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Palladium-Catalyzed Reduction of Carboxylic Acids to Aldehydes with Hydrosilanes in the Presence of Pivalic Anhydride

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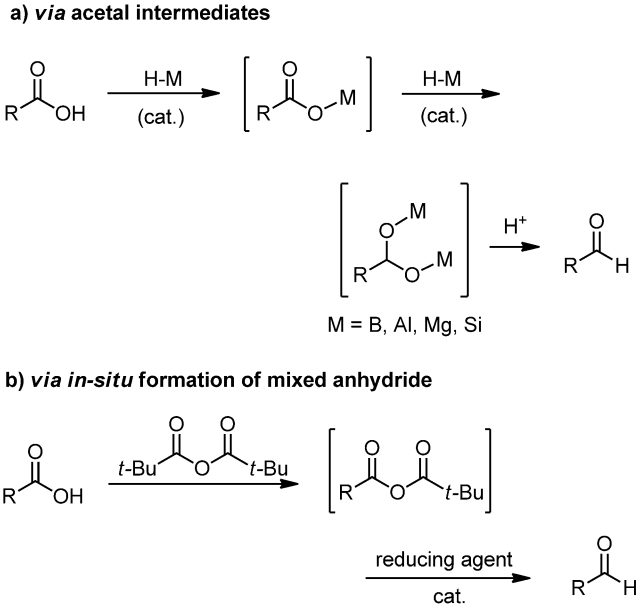
Abstract: A palladium catalyst system that allows the reduction of carboxylic acids to the corresponding aldehydes with hydrosilanes as reducing agent and pivalic anhydride as an indispensable reagent has been developed. A simple mixture of commercially available bis(dibenzylideneacetone)palladium(0) [$Pd(dba)_2$], tri(*para*-tolyl)phosphane and methylphenylsilane realized the reduction of various aliphatic carboxylic acids as well as benzoic acids to aldehydes in good to high yields.

Keywords: aldehydes; carboxylic acids; hydrosilanes; palladium; reduction

Aldehydes are useful intermediates for the synthesis of a wide variety of organic chemicals. Classical methods to synthesize aldehydes involve two-step procedures.[1] Carboxylic acids may be reduced, and the resulting alcohols are oxidized to aldehydes. Otherwise, carboxylic acids are first converted to more reactive derivatives such as acid chlorides[2] or esters,[3] then these derivatives are converted to aldehydes with suitable reducing agents.

On the other hand, carboxylic acids can be employed as substrates in the one-pot reduction to aldehydes (Scheme 1). In Scheme 1a, carboxylic acids react with a borane,[4a–c] alane,[4d,e] Grignard reagent/titanocene catalyst,[4f] or silane[5] to afford the corresponding acetal species, then aldehydes are obtained by hydrolysis of the intermediates. Especially, the reactions with silanes were intensively studied recently.[5] In the reactions, bis-silanes such as 1,2-bis(dimethylsilyl)benzene[5a] and 1,1,3,3-tetramethyldisiloxane[5b] were found to be effective. As for catalysts, ($\mu_3,\eta^2,\eta^3,\eta^5$-acenaphthylene)$Ru_3(CO)_7$,[5a] $Fe(CO)_3$(*trans*-4-phenylbut-3-en-2-one),[5b] and $B(C_6F_5)_3$[5c] showed high activity. However, these reactions have a narrow scope of applicable substrates and often suffer from low functional group compatibility.[4,5]

Alternatively, a pioneering one-pot synthesis of aldehydes from carboxylic acids was reported by Yamamoto et al. by utilizing the *in-situ* formation of mixed anhydrides (in equilibrium) with pivalic anhydride (Scheme 1b).[6] They carried out the reduction under 30 bar pressure of flammable hydrogen in the presence of $Pd(PPh_3)_4$ as a catalyst. Later, Gooßen et al. modified the catalyst and found that $Pd(acac)_2$/$PPhCy_2$[7] was active under even 5 bar of hydrogen. However, in their reaction, only aromatic (not aliphatic) carboxylic acids were successfully converted to the corresponding aromatic aldehydes.[8a] They also used hydrophosphite salts as reducing agents, but the



Scheme 1. One-pot synthesis of aldehydes from carboxylic acids as substrates.

