DOI: 10.1002/adsc.201000418

Low-Pressure Hydrogenation of Arenecarboxylic Acids to Aryl Aldehydes

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Received: May 28, 2010; Published online: September 7, 2010

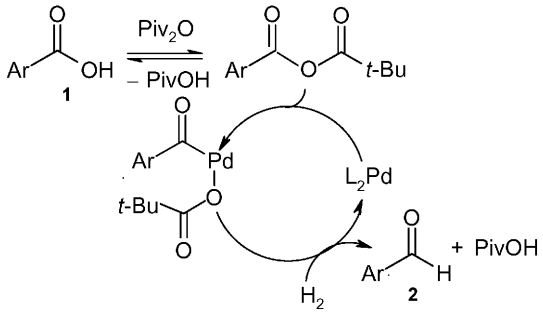
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000418.

Abstract: A highly effective palladium catalyst has been developed that allows the selective hydrogenation of arenecarboxylic acids to the aryl aldehydes in the presence of pivalic anhydride already at 5 bar hydrogen pressure. With the new catalyst, diversely functionalized aromatic and heteroaromatic aldehydes are conveniently accessible from the corresponding carboxylic acids in a single reaction step without any overreduction to the alcohols.

Keywords: aldehydes; carboxylic acids; catalysis; hydrogenation; palladium

The conversion of carboxylic acid derivatives into aldehydes is a frequently used transformation in organic synthesis.[1] It is usually performed using stoichiometric amounts of metal- or metal hydride-based reducing agents.[2,3,4] However, most protocols involve an additional reaction step for the preparation of activated carboxylic acid derivatives. Also, unwanted side reactions, such as the overreduction to alcohols and the reduction of other functional groups, are notoriously hard to suppress. The transition metal-catalyzed hydrogenation of acid chlorides (Rosenmund reduction)[5] is more atom-economic, but overreduction to the alcohols can be avoided only with elaborate flow-through reaction layouts, which are impractical for small-scale syntheses. This is why many chemists still prefer to first reduce the carboxylic acids all the way to the alcohols, and then to selectively reoxidize them to the aldehydes using Swern-type reactions.

A new concept for the direct reduction of carboxylic acids to aldehydes was introduced by Yamamoto et al.[6] In his single-step protocol the carboxylic acids are activated *in situ* by treatment with pivalic anhydride. The resulting equilibrium mixture of anhydrides undergoes a palladium-catalyzed hydrogenation to give the aldehydes along with pivalic acid (Scheme 1). The reaction mechanism involves an oxidative addition of the mixed anhydrides to the Pd(0) center.[7] The high steric demand of the *tert*-butyl group dictates the regiochemistry of this step, so that the acylpalladium(II) pivalate is almost exclusively formed. This complex reacts with molecular hydrogen to liberate the aldehyde along with pivalic acid.



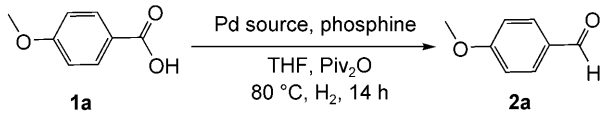
Scheme 1. Hydrogenation of arenecarboxylic acids.

In the original protocol, palladium complexes of PPh_3 and other triarylphosphines were employed as catalyst. However, they are only moderately active, so that high hydrogen pressures of at least 30 bar are necessary for good turnover. The Yamamoto aldehyde synthesis thus requires high-pressure equipment, which is unavailable in many preparative labs throughout industry and academia. This may be the main reason why this elegant transformation has so far found surprisingly little application in organic synthesis. The alternative use of hypophosphite salts as reducing agents is more practical for lab-scale applications, but waste-intensive and usually gives lower yields.[8]

There clearly remained a need for a new generation of more active Pd catalysts that would allow performance of the Yamamoto aldehyde synthesis below 10 bar hydrogen pressures which can be reached with laboratory-scale hydrogenation equipment and industrial-multi purpose reactors.

