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Synthesis of Carboxylic Acids by Palladium-catalyzed Hydroxycarbonylation

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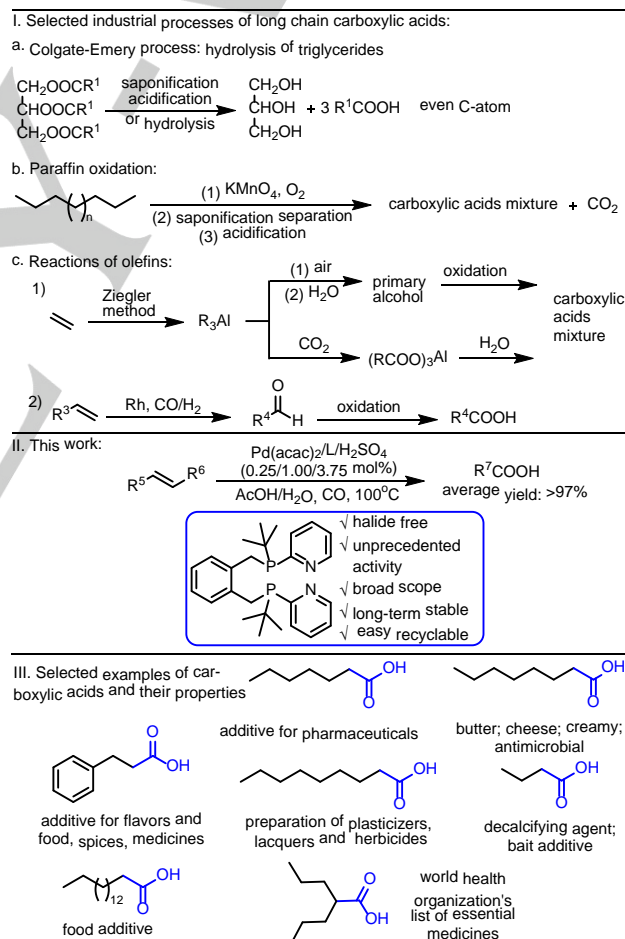
Dedicated to Professor Dr. Pierre H. Dixneuf for more than 50 years of outstanding contribution to organometallic and catalysis.

Abstract: The synthesis of carboxylic acids is of fundamental importance in the chemical industry and the corresponding products find numerous applications for polymers, cosmetics, pharmaceuticals, agrochemicals, and other manufactured chemicals. Although hydroxycarbonylations of olefins are known for more than 60 years, currently known catalyst systems for this transformation do not fulfill industrial requirements, e.g. stability. Herein, we present for the first time an aqueous phase protocol that allows all kinds of olefins including a wide range of sterically hindered and demanding tetra-, tri- and 1,1-disubstituted as well as terminal alkenes to be converted to the corresponding carboxylic acids in excellent yields. The outstanding stability of our catalyst system (26 recycling runs in 32 days without measurable loss of activity), which is unprecedented for Pd-catalyzed hydroxycarbonylations, is showcased in the preparation of an industrially relevant fatty acid. Key-to-success is the use of the "built-in-base" ligand **L20** in acidic aqueous conditions. Due to its efficiency and generality, we expect this catalytic system provides a basis for new cost-competitive processes for the industrial production of carboxylic acids.

Introduction

Carboxylic acids are of major importance in organic chemistry and industry. Due to the specific physical characteristics of this functional group (acidity, polarity, surface properties) numerous applications exist in materials, pharmaceuticals, agrochemicals, coatings, food industry, cosmetic ingredients, disinfecting products, and other manufactured chemicals.[1-6] In addition to all these uses, carboxylic acids serve as central building blocks for the preparation of derivatives like carboxylate salts, anhydrides, esters, nitriles, and amides.[7-13] There is a continuing interest in new applications of organic acids and their market is expected to grow for >5% from 2017 to 2022 to reach a projected value of > $11 billion by 2022.[14] Currently, all major industrial processes for long chain aliphatic acids require multistep syntheses (Figure

1).[15] For example, C4-C11 carboxylic acids are produced from alkenes by hydroformylation with syngas,[16] and subsequent oxidation.[17] In case of acids with longer carbon chains, either paraffin oxidation or hydrolysis of renewable triglycerides constitute viable options.[18] Notably, for the latter methodology only carboxylic acids with an even number of C-atoms are available.[19] Moreover, paraffin oxidation suffer from moderate product yields due to non-selective formation of a variety of acids and CO_2 as well as large recycle streams.[20]

Figure 1. Comparison of major industrial routes towards long chain aliphatic carboxylic acids. (**I**) Industrial routes towards aliphatic carboxylic acids. (**II**) This work. (**III**) Selected examples of important aliphatic carboxylic acids.