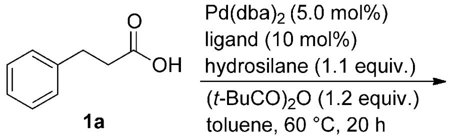
reaction usually gave lower yields and were waste-intensive.[8b]

We have previously reported the palladium-catalyzed reduction of acid chlorides with hydrosilanes, giving the corresponding aldehydes.[9] Although acid chlorides are excellent substrates in transition metal-catalyzed reactions,[10] they must be synthesized from the corresponding carboxylic acids prior to catalytic reactions. Here we report that hydrosilanes are excellent reducing agents in Scheme 1b with a simple mixture of a commercially available palladium complex and a phosphane ligand as a catalyst in the presence of a pivalic anhydride. This new catalytic reaction realizes the reduction of both aliphatic and aromatic carboxylic acids to the corresponding aldehydes with good functional group compatibility.

First, the reaction of 3-phenylpropionic acid (**1a**) was carried out under various conditions (Table 1). A mixture of Pd(dba)_2[7] and $\text{P}(p\text{-Tol})_3$[7] showed a high catalytic activity with H_2SiMePh at 60 °C to afford 3-phenylpropanal (**2a**) in 99% yield (entry 1). Pd(dba)_2 and $\text{P}(p\text{-Tol})_3$ as well as H_2SiMePh are all commercially available. Here, only 1.2 equiv. of pivalic anhydride is sufficient, while an excess amount of the anhydride (2.5[8b]–3.0[6,8a] equiv.) was necessary in the previous reactions. From the reaction mixture, pivalic acid was recovered in 71% yield after hydrolysis followed by silica gel column chromatography. Without any ligand, **1a** did not convert at all (entry 2). As a ligand, PPh_3 and $\text{P}(p\text{-MeOC}_6\text{H}_4)_3$ also afforded **2a** in high yields (entries 3 and 4). A bulky and basic phosphane, PCy_3,[7] was less effective (entry 5). In contrast, with $\text{P}(o\text{-Tol})_3$[7] and P(Mes)_3,[7] conversions of **1a** were quite low and **2a** was afforded in only trace yields, possibly due to the steric hindrance of these ligands (entries 6 and 7). The use of an electron-deficient phosphane, $\text{P(C}_6\text{F}_5)_3$, was not efficient at all (entry 8). As for hydrosilanes, H_2SiEt_2 and H_2SiPh_2 provided **2a** in 90% and 86% yields, respectively (entries 9 and 10), while HSiMe_2Ph, HSiMePh_2, HSiEt_3, HSiPh_3, and H_3SiPh were not suitable for the reaction (entries 11–15). After investigating various bulky carboxylic acid anhydrides such as 1-adamantanecarboxylic anhydride and (2,4,6-trimethylphenyl)-carboxylic anhydride, we found pivalic anhydride was the most suitable additive in terms of yields of the products. Both steric and electronic parameters would be important. As a solvent, the reaction in THF provided **2a** in 99% yield, while in CH_2Cl_2 the yield of **2a** decreased to 43%. Gratifyingly, the present reaction is amenable to scale-up to a gram-scale with 1.0 mol% catalyst loading [Eq. (1)].

$$\underset{20\ \text{mmol}}{\mathbf{1a}} \xrightarrow[\substack{(t\text{-BuCO})_2\text{O (1.2 equiv.)}\\ \text{toluene, 60 °C, 20 h}}]{\substack{\text{Pd(dba)}_2\ (1.0\ \text{mol\%})\\ \text{P}(p\text{-Tol})_3\ (2.0\ \text{mol\%})\\ \text{H}_2\text{SiMePh (1.1 equiv.)}}} \underset{1.8\ \text{g}\ (67\%)}{\mathbf{2a}} \qquad (1)$$

Table 1. Effect of ligands and hydrosilanes on the palladium-catalyzed reduction of 3-phenylpropionic acid.[a]