We began our search for a more active catalyst by studying the hydrogenation of 4-methoxybenzoic acid (**1a**) in the presence of pivalic anhydride and 1 mol% of various palladium catalysts in THF. The model system was chosen based on the fact that this electron-rich benzoic acid is of particularly low reactivity. Using Yamamoto's conditions [$Pd(OAc)_2$/PPh_3, 30 bar H_2], 4-methoxybenzaldehyde (**2a**) was formed only in low yield (Table 1, entry 1). At a reduced H_2 pressure of 15 bar, the activity of this catalyst was unsatisfactory. However, a systematic investigation of various phosphine ligands revealed that with a more electron-rich triarylphosphine, moderate yields are achieved even at this reduced pressure (entries 2 and 3). Sterically demanding, electron-rich trialkylphosphines such as PCy_3 and some of Buchwald's dicyclohexylbiarylphosphines gave even better results (entries 4–9). Full conversion of the carboxylic acid and high yields of the aldehyde were finally achieved with dicyclohexylphenylphosphine, a ligand seldom used in palladium catalysis (entry 10).

Table 1. Optimization of the catalyst system.[a]



Entry	Pd source	Phosphine	H_2 [bar]	**2a** [%]
1	$Pd(OAc)_2$	PPh_3	30	12
2	$Pd(OAc)_2$	P(*p*-MeOPh)$_3$	15	33
3	$Pd(OAc)_2$	P(*p*-tol)$_3$	15	52
4	$Pd(OAc)_2$	SPhos	15	57
5	$Pd(OAc)_2$	XPhos	15	70
6	$Pd(OAc)_2$	DavePhos	15	72
7	$Pd(OAc)_2$	JohnPhos	15	89
8	$Pd(OAc)_2$	PCy_3	15	90
9	$Pd(OAc)_2$	CyJohnPhos	15	93
10	$Pd(OAc)_2$	$PPhCy_2$	15	99
11	$Pd(OAc)_2$	$PPhCy_2$	5	89
12	$Pd(CN)_2$	$PPhCy_2$	5	0
13	$Pd(dba)_2$	$PPhCy_2$	5	64
14	$Pd(F_6\text{-acac})_2$	$PPhCy_2$	5	80
15	$Pd(TFA)_2$	$PPhCy_2$	5	80
16	$Pd(acac)_2$	$PPhCy_2$	5	91
17[b]	$Pd(acac)_2$	$PPhCy_2$	5	87
18[c]	$Pd(acac)_2$	$PPhCy_2$	5	92
19[d]	$Pd(acac)_2$	$PPhCy_2$	1	73

[a] *Reaction conditions:* 1.00 mmol **1a**, 3.00 mmol pivalic anhydride, 1 mol% Pd source, 5 mol% phosphine, 2 mL THF, 80 °C, 14 h. Yields determined by HPLC analysis using propiophenone as internal standard.

[b] 60 °C.

[c] Acetone as solvent.

[d] 3 mol% of $Pd(acac)_2$, 15 mol% of dicyclohexylphenylphosphine, DMF, 50 h.

With dicyclohexylphenylphosphine, the model reaction proceeded well even when reducing the hydrogen pressure to 5 bar. At this low pressure, several Pd precursors were tested (entries 12–16). The best yields were achieved with palladium acetylacetonate, but other Pd(II) salts or Pd(0) precursors can be used as well. A slightly lower conversion to **2a** was observed when reducing the reaction temperature to 60 °C (entry 17). Several other solvents were tested as a replacement for THF. We were pleased to find that not only DMF, but also non-toxic acetone (entry 18) and diethyl ketone were effective solvents. With toluene and acetonitrile, inferior results were obtained.

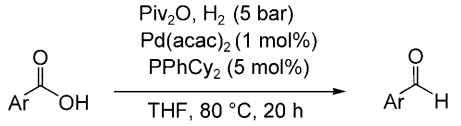
Under the optimal conditions, using 1 mol% of $Pd(acac)_2$, 5 mol% of dicyclohexylphenylphosphine, acetone (2 mL), pivalic anhydride (3 equiv.), 80 °C, 20 h, 4-methoxybenzoic acid was smoothly converted to the corresponding aldehyde in 92% yield at a hydrogen pressure of only 5 bar. In this screening, the catalyst and ligand, although expensive, were used in 1 and 5 mol% loadings, respectively, to ensure good conversion of a range of substrates. On these small scales, further reduction of the catalyst loading resulted in decreased yields.

The reactions can thus be carried out using a standard hydrogenation reactor, for example, a glass autoclave. Most industrial reactors are also certified for pressures of up to 5 bar. The new catalyst system is active even at ambient pressures: With an increased catalysts loading of 3 mol% and using DMF as a more high-boiling solvent, 73% yield was reached.