In general, a number of the problems associated with the synthesis of carboxylic acids *vide supra* can be avoided by employing a direct hydroxycarboxylation of abundantly available olefins. Depending on the catalyst and reactions conditions

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either Reppe-type carbonylations or the Koch-Haaf reactions are known. While the former methodology makes use of Ni-, Pd-, or Co-catalysts, the latter process is less common and requires strong Brønsted or Lewis acids like HCl, HF or SbF$_5$.[21] Today's knowledge of hydroxycarbonylations is based to a large extent on the fundamental work by Reppe and co-workers on the Ni-catalyzed carbonylation of acetylene to acrylic acid.[22-25] In 1969, Kutepow and co-workers rendered this transformation operational using palladium catalysts to obtain branched carboxylic acids.[26] Later on, Fenton studied the influence of process parameters on the conversion of 1-octene in the presence of PdCl$_2$/PPh$_3$ and acetic acid as solvent.[27] Further improvements in reactivity were achieved by introducing halide containing additives, e.g. CuCl$_2$, HCl or LiCl or mixtures of them.[28-32] Despite continuing activities over the past three decades and the introduction of novel ligands as well as the improvement of process conditions by the groups of Drent,[33-41] Sheldon,[42] van Leeuwen,[43-44] Laurenczy,[45] Wendt,[46] and Mecking,[47] todays state-of-the-art hydroxycarbonylation technology still does not meet the requirements for bulk industrial processes. For this purpose, especially improvements regarding catalyst stability and recycling are needed. In this respect, the groups of Monflier and later on Ionescu investigated the recyclability of water-soluble Pd-catalysts.[48-49] While the recycling of the catalyst was possible up to 5 times without significant loss of activity, the general protocol is limited to water-soluble substrates. Notably, Drent *et al.* at Shell claimed the possibility of catalyst recycling using 1,2-bis((di-*tert*-butylphosphanyl)methyl)benzene (d*t*bpx, **L18**, which was previously described by Shaw[50]) for continuous adipic acid generation from water-soluble pentenoic acids.[51-52] However, in this patent the stability of the recycled catalyst is not reported and it is only stated that the catalyst system was "almost exclusively detected in the organic phase". At this point, it should be also noted that in contrast to well-established alkoxycarbonylations, the stability of the phosphine ligands in hydroxycarbonylations and thus the possibility for ligand recycling, is much more problematic. For example, oxidation of Pd(II)-ligated phosphines by water occurs easily in the presence of carboxylic acids, which facilitates catalyst deactivation and palladium black formation.[53-54]

Recently, we developed bidentate ligands with integral basic sites (pyridyl-substituted phosphines), which act as a proton shuttle and improve the rate-determining esterification step in alkoxycarbonylation reactions.[55-57] Furthermore, we demonstrated the superiority of these ligands for selective formic acid decomposition reactions.[58] Based on that work, we got attracted to study the stability of the related catalysts in hydroxycarbonylation reactions. As a result, herein we present the most stable and general hydroxycarbonylation catalyst known to date.

Results and Discussion

At the beginning of our work, the industrially relevant Pd-catalysed hydroxycarbonylation of di-*iso*-butylene (DIB, **1a**, 4 mmol) to give 3,5,5-trimethylhexanoic acid (TMHAc, **2a**) was

investigated in the presence of different ligands (**Figure 2**). Notably, the production (Oxea, BASF, KH Neochem) of >85,000 tons per annum (2017)[59] of **2a** underlines the importance of this product, which is currently made from high purity di-*iso*-butylene by stepwise hydroformylation and subsequent oxidation to give **2a**.[60] Notably, in this model reaction a commercial mixture of internal and terminal olefins is used, which offers several challenges for the desired hydroxycarbonylation with respect to reactivity, selectivity, and solubility (extremely low as 0.023 mmol·L^{-1} in water; around 100 times lower than for styrene).
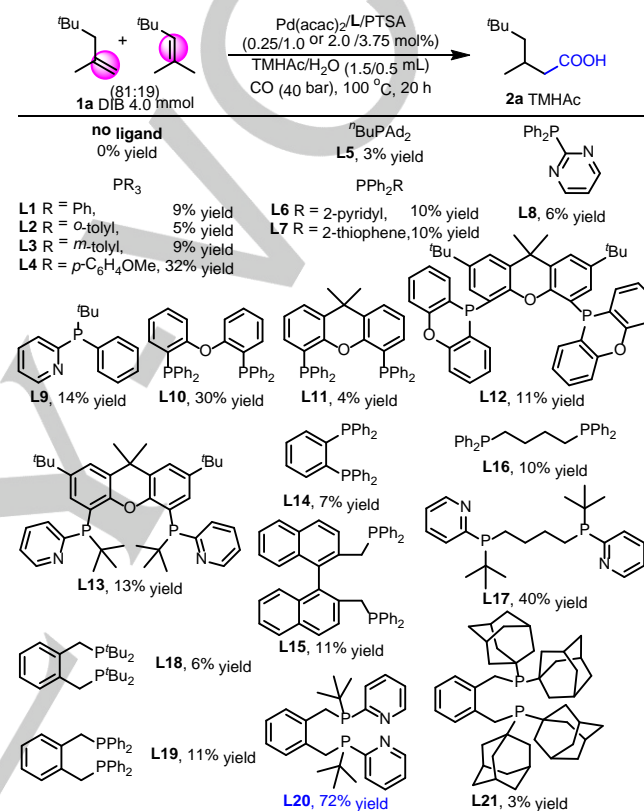

