New Trends in Palladium-Catalyzed Transfer Hydrogenations Using Formic Acid

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Abstract: In the presence of a catalytic amount of organic bases, Pd-catalyzed transfer hydrogenations with formic acid were found to be facile processes. These new conditions produce innocuous carbon dioxide as the by-product compared to the use of ammonium formate, which generates ammonia and carbon dioxide as gaseous by-products which recombine to create unsafe conditions. When the substrate is basic enough to form salts with formic acid, no additional base is necessary. In certain cases, the product of the reaction was used to accelerate the transfer hydrogenation process.

Keywords: aminoarenes, benzyl deprotection, formic acid, hydrogen transfer hydrogenation, nitroarenes, palladium

With the advent of Gleevec® as a magic cancer bullet,[1] interest in heterocyclic aromatic amines as therapeutic agents exploded in the area of oncology. One of the key transformations in the synthesis of these active compounds is the reduction of a nitroarene to an aromatic amine. Several methods[2] have been reported for this transformation in the past, and of particular interest from our point of view are transfer hydrogenations catalyzed by palladium on carbon. In catalytic hydrogenations utilizing hydrogen gas it is necessary to pressurize a reactor with hydrogen gas thus restricting the operational freedom with respect to the reactor type. The use of ammonium formate as the hydrogen transfer agent relieved this restriction, and it enjoyed a wide application over the years. However, this method does have limitations, as the gaseous by-products (ammonia and carbon dioxide) released through the decomposition of ammonium formate recombine and deposit on cold surfaces of the reactor lines, thus creating an unsafe situation.

A recent report[3] by Gowda and co-workers on the use of formic acid alone with a catalytic amount of Pd/C instead of ammonium formate is an interesting alternative as it generates only carbon dioxide as a by-product. However, the reported reaction conditions are not practical due to its highly exothermic nature (30–50% wt of Pd/C and ~12 equivs. of formic acid). When the Pd/C catalyst loading was reduced to a more reasonable 1–10% by weight of the nitroarene substrate, and with 5 equivs. of formic acid, the hydrogenation failed to proceed to any significant extent. A more interesting report[4,5] in this context is the use of potassium formate as reported by Sasson and co-workers. Under these conditions, the only by-product that results is the potassium bicarbonate arising from the decomposition of potassium formate. These conditions are ideal in an overall sense but result in significant leaching of palladium into the product thus ruling it out as a practical method.

These results prompted us to re-evaluate the transfer hydrogenation procedures in a more fundamental sense. It became obvious that the base which is needed to generate the formate ion can be used in catalytic amounts as it is not consumed during the hydrogenation process. We verified this principle and obtained interesting results, which are the subject of this present communication.

Our initial investigations in this area started with the objective of finding an easily scalable method for the conversion of **1** to **2**. As mentioned earlier, nitroarene **1** on treatment with 12.2 equivs. of formic acid in the presence of 26 wt % Pd/C was converted to **2** within minutes (entry 1, Table 1). The reaction was highly exo-
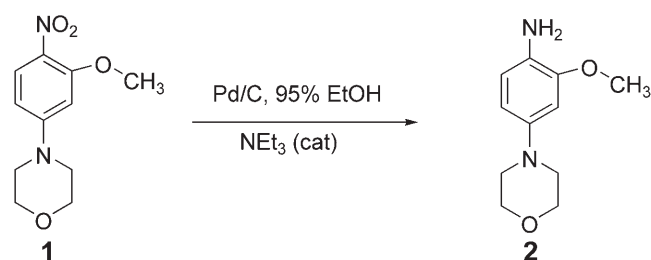
Table 1. Hydrogenation of **1**.

Entry #	Base [equivs.]	Pd/C [wt %]	HCOOH [equivs.]	Temp. [°C]	Time [h]	Conversion [%]
1		26	12.2	25	5 min	100
2		10	5	60	4	<5
3	HCO$_2$K (2.54)	10	0	70	6	80
4	HCO$_2$K (0.1)	20	5	60	3	85
5	NaHCO$_3$ (0.1)	20	5	70	2	85
6	Et$_3$N (0.1)	10	3.6	52	0.3	100
7	DIPEA (0.1)	10	3.6	52	1	100
8	Comp. **2** (0.1)	10	3.6	70	5	<5

Note: All reactions were carried out with 10% Pd/C containing 50% water.

thermic with the evolution of CO$_2$. Obviously these conditions were not practical for large-scale preparation.