Entry	Ligand	Hydrosilane	Yield [%][b]
1	$\text{P}(p\text{-Tol})_3$	H_2SiMePh	99 (75)[c]
2	none	H_2SiMePh	0
3	PPh_3	H_2SiMePh	95
4	$\text{P}(p\text{-MeOC}_6\text{H}_4)_3$	H_2SiMePh	94
5	PCy_3	H_2SiMePh	66
6	$\text{P}(o\text{-Tol})_3$	H_2SiMePh	trace
7	P(Mes)_3	H_2SiMePh	trace
8	$\text{P(C}_6\text{F}_5)_3$	H_2SiMePh	trace
9	$\text{P}(p\text{-Tol})_3$	H_2SiEt_2	90
10	$\text{P}(p\text{-Tol})_3$	H_2SiPh_2	86
11	$\text{P}(p\text{-Tol})_3$	HSiMe_2Ph	62
12	$\text{P}(p\text{-Tol})_3$	HSiMePh_2	24
13	$\text{P}(p\text{-Tol})_3$	HSiEt_3	22
14	$\text{P}(p\text{-Tol})_3$	HSiPh_3	14
15	$\text{P}(p\text{-Tol})_3$	H_3SiPh	trace

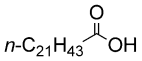
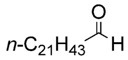
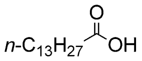
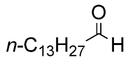
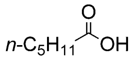
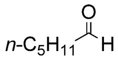
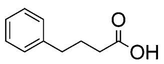
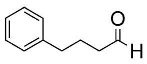
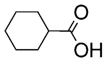
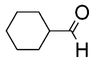
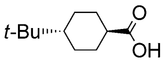
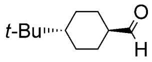
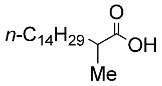
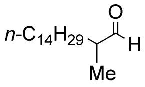
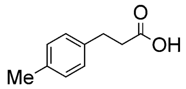
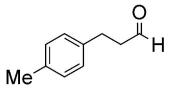
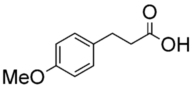
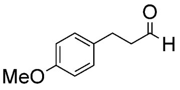
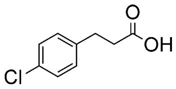
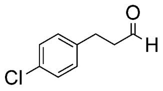
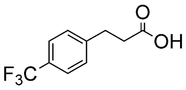
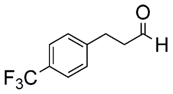
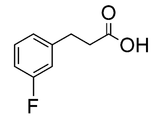
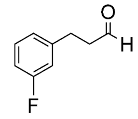
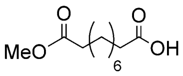
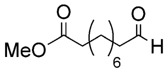
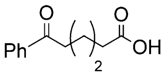
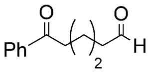
[a] *Reaction conditions:* 3-phenylpropionic acid (**1a**: 0.50 mmol), hydrosilane (0.55 mmol), Pd(dba)_2 (0.025 mmol, 5.0 mol%), ligand (0.050 mmol, 10 mol%), $(t\text{-BuCO})_2\text{O}$ (0.60 mmol) in toluene (1.0 mL) at 60 °C for 20 h.

[b] Yield based on the GC internal standard technique.

[c] Isolated yield of **2a**.

Under the optimal reaction conditions, various aliphatic carboxylic acids were converted smoothly to the corresponding aldehydes in high yields (entries 1–14, Table 2). It is noteworthy that ester (**1n**) and ketone (**1o**) functionalities were tolerated in the reaction (entries 13 and 14). Furthermore, aromatic acid derivatives **1p–z** were also converted to the corresponding aldehydes with $\text{P}(p\text{-MeOC}_6\text{H}_4)_3$ as the ligand in the presence of 1.5 equiv. of pivalic anhydride (Table 3). The substrates with electron-donating (**1q–s**) and electron-withdrawing groups (**1t–w**) afforded the corresponding aldehydes in good to high yields (entries 2–8). The reactions of **1q**, **1r, 1s, 1u, 1w** and **1z** were carried out at 80 °C. 2-Methylbenzoic acid (**1s**) was converted to the corresponding aldehyde in 69% yield (entry 4). However, more sterically hindered 2,4,6-trimethylbenzoic acid could not be converted at all. Chloro (**1t**), cyano (**1u**), formyl (**1v**) and ester (**1w**) functionalities were compatible under the reaction conditions. 2-Naphthalenecarboxylic acid (**1x**) afforded **2x** with $\text{P}(p\text{-Tol})_3$ as the ligand at 60 °C (entry 9). 3-Carboxypyridine (**1y**) was converted to the corresponding aldehyde in good yield (entry 10).