Figure 2. Palladium-catalyzed hydroxycarbonylation of di-*iso*-butene **1a** using a range of different ligands. General conditions: **1a** (4.0 mmol), Pd(acac)$_2$ (0.25 mol%), monodentate ligand **L1-L9** (2 mol%) or bidentate ligand **L10-L21** (1 mol%), PTSA (3.75 mol%), CO (40 bar), solvent (2 mL), 100 °C, 20 h. Yield of **2a** was determined via **1a** conversion by GC analysis using isooctane as the internal standard.

In order to minimize corrosion issues, all experiments except control tests were carried out with halide-free systems, applying comparably low catalyst concentration (0.25 mol% Pd(acac)$_2$) at 100 °C. For practicability, initially the product itself was used as a co-solvent (**2a**/H$_2$O = 1.5/0.5 mL) and additional solubilizers were omitted.

As depicted in Figure 2, the blank reaction without any ligand present gave no desired product. Next, a selection of well-known phosphorous based ligands were investigated: For typical monophosphines **L1-L3, L5**, the yield of **2a** was very low (<10%), although in the presence of P(*p*-PhOMe)$_3$ **L4** the reactivity increased to give 32% of the desired product. Compared with PPh$_3$, heterocycle-modified ligands such as **L6**

Table 1. Palladium-catalyzed hydroxycarbonylation of di-*iso*-butene **1a**: Effect of palladium precursors, acids, solvents and temperature.[a]

Entry	Pd source	co-cat. acid	Solvent (mL)	Yield (%,*n/iso*)
1[b]	Pd(acac)$_2$	PTSA	**2a**/H$_2$O (1.5/0.5)	72 (>99/1)
2[b]	Pd(OAc)$_2$	PTSA	**2a**/H$_2$O (1.5/0.5)	52 (>99/1)
3[b]	Pd(TFA)$_2$	PTSA	**2a**/H$_2$O (1.5/0.5)	56 (>99/1)
4[b]	Pd$_2$(dba)$_3$	PTSA	**2a**/H$_2$O (1.5/0.5)	70 (>99/1)
5[b]	PdCl$_2$	PTSA	**2a**/H$_2$O (1.5/0.5)	51 (>99/1)
6[b]	Pd(MeCN)Cl$_2$	PTSA	**2a**/H$_2$O (1.5/0.5)	47 (>99/1)
7[b]	Pd(acac)$_2$	PTSA	H$_2$O (2.0)	16 (>99/1)
8[b]	Pd(acac)$_2$	PTSA	FA/H$_2$O (1.5/0.5)	48 (>99/1)
9[b,c]	Pd(acac)$_2$	PTSA	AcOH/H$_2$O (1.5/0.5)	>99 (>99/1)
10[b]	Pd(acac)$_2$	PTSA	BTA/H$_2$O (1.5/0.5)	92 (>99/1)
11[b]	Pd(acac)$_2$	PTSA	lactic acid/H$_2$O (1.5/0.5)	99 (>99/1)
12[b]	Pd(acac)$_2$	PTSA	THF/H$_2$O (1.5/0.5)	15 (>99/1)
13[d]	Pd(acac)$_2$	-	AcOH/H$_2$O (1.5/0.5)	80 (>99/1)
14[d]	Pd(acac)$_2$	MSA	AcOH/H$_2$O (1.5/0.5)	99 (>99/1)
15[c,d]	Pd(acac)$_2$	H$_2$SO$_4$	AcOH/H$_2$O (1.5/0.5)	>99 (>99/1)
16[d]	Pd(acac)$_2$	HOTf	AcOH/H$_2$O (1.5/0.5)	99 (>99/1)
17[d]	Pd(acac)$_2$	HCl	AcOH/H$_2$O (1.5/0.5)	35 (>99/1)
18[b,e]	Pd(acac)$_2$	PTSA	**2a**/H$_2$O (1.8/0.2)	98 (>99/1)

Reaction conditions: [a] **1a** (4.0 mmol), [Pd] (0.25 mol%), **L20** (1 mol%), co-cat. acid (3.75 mol%), CO (40 bar), solvent (2 mL), 100 °C, 20 h. The ratios of isomers were determined by GC and NMR analysis. [b] Yield of **2a** is determined via **1a** conversion by GC analysis using isooctane as the internal standard. [c] Isolated yields. [d] Yield of **2a** is determined via NMR analysis using benzyl methyl ether as internal standard after the reaction. [e] 120 °C.