Based on the principle that the base could be used in catalytic amounts, we screened several conditions, and the results are summarized in Table 1. The use of bases such as potassium formate and sodium bicarbonate in catalytic quantity, although effective, needed longer reaction times (entries 4 and 5). In contrast, all organic amines that were used in catalytic amounts were very effective, with 100% conversion in ≤1 h. Under the preferred conditions (entry 6), the reaction was conducted by treating ArNO$_2$ with 3.6 equivalents of formic acid and 10% Pd/C catalyst (50% water, 10% w/w loading) in 95% ethanol. After filtering the catalyst and switching the solvent to acetonitrile, the desired aniline was isolated as the dihydrochloride salt in high yield.

Potassium formate, which is an interesting alternative as a hydrogen source as it generates the non-gaseous by-product potassium bicarbonate, was also studied in great detail. Here the reduction was slow compared to the catalytic use of organic bases. In addition, the residual palladium level in the isolated product was high and unacceptable (Table 2).

The base-catalyzed transfer hydrogenations utilizing formic acid and Pd/C were found to be quite general, and even the sterically crowded 2,6-dimethylnitrobenzene was effectively reduced in quantitative yield to the corresponding aniline.

Nitro compound **3** possessing a much more basic piperazine function is an interesting example in the sense that no additional base may be necessary for the formate ion formation. Gratifyingly, with this substrate, hydrogenation proceeded smoothly with 10% Pd/C in ethanol

and a controlled addition of formic acid. At the end of the addition, the mixture was heated to 70 °C for 2 h, at which time HPLC analysis indicated that the reaction was complete. The product was isolated as the HCl salt **4** after filtering off the catalyst and adding concentrated HCl.
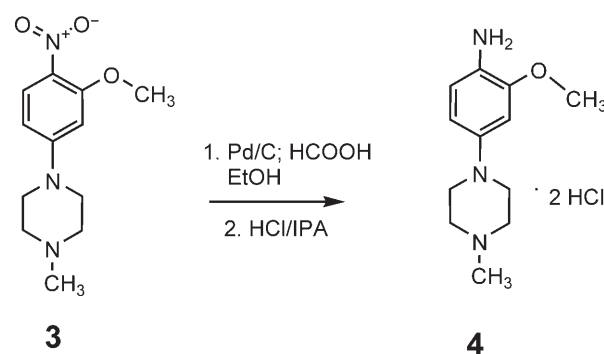

Another interesting aspect we pursued was the possibility of using the product as the catalyst for formic acid decomposition. Initially this principle was applied to the conversion of **1** to **2**. Here 0.1 equiv. of **2** was added to the hydrogenation medium (Table 1, entry 9), but the result was disappointing. However, with compound **6** we were more successful. Deprotection of the benzyloxycarbonyl group of **5** was described earlier[5] with ammonium formate and Pd/C. Liberation of gaseous by-products, i.e., ammonia and carbon dioxide which recombine to form solid deposits on cold surfaces, was a significant problem. Interestingly the catalytic use of the product as the base to generate the formate ion did accelerate the rate as was hoped (Table 3, entries 3 and 5) with quantitative deprotection of the benzyloxycarbonyl group. These conditions compared well with those using triethylamine as a catalyst (Table 3, entries 2 and 4).

In the conversion[6] of benzyl ester **7** to the free acid **8**, we found that 0.3 equivs. of triethylamine were needed for the quantitative conversion with 5 equivs. of HCOOH and 20 wt % Pd/C in absolute ethanol at 60 °C.

Table 2. Residual palladium in the product.