Table 2. Reduction of aliphatic carboxylic acids.[a]

Entry	Carboxylic Acid (**1**)		Aldehyde (**2**)		Yield [%][b]
1	 n-$C_{21}H_{43}COOH$	**1b**	 n-$C_{21}H_{43}CHO$	**2b**	98
2	 n-$C_{13}H_{27}COOH$	**1c**	 n-$C_{13}H_{27}CHO$	**2c**	88
3	 n-$C_5H_{11}COOH$	**1d**	 n-$C_5H_{11}CHO$	**2d**	(99)[c]
4		**1e**		**2e**	78
5[d]		**1f**		**2f**	(90)[c]
6[d]		**1g**		**2g**	69
7[d]		**1h**		**2h**	68
8		**1i**		**2i**	88
9		**1j**		**2j**	82
10		**1k**		**2k**	74
11		**1l**		**2l**	75
12[d,e]		**1m**		**2m**	70
13[d]		**1n**		**2n**	79
14		**1o**		**2o**	79

[a] *Reaction conditions:* carboxylic acid (**1**: 0.50 mmol), $H_2SiMePh$ (0.55 mmol), $Pd(dba)_2$ (0.025 mmol, 5.0 mol%), P(p-Tol)$_3$ (0.05 mmol, 10 mol%), (t-BuCO)$_2$O (0.60 mmol) in toluene (1.0 mL) at 60 °C for 20 h.

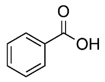
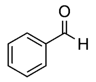
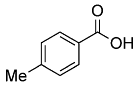
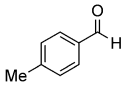
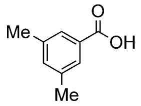
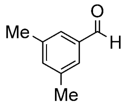
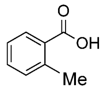
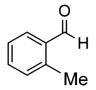
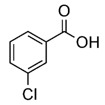
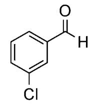
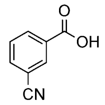
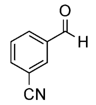
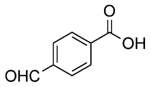
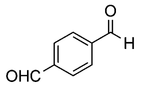
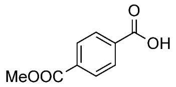
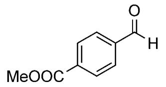
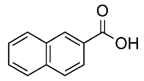
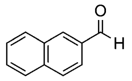
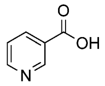
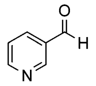
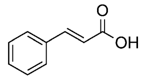
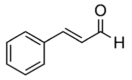
[b] Isolated yield of **2**.

[c] GC yield was given because a product having a low boiling point was considerably lost during the isolation process.

[d] At 80 °C.

[e] (t-BuCO)$_2$O (0.75 mmol) was used.

Table 3. Reduction of benzoic acid derivatives.[a]

Entry	Carboxylic Acid (**1**)		Aldehyde (**2**)		Yield [%][b]
1		**1p**		**2p**	(78)[c]
2[d]		**1q**		**2q**	61
3[d]		**1r**		**2r**	71
4[d]		**1s**		**2s**	69
5		**1t**		**2t**	75
6[d]		**1u**		**2u**	63
7[e]		**1v**		**2v**	68
8[d,e]		**1w**		**2w**	89
9[f,g]		**1x**		**2x**	74
10[f,g]		**1y**		**2y**	60
11[d,e]		**1z**		**2z**	46 (60)[h]

[a] *Reaction conditions:* carboxylic acid (**1**: 0.50 mmol), $H_2SiMePh$ (0.55 mmol), $Pd(dba)_2$ (0.025 mmol, 5.0 mol%), P(p-MeOC$_6$H$_4$)$_3$ (0.050 mmol, 10 mol%), (t-BuCO)$_2$O (0.75 mmol) in toluene (1.0 mL) at 60 °C for 20 h.

