Highly Efficient Rhodium-Catalyzed Transfer Hydrogenation of Nitroarenes into Amines and Formanilides

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Abstract: An efficient and selective rhodium-catalyzed transfer hydrogenation of nitroarenes with formic acid as the hydrogen source to give amines or formanilides has been developed. The addition of iodide ion accelerates the reaction, which can take place at room temperature.

Key words: reduction, hydrogenation, nitroarenes, amines, amides, catalysis, rhodium

Aromatic amines are important intermediates for the synthesis of pharmaceuticals, dyes, and agrochemicals.[1] Among the various methods available for the preparation of aromatic amines, the reduction of nitroarenes is the most widely adopted method in laboratories and on an industrial scale. In industrial-scale production, heterogeneous catalytic hydrogenation of nitroarenes is the preferred route.[2] However, because the handling of hazardous hydrogen gas is not favored in laboratory operations, stoichiometric reduction systems, such as the Béchamp reduction or sulfide reduction, or stoichiometric reducing agents with metal catalysts[3] are commonly used in laboratory reduction of nitro groups. Although convenient, these stoichiometric systems are not environmentally benign, as the reducing agents used are often hazardous and expensive, and they frequently generate large amounts of waste. Transfer hydrogenation,[4] which employs cheap, safe, and easily accessible reducing agents such as isopropanol or formic acid as hydrogen sources, avoids the use of hydrogen gas and is more environmentally friendly than stoichiometric reductions. However, there are only a few examples of homogeneous transfer hydrogenation of nitroarenes.[5] Recently, Beller and coworkers reported that iron[5f] and molybdenum[5g] catalysts can be used as catalysts for the transfer hydrogenation of nitroarenes with formic acid as the hydrogen source. Despite this progress, the efficiency of homogeneous transfer hydrogenation of nitro groups needs to be improved, as most of the systems employ catalyst loadings of more than 1 mol%. Here, we describe a rhodium-catalyzed transfer hydrogenation of nitroarenes with formic acid to form amines or formanilides in a one-pot highly efficient reaction with substrate–catalyst (S/C) ratios of up to 1000.

We recently discovered that combining the simple dimeric precatalyst tetrachlorobis(η^5-pentamethylcyclopentadienyl)dirhodium ($[Cp^*RhCl_2]_2$) with iodide ion permits a highly efficient reduction of various heterocycles with an azeotropic formic acid–triethylamine mixture (2.5:1) as the hydrogen source.[6] To further test the power of this catalytic system, we attempted to use the system in the reduction of nitroarenes. We chose 4-nitroanisole as a model substrate. Treatment of this compound with 1 mol% of $[Cp^*RhCl_2]_2$ and a formic acid–triethylamine (2.5:1) mixture as both the solvent and hydrogen source at 40 °C for four hours did indeed give 4-methoxyaniline (**2a**), but only when potassium iodide was present. No reduction was observed in the absence of potassium iodide (Table 1, entries 1 and 2). Under the conditions used, the maximum activity was achieved by addition of one equivalent of potassium iodide (entries 2–5). By increasing the temperature to 100 °C and the extending the reaction time to 12 hours, full conversion was achieved. However, the major product that was isolated was the formanilide **3a** rather than 4-methoxyaniline (**2a**) (entry 6). The formanilide **3a** was probably formed by the reaction of formic acid with the amine **2a** generated in situ.[7] As formanilides are also important intermediates for various applications,[8] we further optimized the conditions for the formation of formanilide **3a**. When the catalyst loading was lowered to 0.1 mol%, substantial activity was still maintained, and formanilide **3a** was isolated in 35% yield after four hours (entry 7). Isoelectronic iridium and ruthenium complexes showed no activity or much lower activities under these conditions (entries 8 and 9). Studies on the effects of the solvent and the formic acid–triethylamine ratio revealed that a slightly higher yield of 48% could be obtained in dimethyl sulfoxide with 0.1 mol% of the catalyst (entry 10 and Supporting Information, Tables S1 and S2). Further optimization of the reaction conditions in dimethyl sulfoxide by varying the amount of formic acid and prolonging the reaction time (Supporting Information; Table S3) led to a satisfactory isolated yield of 89% of formanilide **3a** (Table 1, entry 12). To probe the role of potassium iodide, we synthesized tetraiodobis(η^5-pentamethylcyclopentadienyl)dirhodium ($[Cp^*RhI_2]_2$) and tested it under

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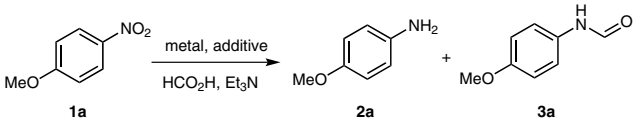
the optimal conditions without the addition of potassium iodide. A slightly lower yield of 30% was obtained, indicating that $[Cp^*RhI_2]_2$ might be the real catalyst in the reaction (entry 11). The addition of nitrogen or phosphine ligands decreased the rate of the reaction without affecting the selectivity (entries 13–16). These results suggest that the selectivity between the amine and formanilide products was unaffected by the catalyst, but was affected by the temperature. At 100 °C, formanilide was the major product (entries 6–16), whereas at lower temperatures, the amine product was obtained exclusively (entries 2–5).

