New Pd-catalyzed selective reduction of carboxylic acids to aldehydes

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A catalyst generated *in situ* from palladium acetate and tricyclohexylphosphine efficiently catalyzes the reduction of carboxylic acids with sodium hypophosphite in the presence of pivalic anhydride to give aldehydes with high selectivity. The low cost and convenient handling of the reagents makes this process a valuable alternative to hydrogenations and metal hydride reductions.

The synthesis of aldehydes from carboxylic acid derivatives is an important transformation often used in commercial and laboratory scale organic synthesis.[1] Several suitable reducing agents have been reported for the selective reduction of acids, esters, and amides such as lithium tris-*tert*-butoxyaluminium hydride,[2] aminoaluminium hydrides,[3] DIBAL-H,[4] and NaAlH$_4$.[5] Alternatively, the sensitive and highly reactive acid chlorides can be hydrogenated in a Rosenmund catalytic reduction[6] and related reactions using metal hydrides.[7,8] However, in all these methods, the acid derivatives have to be generated in an additional reaction step and the handling of the metal hydrides requires extreme caution and rigorous exclusion of air and moisture. Recently, Yamamoto *et al.* developed an elegant process for the direct hydrogenation of carboxylic acids to aldehydes by using pivalic anhydride to convert the acids *in situ* into mixed anhydrides, and reducing these at high hydrogen gas pressures.[9,10] The mixed anhydrides are selectively hydrogenated at the sterically less demanding site, so that pivalic acid is always produced as the by-product along with the desired aldehyde.[9] Pivalic anhydride itself is inert under these conditions. Although this reaction protocol is excellent for industrial scale applications, the need for high-pressure equipment makes it rather inconvenient for small-scale laboratory applications.

We herein present a practical and simple process for the selective hydrogenation of carboxylic acids to aldehydes using cheap and easy-to-handle aqueous sodium hypophosphite solution as the reductant (Scheme 1).

In some initial experiments, we observed that in contrast to other reducing agents such as silanes, boranes, metal hydrides, or formates, hypophosphorous acid salts could selectively reduce carboxylic anhydrides into aldehydes in the presence of Pd–phosphine complexes. This was surprising since hypophosphites had been used to reduce aldehydes to alcohols in the presence of Pd/C or Raney nickel.[11] Intrigued by this observation, we studied the reduction of a mixture of benzoic acid **1a** and pivalic anhydride **2** in some detail, screening several Pd–phosphine complexes under various conditions in order to identify an efficient catalyst system (Scheme 1). Selected results are shown in Table 1.

In good accordance with the findings described above,[11] the desired selectivity for the aldehyde **3a** was achieved only with Pd–phosphine complexes as catalysts (Entries 1–3, 7). Whenever this catalyst decayed during the reaction and non-ligated palladium formed, the benzyl alcohol **5a** was produced in

significant quantities (Entry 2). The addition of a mild base was found to stabilize the palladium complexes and ensure a high selectivity for the aldehyde *versus* the alcohol. In this respect, potassium phosphate and sodium carbonate were most effective (Entries 3–7). Besides sodium hypophosphite, other hypophosphite salts can be used (Entries 8 and 9) but did not appear advantageous. When hypophosphorous acid itself was used as the reducing agent in the absence of a base, no product was formed (Entry 10).

Among all phosphines tested, the electron rich, sterically demanding cyclohexylphosphine gave the best results (Entries 11–16). Among the palladium precursors, palladium acetate was most effective (Entries 17–19).