(2-pyridyl), **L7** (2-thiophenyl), **L8** (2-pyrimidinyl) as well as **L9** with both 2-pyridyl and *tert*-butyl groups did not led to significant improvements (3-14% yield). On the other hand, the bidentate ligand DPEphos **L10**, which is known to catalyze the hydroxycarbonylation of olefins using HCOOH via *in situ* generated acid anhydride,[61] gave the desired acid **2a** in 30% yield. Further testing of different Xantphos derivatives **L11**-**L13**, which contain a state-of-the-art scaffold for diphosphine ligands, revealed no improvement. Other bidentate ligands such as DPPBz **L14**, Naphos **L15** and DPPB **L16** also gave disappointingly low yields (7-11%). Notably, d^{t}bpx **L18**, which is currently used for ethylene alkoxycarbonylation on multi-100.000 ton-scale,[62-63] afforded the desired product **2a** only in 6% yield.

Similarly, in the presence of analogous **L19** and **L21** no significant improvement of **2a** was achieved. In most of these test reactions formation of palladium black was observed, apparently as a result of the low catalyst stability under acidic aqueous conditions. Finally, a breakthrough in the benchmark reaction was achieved when testing **L20** with pyridine substituent as "built-in base" to give **2a** in 72% yield. The importance of this particular substitution pattern is also evident for **L17**, whereby the reactivity three times increased compared with the parent ligand DPPB.

Further investigations of the reaction conditions applying the optimal ligand **L20** revealed substantial effects of the palladium precursor, the solvent, its concentration (SI-Table S1), the amount of water, and the acidic co-catalyst. More specifically, variation of palladium salts in the presence of the optimal ligand **L20** showed reactivity for both Pd(II) as well as Pd(0) pre-catalysts (Table 1, entries 1-6). In general, the presence of halide ions decreased the reactivity (Table 1, entries 5 and 17). Considering the low reactivity of the benchmark substrate, it is remarkable that this process can be accomplished in pure water as solvent, too (Table 1, entry 7). Gratifyingly, testing other acids improved the yield of the desired **2a**. Especially, using short-chain acids such as butyric acid (BTA) and lactic acid as co-solvent gave improved results (>90%) (Table 1, entries 9-11). Quantitative conversion and excellent yield (>99%) of **2a** was achieved using inexpensive acetic acid (AcOH) as co-solvent. The positive effect of protic solvents becomes clear in comparing acetic acid with aprotic THF, which have similar dielectric constants (6.2/7.5) and dipole moments (1.74 D/1.75 D) (Table 1, entries 9 and 12).[64] From a practical point of view, it is advantageous to perform the reaction in **2a** as solvent, which led to a product yield of 98% (Table 1, entry 18).

To demonstrate the broader use of this novel hydroxycarbonylation process a number of olefins were reacted under the best conditions. Besides **1a**, industrially-relevant terminal olefins such as ethylene (**1b**), propene (**1c**), and isobutylene (**1d**) reacted smoothly, affording the corresponding products (**2b**-**2d**) in excellent yields (Table 2, entries 1-3). Similarly, C5-C8 terminal olefins were carbonylated into desired carboxylic acids (**2g**-**2l**) in high yields (Table 2, entries 6-11). Among these substrates, particularly *tert*-butyl ethylene (**1i**) and 2,3-dimethyl-1-butene (**1j**) gave also excellent linear selectivity (>99%). Due to their often lower price, internal alkenes, especially mixtures of internal and terminal olefins are preferred for the manufacture of bulk chemicals. Accordingly, our catalytic system converted C4 olefin mixtures (raffinate-1 (**1e**)[65] and -2 (**1f**)[66]) as well as 2-octene (**1m**), mixture of *n*-octenes (**1n**), and di-*n*-butenes (**1o**) – an industrial feedstock consisting numerous octene, methylheptene, and dimethylhexene isomers - into the corresponding acids with high yields (Table 2, entries 4-5,12-14). The substantial advantage of this novel procedure compared to previously known catalysts becomes clear in the hydroxycarbonylation of industrially important longer chain olefins >C10. Evidently, the solubility of alkenes decreases with increasing chain length.[67-68] Nevertheless, 1-decene, 1-dodecene, 1-tetradecene, and even 1-hexadecene led to the corresponding acids in >95% yield (Table 2, entries 15-18). In addition, cyclic olefins such as cyclopentene (**1t**), cyclohexene (**1u**), cycloheptene (**1v**) and cyclooctene (**1w**) were transformed

Table 2. Palladium-catalyzed hydroxycarbonylation of industrial aliphatic alkenes.[a]

alkenes $\xrightarrow[\text{AcOH/H}_2\text{O (1.5/0.5 mL), CO (40 bar), 100 °C, 20 h}]{\text{Pd(acac)}_2/\textbf{L20}/\text{H}_2\text{SO}_4 \text{ (0.25/1.00/3.75 mol%)}}$ carboxylic acids