[b] Isolated yield **2**.

[c] GC yield was given because a product having a low boiling point was considerably lost during the isolation process.

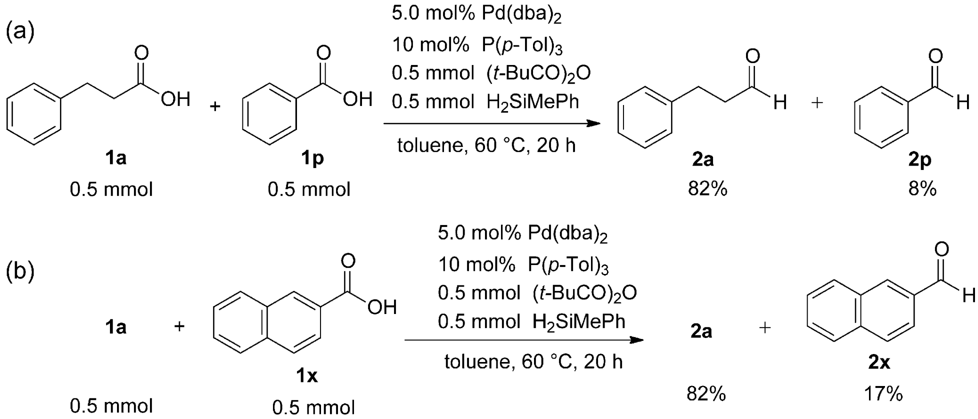
[d] At 80 °C.

[e] (t-BuCO)$_2$O (1.0 mmol) was used.

[f] P(p-Tol)$_3$ (0.050 mmol) was used instead of P(p-MeOC$_6$H$_4$)$_3$.

[g] (t-BuCO)$_2$O (0.60 mmol) was used.

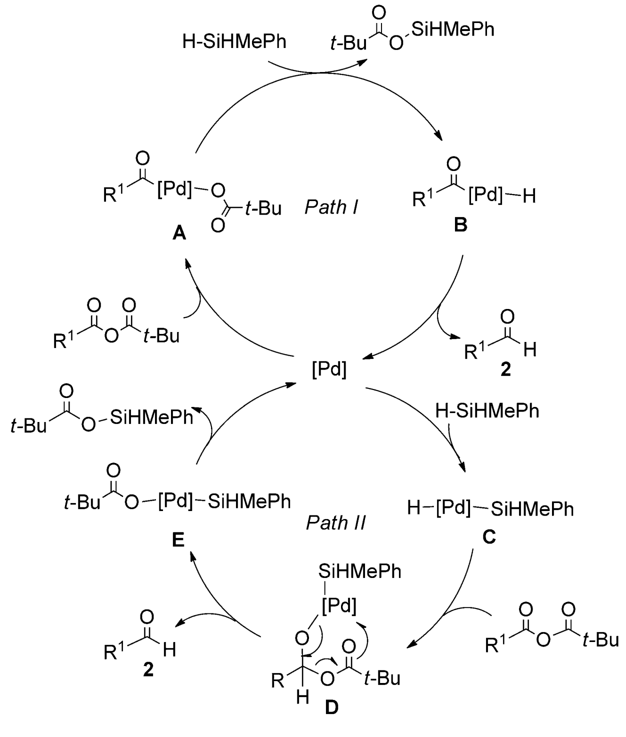
[h] GC yield based on the internal standard technique. As a by-product, **2a** was detected in 7% yield.



Scheme 2. Preferential reduction of **1a** in the presence of aromatic carboxylic acid derivatives (**1p** and **1x**).

Cinnamic acid also gave the corresponding aldehyde in moderate yield (entry 11). Unfortunately, 4-iodo- and 4-bromobenzoic acids could not be used as substrates. Substrates bearing alkenyl and alkynyl moieties provided complex mixtures. We also carried out the reaction of phenylglyoxylic acid. However, under the reaction conditions, the substrate was decomposed and no corresponding aldehyde was obtained.