Base Used	Residual Palladium [ppm]	
	Compound **2**	Compound **2**·HCl salt
HCOOK	NA	1349
Et$_3$N	40	0.2
DIPEA	116	0.1

Table 3. Hydrogenation of **5**.
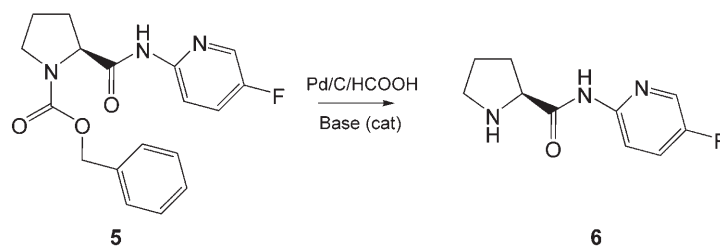
Entry #	Base [equivs.]	Pd/C [wt %]	Solvent	HCOOH [equivs.]	Temp. [°C]	Time [h]	Conversion [%]
1		10	95% EtOH	3.5	55	4	0
2	Et₃N (0.1)	10	95% EtOH	3.5	45	0.7	100
3	Comp. **6** (0.1)	10	95% EtOH	3.5	55	1	100
4	Et₃N (0.1)	10	1-Penatanol	3.5	45	1.7	83
5	Comp 6 (0.1)	10	1-Penatanol	3.5	55	1	100

Note: All reactions were carried out with 10% Pd/C, containing 50% water.
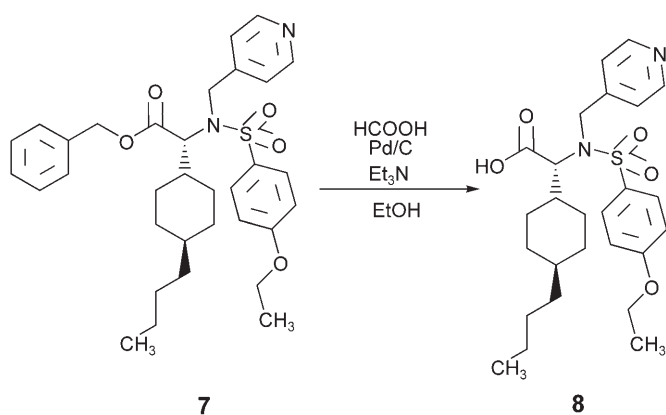
Didebenzylation of **9** typically took 20 h when ammonium formate was used (Table 4, entry 1). By using organic amines in catalytic amounts, the reaction time was reduced significantly (Table 4).

In summary, we have redefined the transfer hydrogenation conditions using formic acid. Ammonium formate is replaced by formic acid and a catalytic amount of an organic base such as triethylamine. When the substrate that needs to be reduced is basic enough to form salts with formic acid, no additional base is necessary. In certain cases, the product of the reaction was used to accelerate the transfer hydrogenation process.

Experimental Section

All chemicals were obtained from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded at 500 or 300 and at 125 and 75 MHz, respectively, in CDCl$_3$ unless otherwise mentioned. Proton and carbon

Table 4. Hydrogenation of **9**.
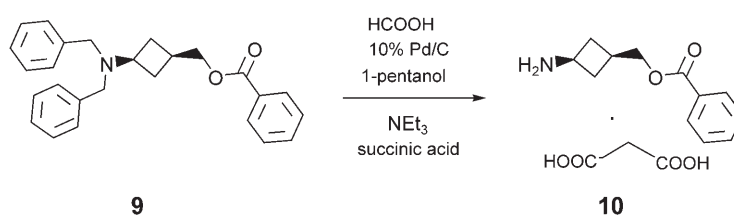
Entry #	Base [equivs.]	HCOOH [equivs.]	Time [h]	Conversion [%]
1	–	HCOONH₄ (5)	20	97
2	Et₃N (0.1)	5	2	99
3	1-Me-piperazine (0.1)	5	2	99
4	(*i*-Pr)₂NEt (0.1)	5	2	98
5	DABCO (0.1)	5	2	98

Note: All reactions were carried out in *n*-pentanol using a concentration of 0.6 M of substrate. The catalyst was 10% Pd/C containing 50% water, and the loading was 20% by weight. The temperature was 60 °C for all reactions.

chemical shifts are expressed in ppm relative to internal tetramethylsilane; coupling constants (J) are expressed in Hertz. Melting points were measured on a Büchi 535 melting point apparatus.