The reaction proceeds best in THF as the solvent (Entries 7, 20–22) and the presence of water is beneficial (Entries 7, 23, 24). In the absence of water, the reaction is extremely slow, probably due to the insolubility of the reducing agent. If too much water is added, the hydrolysis of the anhydrides becomes most prevalent, thus lowering the yield. The reaction is not particularly sensitive towards oxygen; however, it is beneficial
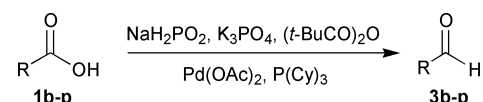
Table 1 Optimization of the reaction conditions

Entry	Catalyst	Base	Solvent	**3a** (%)	**5a** (%)
1	Pd(OAc)$_2$	—	THF	< 1	< 1
2	Pd(OAc)$_2$	K$_3$PO$_4$	THF	4	13
3	Pd(OAc)$_2$/P(Cy)$_3$	—	THF	< 1	< 1
4	Pd(OAc)$_2$/P(Cy)$_3$	Na$_2$CO$_3$	THF	82	3.4
5	Pd(OAc)$_2$/P(Cy)$_3$	K$_2$CO$_3$	THF	45	< 1
6	Pd(OAc)$_2$/P(Cy)$_3$	Et$_3$N	THF	< 1	< 1
7	Pd(OAc)$_2$/P(Cy)$_3$	K$_3$PO$_4$	THF	82	< 1
8^a	Pd(OAc)$_2$/P(Cy)$_3$	K$_3$PO$_4$	THF	36	< 1
9^b	Pd(OAc)$_2$/P(Cy)$_3$	K$_3$PO$_4$	THF	68	< 1
10^c	Pd(OAc)$_2$/P(Cy)$_3$	—	THF	< 1	< 1
11	Pd(OAc)$_2$/PPh$_3$	K$_3$PO$_4$	THF	10	< 1
12	Pd(OAc)$_2$/P(*o*-Tol)$_3$	K$_3$PO$_4$	THF	5	< 1
13	Pd(OAc)$_2$/P(*p*-MeOPh)$_3$	K$_3$PO$_4$	THF	19	< 1
14	Pd(OAc)$_2$/P(*t*-Bu)$_3$	K$_3$PO$_4$	THF	< 1	< 1
15	Pd(OAc)$_2$/BINAP	K$_3$PO$_4$	THF	< 1	< 1
16	Pd(OAc)$_2$/DPPF	K$_3$PO$_4$	THF	10	< 1
17	PdCl$_2$/P(Cy)$_3$	K$_3$PO$_4$	THF	< 1	< 1
18	Pd(acac)$_2$/P(Cy)$_3$	K$_3$PO$_4$	THF	16	7.5
19	(dba)$_3$Pd$_2$/P(Cy)$_3$	K$_3$PO$_4$	THF	28	< 1
20	Pd(OAc)$_2$ /P(Cy)$_3$	K$_3$PO$_4$	Toluene	20	3.0
21	Pd(OAc)$_2$ /P(Cy)$_3$	K$_3$PO$_4$	DMSO	< 1	< 1
22	Pd(OAc)$_2$ /P(Cy)$_3$	K$_3$PO$_4$	DME	34	< 1
23^d	Pd(OAc)$_2$/P(Cy)$_3$	K$_3$PO$_4$	THF	< 5	< 1
24^e	Pd(OAc)$_2$/P(Cy)$_3$	K$_3$PO$_4$	THF	42	< 1

Conditions: 1 mmol benzoic acid, 3 mol% Pd(OAc)$_2$, 7 mol% ligand, 1 equiv. base, 2.5 equiv. pivalic anhydride, 6 equiv. H$_2$O, 16 h, 60 °C, yields determined by GC;^{a} With KH$_2$PO$_2$; ^{b} With CaH$_4$P$_2$O$_4$; ^{c} With H$_3$PO$_2$; ^{d} Without H$_2$O; ^{e} With 30 equiv. H$_2$O.
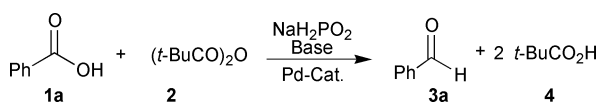
Scheme 1 Reduction of benzoic acid with sodium hypophosphite.

Scheme 2 Pd-catalyzed reduction of acids to aldehydes.