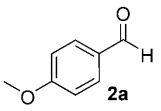
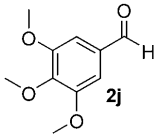
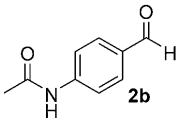
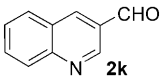
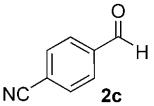
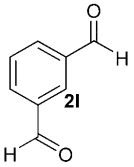
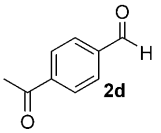
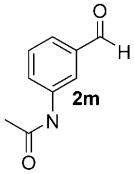
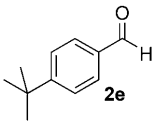
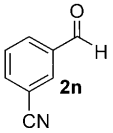
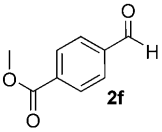
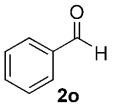
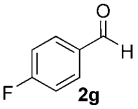
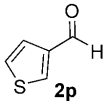
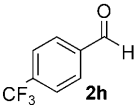
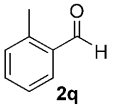
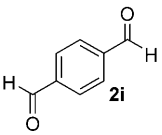
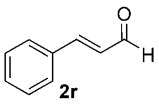
Having thus established a reliable low-pressure protocol for the Yamamoto aldehyde synthesis, we next tested its generality by applying it to the hydrogenation of various carboxylic acids. As can be seen from Table 2, the new catalyst allows the smooth conversion of aromatic and heteroaromatic carboxylic acids. In particular, *para*-, *meta*- and *ortho*-substituted benzoic acids reacted equally well. Five-ring heterocycles, quinolines and terephthalic acid were also hydrogenated in high yields. Many functional groups are tolerated: Carboxylic acids containing alkoxy, keto, cyano, protected amino, and even ester groups were successfully converted without competing reduction of double bonds or of functional groups.

In conclusion, the new catalyst system, generated *in situ* from $Pd(acac)_2$ and dicyclohexylphenylphosphine, allows the selective hydrogenation of arenecarboxylic acids to aryl aldehydes already at low hydrogen pressures. The new protocol is convenient for applications on both laboratory and industrial scales, and might convince organic chemists to add the Yamamoto aldehyde synthesis to their chemical toolbox.

Table 2. Hydrogenation of arenecarboxylic acids **1**.[a]



1a – r **2a – r**

Product	Yield [%]	Product	Yield [%]
 **2a**	91	 **2j**	89
 **2b**	91	 **2k**	74
 **2c**	75	 **2l**	42
 **2d**	92	 **2m**	92
 **2e**	80	 **2n**	75
 **2f**	80	 **2o**	79
 **2g**	80	 **2p**	70
 **2h**	80	 **2q**	88
 **2i**	85	 **2r**	81[b]

[a] *Reaction conditions:* 1.00 mmol of benzoic acid **1**, 1 mol% $Pd(acac)_2$, 5 mol% dicyclohexylphenylphosphine, pivalic anhydride (3 equiv.), THF (2 mL), 80 °C, H_2 (5 bar), 20 h.

[b] HPLC yields.

Experimental Section

General Procedure for the Synthesis and Characterization of the Aldehydes (1a–r)

An oven-dried, argon-flushed 10-mL glass vessel with septum top was charged with benzoic acid **1a–r** (1.00 mmol), $Pd(acac)_2$ (3.05 mg, 0.01 mmol), and dicyclohexylphenylphosphine (13.7 mg, 0.05 mmol). Degassed THF (2 mL) and degassed pivalic anhydride (0.62 mL, 3.00 mmol) were added. The vessel was placed in a steel autoclave, which was then purged with hydrogen and then pressurized with 5 bar of hydrogen. The reaction mixture was stirred at 80 °C for 20 h, then cooled to room temperature. The autoclave pressure was released, the reaction mixture diluted with 10 mL saturated $NaHCO_3$ solution and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with water and brine and dried over $MgSO_4$, filtered, and the volatiles were removed under vacuum. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane gradient) yielding the corresponding aldehydes.