Entry	Alkene	Linear acid	Yield (%) (n/iso)	Entry	Alkene	Linear acid	Yield (%) (n/iso)
1[b,c,e]	1b	2b	99	13[d,f]	mixture of n-octenes 1n	2l	99 (67/33)
2[b,c,e]	1c	2c	99 (69/31)	14[d,f]	di-n-butene 1o (C8 mixtures)	C9 acid mixture 2o	97
3[b,c,e]	1d	2d	99 (>99/1)	15	1p	2p	99 (73/27)
4[b,e]	raffinate-1 1e (C4 mixtures)	C5 acid mixture 2e	93	16	1q	2q	99 (72/28)
5[b,e]	raffinate-1 1f (C4 mixtures	C5 acid mixture 2e	90	17	1r	2r	99 (72/28)
6	1g	2g	99 (81/19)	18	1s	2s	95 (71/29)
7[b]	1h	2h	99 (78/22)	19	1t	2t	99
8	1i	2i	99 (>99/1)	20	1u	2u	99
9	1j	2j	99 (>99/1)	21	1v	2v	99
10	1k	2k	99 (74/26)	22	1w	2w	99
11	1l	2l	99 (74/26)	23	1x	2j	99 (>99/1)
12	n-C5H11 1m	2l	99 (71/29)				

[a] Reaction conditions: **1** (4.0 mmol), Pd(acac)$_2$ (0.25 mol%), **L20** (1 mol%), H$_2$SO$_4$ (3.75 mol%), CO (40 bar), AcOH/H$_2$O (1.5/0.5 mL), 100 °C, 20 h. Isolated yields. The ratios of isomers were determined by the lower of GC and NMR analysis. [b] Yields determined via peeling weighing method. [c] Yields determined via NMR analysis using benzyl methyl ether as an internal standard after the reaction. [d] Yield is determined via **1** conversion by GC analysis using isooctane as the internal standard. [e] 100 mL autoclave: **1** (0.5~2g), Pd(acac)$_2$ (20 μmol), **L20** (80 μmol), H$_2$SO$_4$ (0.3 mmol), AcOH/H$_2$O (15/5 mL), CO (40 bar),100 °C. [f] 100 mL autoclave: **1** (40 mmol).

into the desired acids in excellent yields (Table 1, entries 19-22). For the first time ever hydroxycarbonylation of tetra-

methylethylene (**1x**) was achieved in aqueous phase (99% yield and selectivity; Table 2, entry 23).

Table 3. Practical Palladium-catalyzed hydroxycarbonylation of aromatic and other functionalized alkenes.[a]

$$\text{alkenes} \xrightarrow[\text{AcOH/H}_2\text{O (1.5/0.5 mL), CO (40 bar), 100 }^{\circ}\text{C, 20 h}]{\text{Pd(acac)}_2/\textbf{L20}/\text{H}_2\text{SO}_4 \text{ (0.25/1.00/3.75 mol\%)}} \text{carboxylic acids}$$

Entry	Alkene	Linear acid	Yield [%] (n/iso)	Entry	Alkene	Linear acid	Yield [%] (n/iso)
1	Ph⁼ **1y**	Ph–CH₂CH₂COOH **2y**	99 (83/17)	10	**1h'**	**2h'**	99 (>99/1)
2	Ph **1z**	Ph **2z**	99 (78/22)	11	n-C₄F₉ **1i'**	n-C₄F₉ **2i'**	99 (>99/1)
3	Ph **1a'**	Ph **2a'**	99 (76/24)	12[b]	**1j'**	**2j'**	99 (>99/1)
4	**1b'**	**2b'**	99 (>99/1)	13[b]	**1k'**	**2k'**	85 (86/14)
5	F **1c'**	F **2c'**	99 (>99/1)	14	with 8% internal olefin isomers **1l'**	with 8% isomers **2l'**	99 (92/8)
6	Cl **1d'**	Cl **2d'**	99 (>99/1)	15[b]	**1m'**	**2m'**	99 (>99/1)
7[b,d]	**1e'**	**2e'**	99 (>99/1)	16	**1n'**	**2n'**	82 (>99/1)
8[b]	**1f'**	**2f'**	99 (>99/1)	17[c,d]	**1o'**	**2o'**	99 (67/33)
9	Ph, Ph **1g'**	Ph, Ph **2g'**	99 (>99/1)				

[a] Reaction conditions: **1** (4.0 mmol), Pd(acac)₂ (0.25 mol%), **L20** (1 mol%), H₂SO₄ (3.75 mol%), CO (40 bar), AcOH/H₂O (1.5/0.5 mL), 100 °C, 20 h. Isolated yields. The ratios of isomers were determined by the lower of GC and NMR analysis. [b] **1** (1.0 mmol). [c] **1** (2.0 mmol). [d] Yield is determined via **1** conversion by GC analysis using isooctane as the internal standard.