2-Methoxy-4-morpholinoaniline Dihydrochloride (2)

A 250-mL, round-bottomed flask was charged with 10% Pd/C (50% water, 1.77 g), **1** (8.86 g, 37.2 mmol), triethylamine (0.379 g, 3.75 mmol), and 95% ethanol (54.7 g). The resulting suspension was heated to $53 \pm 5\,^\circ$C and formic acid (6.25 g, 135.8 mmol) added slowly while maintaining the temperature at $53 \pm 5\,^\circ$C. The suspension was held at $53 \pm 5\,^\circ$C for 1 h after the addition. The reaction with was monitored by HPLC. After completion of the reaction, the mixture was cooled to $20 \pm 5\,^\circ$C, the suspension filtered through Celite, and the Celite washed with 95% ethanol. The filtrate was concentrated under vacuum at $50\,^\circ$C until the volume of the residue was about 27.9 mL. The suspension was cooled to $20 \pm 5\,^\circ$C and HCl (concentrated, 7.44 g) slowly added. The suspension to was heated $60\,^\circ$C and held at this temperature for 45 min. Then it was cooled to $20 \pm 5\,^\circ$C and acetonitrile (41.4 g) added. After stirring at this temperature for 1 h, the solids were filtered, and washed with acetonitrile (11.7 g). The solid was dried in the oven at $70\,^\circ$C for 16 h to give **2**; yield: 9.4 g (90%); mp $200\,^\circ$C (dec.). ^{1}H NMR (D$_2$O): $\delta = 3.63-3.66$ (m, 2H), 3.91 (s, 3H), 4.02–4.04 (m, 4H), 7.17 (d, $J = 8.64$ Hz, 1H), 7.24 (s, 1H), 7.48 (d, $J = 8.64$ Hz, 1H); ^{13}C NMR (D$_2$O): $\delta = 54.71$, 56.99, 64.68, 105.62, 113.27, 120.27, 125.66, 125.76, 143.60, 154.20; MS (M$^+$): $m/z = 208$; anal. calcd. for C$_{11}$H$_{18}$N$_2$Cl$_2$O$_2 \cdot$H$_2$O: C 44.16, H 6.74, N 9.36, Cl 23.70; found: C 43.98, H 6.54, N 9.32, Cl 23.50.

2-Methoxy-4-(4-methyl-1-piperazinyl)aniline Dihydrochloride (4)

A solution of **3** (9.80 g, 39 mmol) in absolute ethanol (60 mL) was added to 0.98 g of 10% Pd/C (50% water). To this mixture was added 96% formic acid (9.35 g, 195 mmol) dropwise over 30 min. The reaction mixture was then heated at $70\,^\circ$C for 2 h and allowed to cool to $20\,^\circ$C. The catalyst was removed by suction filtration through Celite, and the solids were washed with absolute ethanol (25 mL). The combined filtrate and wash was added to a mixture of 2-propanol/12 N HCl (120 mL/6.5 mL) dropwise. The resulting solution was treated with ethyl acetate (30 mL), and the suspension thus obtained was left at $4\,^\circ$C overnight. The solid was filtered with suction, washed with ethyl acetate (10 mL), and dried at $50\,^\circ$C under reduced pressure to give **4**; yield: 8.8 g (77%); mp $150-151\,^\circ$C;.

(2S)-2-{[[(5-Fluoro-2-pyridinyl)amino]carbonyl}-1-pyrrolidine (6)

A 100-mL, round-bottomed flask was charged with 10% Pd/C (50% water, 0.34 g), **5** (3.43 g, 10 mmol), triethylamine (0.14 mL, 0.99 mmol), and 95% ethanol (18 mL). The resulting suspension was heated to $53\,^\circ$C and formic acid (0.46 mL, 12.2 mmol) slowly added while maintaining the temperature at $53\,^\circ$C. The suspension was kept at $53\,^\circ$C for 1 h after the addition. The reaction was monitored with HPLC. After comple-