Product No.	Product structure	Yield (%)
3b	2-methylbenzaldehyde	70
3c	3-methylbenzaldehyde	73
3d	4-ethylbenzaldehyde	74
3e	3-acetoxybenzaldehyde	73
3f	3-cyanobenzaldehyde (NC)	53
3g	4-methoxybenzaldehyde	65
3h	4-acetamidobenzaldehyde	69
3i	3-phenylpropanal	72
3j	cinnamaldehyde (3-phenyl-2-propenal)	62
3k[a]	4-hydroxybenzaldehyde (HO)	68
3l	2-naphthaldehyde	70
3m	5-oxo-5-phenylpentanal	75
3n	undecanal (aliphatic aldehyde)	63
3o	methyl 9-oxononanoate	60
3p	cyclohexanecarbaldehyde	59

Conditions: 1 mmol substrate, 3 mol% Pd(OAc)$_2$, 7 mol% ligand, 1 equiv. base, 2.5 equiv. pivalic anhydride, 6 equiv. H$_2$O, 16 h, 60 °C; yields are isolated yields.[a] The crude product contained some pivaloyl ester, which cleaved during workup.

to purge the reaction mixture with argon and handle the products under argon to avoid re-oxidation of the aldehydes.

In order to investigate the scope and limitations of our new procedure, we applied it to a variety of different functionalized carboxylic acids (Scheme 2).†

As can be seen in Table 2, aliphatic, aromatic and unsaturated carboxylic acids are equally suitable substrates. The steric bulk of the substrate was also found to have little effect on the yields. Many functional groups are tolerated: carboxylic acids containing alkoxy, keto, cyano, protected amino groups and even hydroxy groups were successfully converted. No competing reduction of double bonds or of functional groups was observed.

In summary, the disclosed palladium-catalyzed transfer reduction of carboxylic acids with sodium hypophosphite represents a mild and general aldehyde synthesis. The simple reaction protocol which involves only air-stable chemicals, does not require high pressure equipment and does not call for dry solvents makes this reaction a valuable alternative to the existing protocols especially for applications in combinatorial chemistry and drug discovery.

Notes and references

† Synthesis of 4-acetamidobenzaldehyde (**3h**): A 100 mL flask was charged with 4-acetamidobenzoic acid (**1h**) (1.79 g, 10.0 mmol), potassium phosphate (2.12 g, 10.0 mmol) and sodium hypophosphite monohydrate (1.59 g, 15.0 mmol). The reaction vessel was purged with argon and degassed THF (50 mL) was added. Then, a solution of palladium acetate (67.3 mg, 0.30 mmol) and tri-cyclohexylphosphine (196 mg, 0.70 mmol) in THF (10 ml) and pivalic anhydride (4.65 g, 25 mmol) and finally water (1 mL) were added by syringe and the reaction mixture was stirred at 60 °C overnight. After removal of the volatiles *in vacuo*, the residue was filtered through silica gel using hexane–MTBE (MTBE = *tert*-butyl methyl ether) gradient as eluent. The compound was eluted with 50% MTBE in hexane. After removal of the volatiles and crystallization of the residue from hexane, 4-acetamidobenzaldehyde **3h** (1.14 g, 69 %) was obtained as colorless crystals. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C, TMS): δ = 9.98 (s, 1H), 7.85 (d, *J* (H,H) = 8 Hz, 2H), 7.70 (d, *J* (H,H) = 8 Hz, 2H), 2.23 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C, TMS): δ = 191.0, 168.7, 143.5, 132.2, 131.1, 119.2, 24.8 ppm; MS (70 eV): *m/z* (%): 163(63) [M$^+$], 146(4), 134(4), 120(100), 92(20); HRMS: calcd. for C$_9$H$_9$NO$_2$ [M$^+$]: 163.063328; found: 163.063352. The reactions in Table 1 and Table 2 were performed at least twice on 1 mmol scale using 0.05 mL tetradecane as an internal GC standard. The products were isolated by column chromatography (SiO$_2$, hexane–MTBE) and characterized by means of ^{1}H and ^{13}C NMR as well as by GC–MS and HRMS.

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