After demonstrating the viability of our system for industrial aliphatic olefins, we were interested in the hydroxycarbonylation of aromatic and functionalized alkenes, which are of interest for fine chemicals, specialties and organic synthesis (Table 3).[69-75] As an example, styrene (**1y**) was completely converted with 83% regioselectivity towards 3-phenyl propionic acid (**2y**) (Table 3, entry 1). Employing allyl benzene (**1z**) and 4-phenyl-1-butene (**1a'**) the corresponding products **2z-2a'** were afforded again in excellent (99%) yields (Table 3, entries 2-3).

Similarly, derivatives of α-methylstyrene with various substituents on the phenyl ring (**1b'-1f'**) as well as α-phenylstyrene (**1g'**) gave quantitative yields of aliphatic acids with >99% regioselectivity (Table 3, entries 4-9). Furthermore, the dihydroxycarbonylated compound **2h'** was smoothly obtained from **1h'** (Table 3, entry 10). From a synthetic point of view, it is important that various functionalized olefins containing carboxylic acid, ketone, imide, halides and phosphorus groups were tolerated. For instance, fluorinated olefins 1*H*,1*H*,2*H*-

perfluoro-1-hexene (**1i'**) and pentafluoro-styrene (**1j'**) are quantitatively transformed to the desired acids with >99% linear selectivity (Table 3, entries 11-12). Using allylacetone (**1k'**), the corresponding acid can be obtained in both good yield and selectivity (Table 3, entry 13).

Exemplarily, the renewable substrate (+)-dihydrocarvone (**1l'**) yielded the desired acid again in excellent yield with good linear selectivity (Table 3, entry 14). Additionally, N-vinylphthalimide (**1m'**) and vinylphosphonic acid (**1n'**) produced exclusively the corresponding linear acids (Table 3, entries 15-16). Finally, the hydroxycarbonylation of the unsaturated fatty acid (**1o'**) afforded the long-chain α,ω-dicarboxylic acids product **2o'** in excellent yield (Table 3, entry 17).
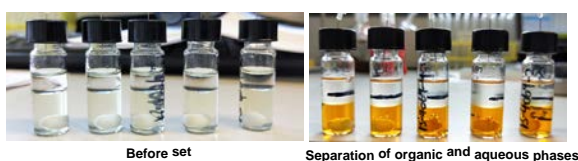

Figure 3. Recycling of the homogenous catalytic hydroxycarbonylation system for long chain (≥C5) alkenes.

For any real-world application, the long term stability and recycling of the catalytic system, plays a crucial role. Indeed, these factors are often decisive for failure or success in industry. In our case, carboxylic acids generated from ≥C5 alkenes can be easily isolated by the separation of an organic and aqueous phase (Figure 3, for details see SI-3.1). Advantageously, the pyridyl-containing ligand not improves the actual carbonylation catalysis, but also ensures that the catalyst system remains preferentially in the polar aqueous (H_2O/AcOH) phase. Comparing related d^{t}bpx-type ligands (**L18**, **L19** and **L21**) with **L20** under the recycling conditions, demonstrated clearly the unique behavior of the latter ligand. All the other catalyst systems are completely deactivated or show only negligible activity even in the first recycling run (for details see SI, Figure S2). NMR studies (Scheme 1, **I-III**) of d^{t}bpx (**L18**) and py^{t}bpx (**L20**) in acidic aqueous phase under N_2 atmosphere proved the increased stability of **L20**. The ^{31}P NMR signal of pure **L18** at δ = 26.11 moved to high field (50-60 ppm) after adding Pd^0(dba)$_2$ at room temperature. After heating, the ^{31}P NMR peak of the coordinated ligand (around 57-60 ppm) increased in the first 5-6 h, but soon decreased and could not be detected after 24h. Meanwhile, visible palladium black particles were generated (SI, Figure S2), which proves immediate catalyst decomposition.[76]

