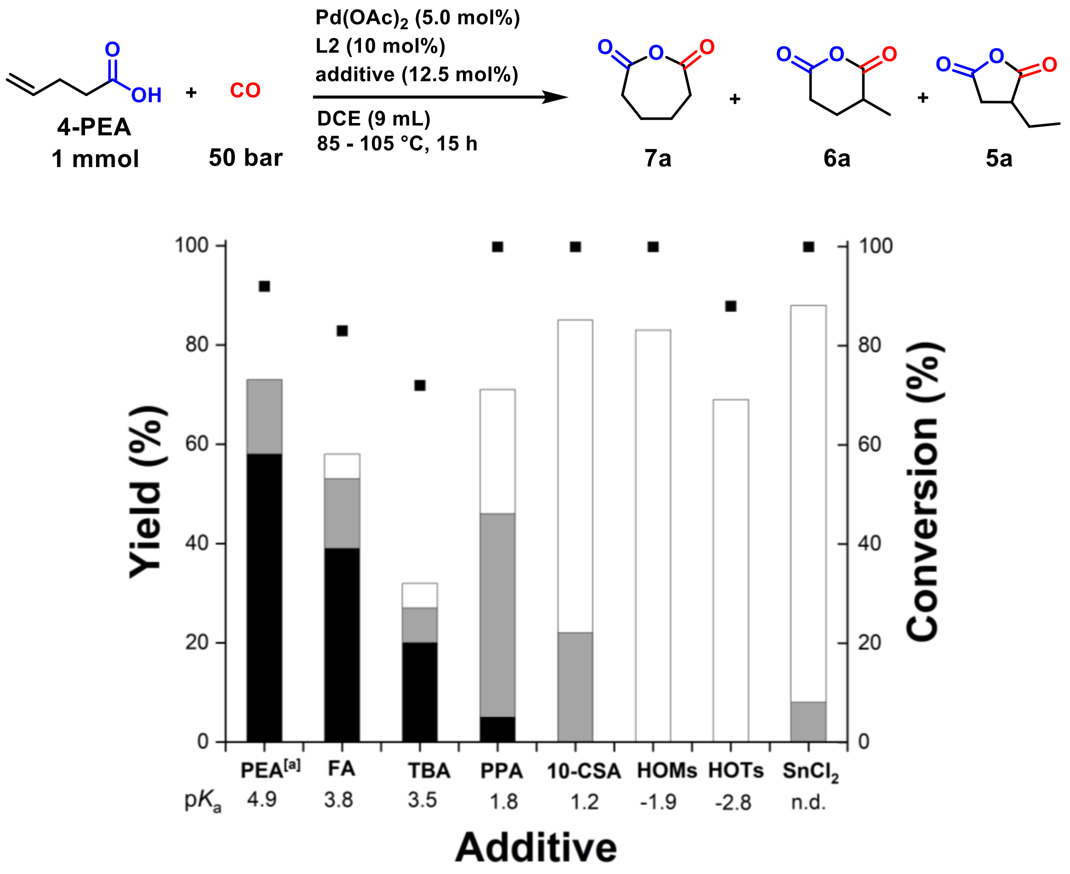


Figure 4.2. Conversion of PEA, yield of and selectivity for cyclic anhydrides for catalytic systems comprising different additives in cyclocarbonylation of 4-PEA. Reaction conditions: 4-PEA (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), **L2** (0.10 mmol), additive (0.125 mmol), CO (50 bar), 85 °C, DCE (9 mL), 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).

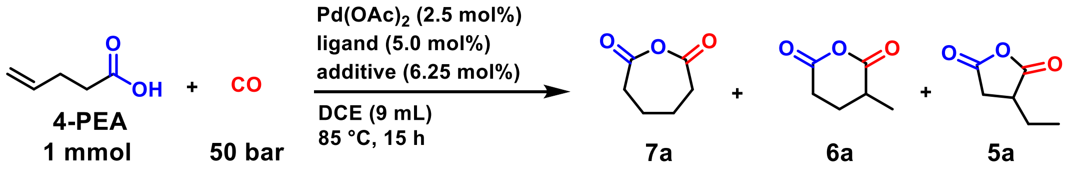
*Attempts to improve selectivity for **7a***. The use of a catalytic system with isomerization activity is important in order to obtain a single product from the mixture of pentenoic acid isomers that is obtained from GVL. Additionally, a bulky ligand will be necessary to enforce isomerization to the 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.

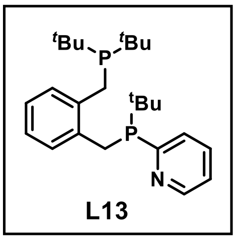
Addition of a strong acid to the catalytic system comprising the electron-donating ligand **L7** resulted in some catalytic activity, but unfortunately gave mostly **6a** and trace amounts of **7a**, albeit in very low yield (Table 4.1, entry 1). Use of the more strongly chelating ligand **L5** (as compared 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**.