The particularly volatile aldehydes **2a**, **e**, **g**, **h**, **o**, **p**, and **q** were isolated as bisulfite adducts: after releasing the pressue from the autoclaves, 38% sodium bisulfite solution (1.50 mL, 8.10 mmol) was added *via* syringe to the reaction vessel. The residue mixture was stirred at 50 °C for 4 h, then cooled to room temperature. The white crystalline adducts were filtered off and washed with chloroform (10 mL) and water (0.50 mL), dried under vacuum, and weighed to determine the yield. For the spectroscopic characterization, part of the aldehydes was then liberated by adding the adduct to saturated aqueous $NaHCO_3$ solution (2.0 mL), followed by extraction with $CDCL_3$ (2.0 mL). The NMR samples were then washed with water and brine, dried over $MgSO_4$ and filtered.

4-Methoxybenzaldehyde (2a): Compound **2a** was prepared from 4-methoxybenzoic acid (**1a**) (152 mg, 1.00 mmol) affording **2a** as a colorless oil; yield: 124.9 mg (90.8%). The spectroscopic data matched those reported in the literature for 4-methoxybenzaldehyde [CAS: 123-11-5].

4-Acetamidobenzaldehyde (2b): Compound **2b** was prepared from 4-acetamidobenzoic acid (**1b**) (179 mg, 1.00 mmol) affording **2b** as a colorless crystalline solid; yield: 149 mg (91%). The spectroscopic data (NMR) matched those reported in the literature for 4-acetamidobenzaldehyde [CAS: 122-85-0].

4-Cyanobenzaldehyde (2c): Compound **2c** was prepared from 4-cyanobenzoic acid (**1c**) (149 mg, 1.00 mmol) affording **2c** as a colorless crystalline solid; yield: 98.6 mg (75%). The spectroscopic data (NMR) matched those reported in the literature for 4-cyanobenzaldehyde [CAS: 105-07-7].

4-Acetylbenzaldehyde (2d): Compound **2d** was prepared from 4-acetylbenzoic acid (**1d**) (164 mg, 1.00 mmol) affording **2d** as a colorless crystalline solid; yield: 137 mg (92%). The spectroscopic data (NMR) matched those reported in the literature for 4-acetylbenzaldehyde [CAS: 3457-45-2].

4-*tert*-Butylbenzaldehyde (2e): Compound **2e** was prepared from 4-*tert*-butylbenzoic acid (**1e**) (180 mg, 1.00 mmol) affording **2e** as a colorless oil; yield: 123 mg (75.8%). The spectroscopic data (NMR) matched those reported in the literature for 4-*tert*-butylbenzaldehyde [CAS: 939-97-9].

4-Methoxycarbonylbenzaldehyde (2f): Compound **2f** was prepared from 4-methoxycarbonylbenzoic acid (**1f**) (180 mg, 1.00 mmol) affording **2f** as a colorless crystalline solid; yield: 132 mg (80%). The spectroscopic data (NMR) matched those reported in the literature for 4-methoxycarbonylbenzaldehyde [CAS: 1571-08-0].

4-Fluorobenzaldehyde (2g): Compound **2g** was prepared from 4-fluorobenzoic acid (**1g**) (143.0 mg, 1.00 mmol) affording **2g** as a colorless oil; yield: 90 mg (80%). The spectroscopic data (NMR) matched those reported in the literature for 4-fluorobenzaldehyde [CAS: 459-57-4].

4-(Trifluoromethyl)benzaldehyde (2h): Compound **2h** was prepared from 4-(trifluoromethyl)benzoic acid (**1h**) (190 mg, 1.00 mmol) affording **2h** as a colorless oil; yield: 139 mg (80%). The spectroscopic data (NMR) matched those reported in the literature for 4-(trifluoromethyl)benzaldehyde [CAS: 455-19-6].

1,4-Benzenedicarboxaldehyde (2i): Compound **2i** was prepared from 1,4-benzenedicarboxalic acid (**1i**) (166 mg, 1.00 mmol) affording **2i** as a colorless crystalline solid; yield: 114 mg (85%). The spectroscopic data (NMR) matched those reported in the literature for 1,4-benzenedicarboxaldehyde [CAS: 623-27-8].

3,4,5-Trimethoxybenzaldehyde (2j): Compound **2j** was prepared from 3,4,5-trimethoxybenzoic acid (**1j**) (212 mg, 1.00 mmol) affording **2j** as a colorless crystalline solid; yield: 174 mg (75.8%). The spectroscopic data (NMR) matched those reported in the literature for 3,4,5-trimethoxybenzaldehyde [CAS: 86-81-7].