In contrast, the ^{31}P NMR signal of **L20** moved to low field in the presence of Pd^0(dba)$_2$ and no phosphorus oxides were detected even after prolonged time (Scheme 1, **II**). Remarkably, when using **L20** with 1.0 mol% Pd^{II}(acac)$_2$ (high loading) under the hydroxycarbonylation conditions, the reaction finished in 3 h without detection of the corresponding phosphorus oxide (Scheme 1, **IV**). In agreement with this, no palladium black was observed when using **L20** in contrast to **L18**.
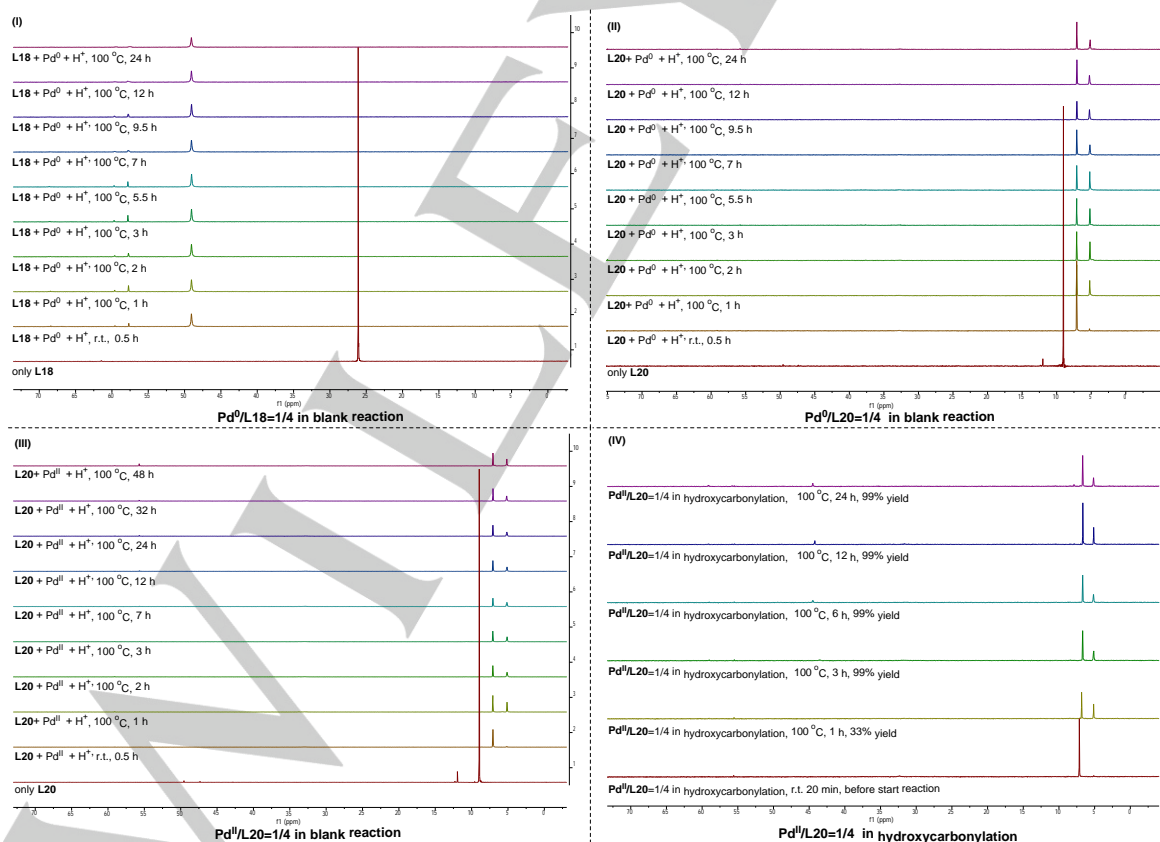
Scheme 1. NMR studies of Pd-catalyst systems in aqueous acidic systems.

Surprisingly, comparing the known alkoxycarbonylation of di-*iso*-butene with the hydroxycarbonylation of the same olefin under optimal conditions showed that the catalyst is more efficient in the latter reactions (Scheme 2).