The reaction of an equimolar mixture of **1a** and **1p** afforded **2a** and **2p** in 82% and 8% yields, respectively (Scheme 2a). Similarly, in the reaction of **1a** and **1x**, the aldehyde from the aliphatic acid was obtained preferentially in 82% yield (Scheme 2b). Noteworthy is that, in contrast to previous reduction under hydrogen pressure,[8a] the present catalyst system preferentially reduces aliphatic carboxylic acids in the presence of aromatic analogues. An aliphatic acid would afford the corresponding mixed anhydride faster than aromatic carboxylic acids. Actually, the reduction of aromatic carboxylic acids required a somewhat larger amount of pivalic anhydride (1.5 equiv.) as compared to aliphatic carboxylic acids (1.2 equiv.).



Scheme 3. Plausible reaction mechanism

A plausible mechanism for the catalytic reaction is shown in Scheme 3. Carboxylic acids provide mixed anhydrides[11] in equilibrium with pivalic anhydride. As shown in path I, the oxidative addition of the mixed anhydrides[12] to the palladium catalyst center affords an intermediate (**A**). The selective oxidative addition of one of two C–O bonds in the mixed anhydride would be realized by steric hindrance of the *tert*-butyl group. Then, an acyl(hydride)palladium intermediate (**B**) is formed by the σ-bond metathesis with hydrosilanes. Actually, pivalic acid silyl ester *t*-BuCO$_2$SiHMePh was detected by ^{29}Si NMR measurements of the resulting reaction mixture ($\delta = -11.4$ ppm, without ^{1}H decoupling, d, $J_{\mathrm{Si,H}} = 6.0$ Hz). Finally, the reductive elimination affords an aldehyde (**2**) and the Pd(0) species regenerates. An alternative mechanism of the reaction is shown in path II in Scheme 3. It is also possible to envisage an oxidative addition of the silane to Pd(0), giving a Pd–H intermediate (**C**). Insertion of a C–O moiety to the Pd–H bond takes place to form an intermeidate **D**. After elimination of **2** followed by reductive elimination, the Pd(0) species regenerates.

Under the reaction conditions, a stoichiometric amount of pivalic acid and pivalic acid silyl ester was formed. From the reaction mixture, pivalic acid can be recovered and must be easily converted to pivalic anhydride. Actually, from the reaction mixture in entry 1 of Table 1, pivalic acid was recovered in 71% yield by column chromatography.

In conclusion, we have developed the palladium-catalyzed reduction of carboxylic acids to the corresponding aldehydes in the presence of hydrosilanes as reducing agent and pivalic anhydride. A simple mixture of commercially available Pd(dba)$_2$ and P(p-Tol)$_3$ as a catalyst realized the reduction of various aliphatic and aromatic carboxylic acids to aldehydes with good functional group compatibility.

Experimental Section

Typical Procedure for the Palladium-Catalyzed Reduction of 3-Phenylpropionic acid (1a) with H$_2$SiMePh (Table 1, entry 1)

Acid **1a** (75 mg, 0.50 mmol), Pd(dba)$_2$ (14 mg, 0.025 mmol) and P(p-Tol)$_3$ (15 mg, 0.050 mmol) were added to a 10-mL Schlenk flask with a magnetic stir bar. The flask was evacuated and backfilled with argon three times. Then, toluene (1.0 mL) was added to the flask and the resultant solution was stirred at room temperature for 2 min. Pivalic anhydride (120 μL, 0.60 mmol) was added and the mixture was further stirred for 15 min. Then, H$_2$SiMePh (76 μL, 0.55 mmol) was added to the flask and the reaction mixture was stirred at 60°C for 20 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was diluted with diethyl ether (5.0 mL) and tetradecane (50 μL, 0.19 mmol) as an internal standard was added. The yield of 3-phenylpropanal (**2a**; 99%) was analyzed by gas chromatography. **2a** was isolated by silica gel column chromatography (hexane: EtOAc = 13:1) as a colorless oil; yield: 50 mg (75%).

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[7] Abbreviations: dba: dibenzylideneacetone, PPhCy$_2$: dicyclohexylphenylphosphane, P(p-Tol)$_3$: tri-*para*-tolylphosphane, PCy$_3$: tricyclohexylphosphane, P(o-Tol)$_3$: tri-*ortho*-tolylphosphane, P(Mes)$_3$: tris(2,4,6-trimethylphenyl)phosphane.

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