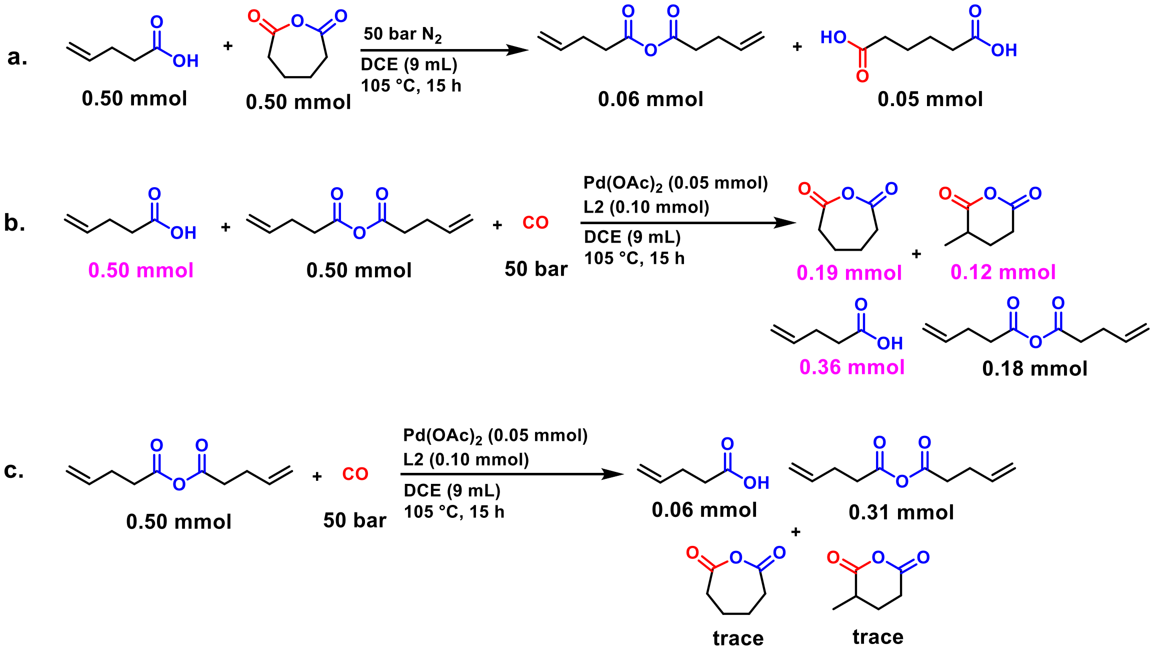
L13

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.

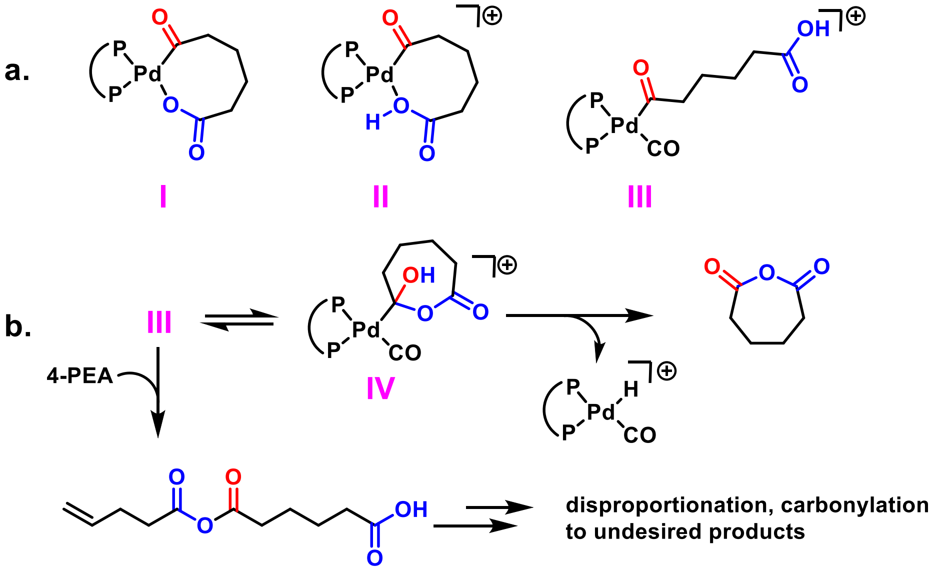
We carried out some test reactions in order to determine the fate of the desired reaction products under reaction conditions. Heating a mixture of **7a** and 4-PEA under N_2 resulted in substantial loss of **7a** and mass balance, formation of 4-PEAn along with small amounts of unknown products was observed 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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