tion of the reaction, the mixture was cooled to $20\,^\circ$C, the suspension filtered through Celite, and the Celite washed with 95% ethanol. The filtrate was concentrated, treated with 2 N HCl (8 mL), and washed with TBME (25 mL). 6 N NaOH (3.6 mL) was added to the aqueous layer, the solids were collected and dried at $40\,^\circ$C for 16 h to give of the desired product; yield: 1.67 g (80%); mp $67-68\,^\circ$C. ^{1}H NMR (CDCl$_3$): $\delta = 1.72-1.81$ (m, 2H), 1.97–2.01 (m, 1H), 2.16–2.26 (m, 2H), 2.97–3.12 (m, 2H), 3.87–3.90 (m, 1H), 7.39–7.46 (m, 1H), 8.13 (s, 1H), 8.26–8.31 (m, 1H), 10.24 (br s, 1H); ^{13}C NMR(CDCl$_3$): $\delta = 26.61$, 31.21, 47.69, 61.26, 114.59, 114.65, 125.29, 125.55, 135.54, 135.88, 147.83, 147.86, 154.98, 158.31, 174.48; MS: $m/z = 210$ (M$+$H$^+$).

trans-(*R*)-{[*N*-(4-Ethoxyphenylsulfonyl)-*N*-(4-pyridinylmethyl)]amino}-4-propoxycyclohexaneacetic Acid (8)

The benzyl ester **7** (54.75 g, 94.3 mmol) was dissolved in absolute ethanol (1.1 L) at $40\,^\circ$C, allowed to cool to $30\,^\circ$C, and added to 10% Pd/C, (50% water, 11.0 g). Triethylamine (2.88 g, 28.5 mmol) was added followed by the dropwise addition of 96% formic acid (22.76 g, 471.5 mmol) over 5 min. The dark suspension was heated at $60\,^\circ$C for 1.5 h and filtered while hot through Celite. The filtrate was allowed to cool slowly to room temperature, and the resulting solid was filtered with suction, washed with absolute ethanol (100 mL), and dried at $50\,^\circ$C under reduced pressure to give **8** as a white solid; yield: 27.9 g (60%); mp $206-208\,^\circ$C. ^{1}H NMR (DMSO-d_6): $\delta = 12.91$ (br s, 1H), 8.48 and 7.37 (d of d, $J = 5.0$ Hz, 4H), 7.78 and 7.03 (d of d, $J = 10.0$ Hz, 4H), 4.62 (m, 2H), 4.10 (q, $J = 6.2$ Hz, 2H), 3.96 (d, $J = 11.2$ Hz, 1H), 3.25 (t, $J = 7.50$ Hz, 2H), 3.02 (m, 1H), 1.88 (m, 1H), 1.72 (m, 1H), 1.54 (m, 1H), 1.37 (m, 7H), 0.93 (m, 2H), 0.78 (t, $J = 7.50$ Hz, 3H), 0.75 (m, 1H), 0.52 (m, 1H); MS: $m/z = 491$ (M$^+$); anal. calcd. for C$_{25}$H$_{34}$N$_2$O$_6$S: C 61.20, H 6.98, N 5.71, S 6.54; found: C 61.19, H 6.92, N 5.69, S 6.48.

cis-3-Aminocyclobutanemethyl Benzoate Butanedioate (1:1 salt) (10)

The substrate **9** (free base) (18.4 g, 47.7 mmol) was dissolved in *n*-pentanol (87 mL) and added to 10% Pd/C (50% water, 4.03 g). Triethylamine (0.48 g, 4.77 mmol) was added followed by 96% formic acid (11.48 g) added dropwise. After the addition was complete, the reaction mixture was stirred at $60\,^\circ$C for 2 h. The catalyst was removed by filtration through Celite, and the solids were rinsed with *n*-pentanol (20 mL). The solution was washed with water (2×15 mL) and warmed to $50\,^\circ$C at which time an additional amount of water separated and was removed. Succinic acid (5.65 g, 47.8 mmol) was added and the mixture was heated at $95\,^\circ$C to dissolve the solids and then allowed to cool to room temperature over several hours. The solution was seeded, and heptane (90 mL) was added. After stirring for 18 h at room temperature, the solids were removed by filtration, washed with 1:1 *n*-pentanol and heptane (30 mL), and dried in a vacuum oven at $50\,^\circ$C/40 mbar to afford **10**; yield: 80%; mp $165-170\,^\circ$C. ^{1}H NMR (DMSO-d_6): $\delta = 9.8$ (br s, 4H), 7.95 (d, 2H), 7.60 (m, 3), 4.25 (d, 2H), 3.55 (m, 1H), 2.4 (m, 7H), 1.90 (m, 2H).

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