3-Quinolinecarboxaldehyde (2k): Compound **2k** was prepared from 3-quinolinecarboxylic acid (**1k**) (177 mg, 1.00 mmol) affording **2k** as a colorless crystalline solid; yield: 102 mg (78%). The spectroscopic data (NMR) matched those reported in the literature for 3-quinolinecarboxaldehyde [CAS: 13669-42-6].

1,3-Benzenedicarboxaldehyde (2l): Compound **2l** was prepared from 1,3-benzenedicarboxylic acid (**1l**) (166 mg, 1.00 mmol) affording **2l** as colorless crystals; yield: 56.0 mg (42%). The spectroscopic data (NMR) matched those reported in the literature for 1,3-benzenedicarboxaldehyde [CAS: 626-19-7].

3-Acetamidobenzaldehyde (2m): Compound **2m** was prepared from 3-acetamidobenzoic acid (**1m**) (179 mg, 1.00 mmol) affording **2m** as a colorless crystalline solid; yield: 150 mg (92%). The spectroscopic data (NMR) matched those reported in the literature for 3-acetamidobenzaldehyde [CAS: 59755-25-8].

3-Cyanobenzaldehyde (2n): Compound **2n** was prepared from 3-cyanobenzoic acid (**1n**) (150 mg, 1.00 mmol) affording **2n** as colorless crystals; yield: 102 mg (78%). The spectroscopic data (NMR) matched those reported in the literature for 3-cyanobenzaldehyde [CAS: 24964-64-5].

Benzaldehyde (2o): Compound **2o** was prepared from benzoic acid (**1o**) (122 mg, 1.00 mmol) affording **2o** as colorless oil; yield: 84.0 mg (79%). The spectroscopic data (NMR) matched those reported in the literature for benzaldehyde [CAS: 100-52-7].

3-Thiophenecarboxaldehyde (2p): Compound **2p** was prepared from 3-thiophenecarboxylic acid (**1p**) (128 mg, 1.00 mmol) affording **2p** as a colorless oil; yield: 79.0 mg (70%). The spectroscopic data (NMR) matched those reported in the literature for 3-thiophenecarboxaldehyde [CAS: 498-62-4].

2-Methylbenzaldehyde (2q): Compound **2q** was prepared from 2-methylbenzoicacid (**1q**) (138 mg, 1.00 mmol) affording **2q** as a colorless oil; yield: 106.0 mg (88%). The spectroscopic data (NMR) matched those reported in the literature for 2-methylbenzaldehyde [CAS: 529-20-4].

(2*E*)-3-Phenylprop-2-enal (2r): Compound **2r** [CAS: 16939-04-1] was prepared from (*E*)-3-phenylprop-2-enoic acid (**1r**) (148 mg, 1.00 mmol). Unfortunately, the adduct formation did not take place. Therefore, the identity of the product **2r** was confirmed by GC-MS and the yield determined by quantative HPLC to be 81% based on a response factor obtained with commercial (2*E*)-3-phenylprop-2-enal (**2r**) [CAS: 104-55-2] using propiophenone (25 μL) as an internal HPLC standard.

Preparative-Scale Synthesis of 4-Acetamidobenzaldehyde: A 300-mL hydrogenation reactor was charged with 4-acetamidobenzoic acid (**1a**) (5.00 mmol, 896 mg), $Pd(acac)_2$ (15.2 mg, 0.05 mmol) and dicyclohexylphenylphosphine (72.2 mg, 0.25 mmol). THF (15.0 mL) and pivalic anhydride (3.0 mL, 15.0 mmol) were added *via* syringe. The autoclave was purged with hydrogen and then pressurized with 5 bar of hydrogen. The reaction was stirred at 80 °C for 20 h, then cooled to room temperature. The pressure was released, the reaction mixture diluted with saturated $NaHCO_3$ solution (25 mL) and extracted with ethyl acetate (3×25.0 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the volatiles were removed under vacuum. The residue was taken up in of diethyl ether (10 mL) causing the product 4-acetamidobenzaldehyde (**2b**) to precipitate in spectroscopically pure form; yield: 584 mg (71%).

Acknowledgements

We thank HEC Pakistan for a scholarship to B.A.K.

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