After demonstrating the increased stability of the Pd/**L20** system on a molecular level, finally we performed two industrial case studies. For the hydroxycarbonylation of 1-dodecene the second best (and cheapest) acidic co-catalyst H_2SO_4 was used (SI, Scheme S2). As shown in Figure 4, our system displayed unprecedented recyclability and afforded the desired product **2q** even after 26 runs without measurable loss of activity (Figure 4, **I**; details see SI). Performing the synthesis of **2q** on 10-gram-scale delivered more than 350 g of the desired product in high purity (>98%; catalyst turnover number >11,000). Secondly, the synthesis of propionic acid using ethylene (~3 ppm Pd-cat.),which is of special economic interest, can be easily upscaled and resulted after 24 h in a catalyst turnover number > 350,000 with TOF >15,000. We believe both examples indicate the general feasibility of this methodology for applications.
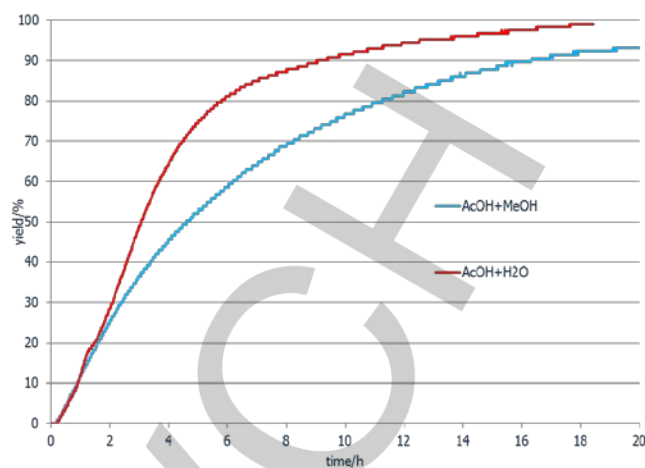
Scheme 2. Comparison of Pd-catalyzed carbonylation of di-*iso*-butene using **L20** for methoxycarbonylation and hydroxycarbonylation.
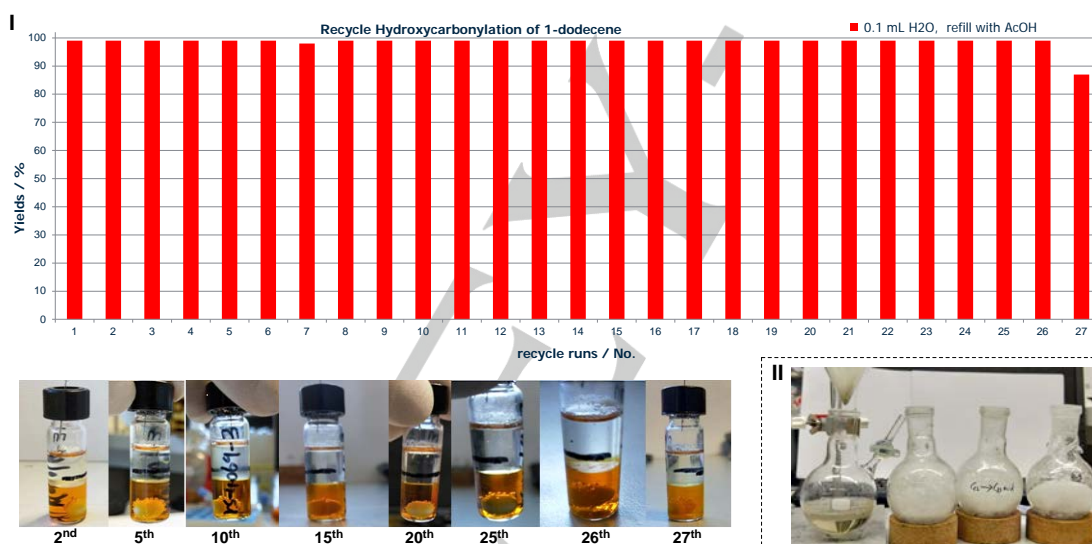
Figure 4. Long term stability and recycling of the homogenous catalytic hydroxyl-carbonylation of 1-dodecene. (**I**) Recycle conditions: **1g** (4.0 mmol), Pd(acac)$_2$ (0.25 mol%), **L20** (1 mol%), H_2SO_4 (3.75 mol%), CO (40 bar),100 $^{\circ}$C, 20h. (**II**) multiplicative reaction – 10g scale recycle hydroxycarbonylation of 1-dodecene.

Conclusion

In conclusion, in this study a new state-of-the-art palladium catalyst containing **L20** as ligand for mild and versatile hydroxycabonylation of olefins is presented. This specific catalyst allows producing carboxylic acids under halide-free mild reaction conditions. The catalyst shows outstanding stability and can be easily recycled (>25 runs) without measurable loss of reactivity. For industrially relevant olefins, e.g. ethylene, excellent catalyst turnover numbers and frequencies are obtained (TON >350,000, TOF >15,000 for propionic acid). To the best of our knowledge, this is the first hydroxycarbonylation system, which shows such high degree of productivity and recyclability. In principle, a wide range of olefins can be transformed to the corresponding carboxylic acids regardless the substitution degree. Based on the here reported catalyst and further developments, we believe this 100% atom-efficient carbonylation route will be in the future more often considered for environmentally friendly and sustainable carboxylic acid production.

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RESEARCH ARTICLE

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RESEARCH ARTICLE

RESEARCH ARTICLE

"**Angewandte Chemie**" **for industrially relevant carboxylic acids.** The outstanding stability of the catalyst system (>25 recycling runs in 32 days without measurable loss of activity), which is unprecedented for Pd-catalyzed hydroxycarbonylations, is showcased in the preparation of an industrially relevant fatty acid. Due to its efficiency and generality, we expect it provides a basis for new cost-competitive processes for the industrial production of carboxylic acids.

Pd(acac)$_2$/L/H$_2$SO$_4$
(0.25/1.00/3.75 mol%)
AcOH/H$_2$O, CO, 100°C

R → R COOH

average yield: >97%

√ halide free
√ unprecedented activity
√ broad scope
√ long-term stable
√ easy recyclable
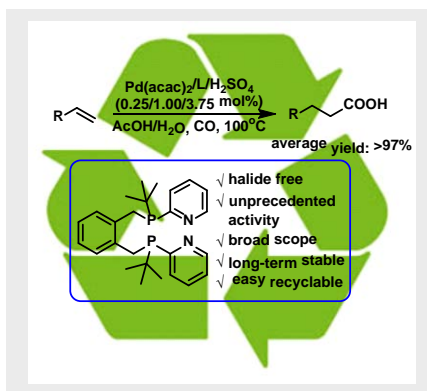
Rui Sang, Peter Kucmierczyk, Ricarda Dühren, Rauf Razzaq, Kaiwu Dong, Jie Liu, Robert Franke*, Ralf Jackstell, and Matthias Beller*

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Synthesis of Carboxylic Acids by Palladium-catalyzed Hydroxycarbonylation: Breakthrough in Long-term Stability and Recycling