The substrate scope for the N-formylation of various nitroarenes was examined with $[Cp^*RhCl_2]_2$ as catalyst (S/C = 1000) and formic acid–triethylamine (3:1) as the hydrogen source in dimethyl sulfoxide.[9] Substantial amounts of amines **2** were obtained from various substrates under the optimized conditions (Table 2); however, their formation could be suppressed simply by increasing the concentration of formic acid. When 20 equivalents of formic acid were used, the amine was completely converted into the corresponding formanilide (entries 3–14). Nitroarenes with electron-donating substituents in the position *para* to the nitro group generally showed better activity than those with electron-withdrawing substituents (entries 1–7). Isolated yields of over 80% were obtained with 4-methoxy- and 4-methyl-substituted substrates (entries 1 and 3, respectively). Halo groups were tolerated, except for iodide (entries 5–8, 10, and 12). 1-Iodo-4-nitrobenzene underwent dehalogenation to give the formanilide **3b** in moderate yield (entry 8). 1-Methylsulfanyl-4-nitrobenzene required 2 mol% of catalyst to obtain an acceptable yield, possibly because of the strongly coordinating nature of the sulfur atom (entry 9). Nitroarenes with *meta*-substituents reacted equally as well as their *para*-substituted analogues (entries 11 and 12). When a reducible carbonyl group was presented, the nitro group was selectively reduced and the carbonyl remained intact (entries 11, 17, and 18). However, substrates bearing

Table 1 Effects of Additives and Temperature on the N-Formylation of 4-Nitroanisole (**1a**)[a]



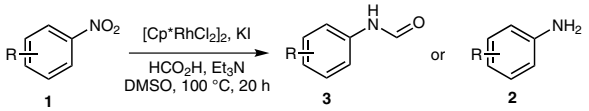
1a **2a** **3a**

Entry	Metal[b] (mol%)	Additive (equiv)	Ligand[c] (mol%)	HCO_2H (equiv)	Et_3N (equiv)	DMSO (mL)	Temp (°C)	Time (h)	Yield[d] (%) of **2a**	Yield[d] (%) of **3a**
1	[Rh] (1)	–	–	25	10	–	40	4	n.r.	
2	[Rh] (1)	KI (0.1)	–	25	10	–	40	4	5[e]	n.d.
3	[Rh] (1)	KI (0.5)	–	25	10	–	40	4	20[e]	n.d.
4	[Rh] (1)	KI (1)	–	25	10	–	40	4	28[e]	n.d.
5	[Rh] (1)	KI (3)	–	25	10	–	40	4	29[e]	n.d.
6	[Rh] (1)	KI (1)	–	25	10	–	100	12	n.d.	80
7	[Rh] (0.1)	KI (1)	–	25	10	–	100	4	3	35
8	[Ir] (0.1)	KI (1)	–	25	10	–	100	4	<1	n.r.
9	[Ru] (0.1)	KI (1)	–	25	10	–	100	4	<1	5
10	[Rh] (0.1)	KI (1)	–	15	5	2	100	4	4	48
11	[RhI] (0.1)	–	–	15	5	2	100	4	2	30
12	[Rh] (0.1)	KI (1)	–	15	5	2	100	20	<5	89
13	[Rh] (0.1)	KI (1)	bpy (0.2)	15	5	2	100	4	0	9
14	[Rh] (0.1)	KI (1)	Cy_3P (0.4)	15	5	2	100	4	0	9
15	[Rh] (0.1)	KI (1)	dppp (0.2)	15	5	2	100	4	0	10
16	[Rh] (0.1)	KI (1)	BINAP (0.2)	15	5	2	100	4	0	8

[a] Reaction conditions: 4-nitroanisole (**1a**; 1.6 mmol), metal catalyst, KI (if added), HCO_2H (40 mmol, 25 equiv), Et_3N (16 mmol, 10 equiv), ligand (if added), DMSO (if added), 4 h, under argon.
[b] [Rh] = $[Cp^*RhCl_2]_2$; [Ir] = $[Cp^*IrCl_2]_2$; [Ru] = $[Ru(p\text{-cymene})Cl_2]_2$; [RhI] = $[Cp^*RhI_2]_2$.
[c] dppp = $Ph_2P(CH_2)_3PPh_2$.
[d] Isolated yield; n.r. = no reaction; n.d. = not determined.
[e] Determined by HPLC.

ortho-substituents gave less than 50% conversions, even with 2 mol% of catalyst, possibly as a result of steric hindrance (entries 12 and 13). More notably, amines were obtained as products from several electron-deficient substrates, presumably as a result of the reluctance of the amine products to add to formic acid (entries 16–18). The strongly electron-withdrawing nitrile group also inhibited the reduction of the nitro group, but was not itself reduced (entry 16).

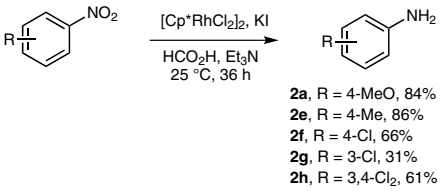
Table 2 N-Formylation of Nitroarenes[a]



Entry	R	Product	Catalyst (mol%)	Yield[b] (%)
1[c]	4-MeO	**3a**	0.1	89
2[c]	H	**3b**	0.1	69
3	4-Me	**3c**	0.1	82
4	4-*t*-Bu	**3d**	0.2	77
5	4-F	**3e**	0.2	76
6	4-Cl	**3f**	0.1	73
7	4-Br	**3g**	0.1	78
8	4-I	**3b**	0.1	68
9	4-MeS	**3h**	2	63
10	3-Cl	**3i**	0.1	86
11	3-Ac	**3j**	0.2	68
12	2-Cl	**3k**	2	38
13	2-MeO	**3l**	2	35
14	3,4-Cl_2	**3m**	0.1	89
15	3,4-$(MeO)_2$	**3n**	0.1	68
16	4-NC	**2b**	0.1	46
17	4-Ac	**2c**	0.2	68
18	2-Ac	**2d**	0.2	97

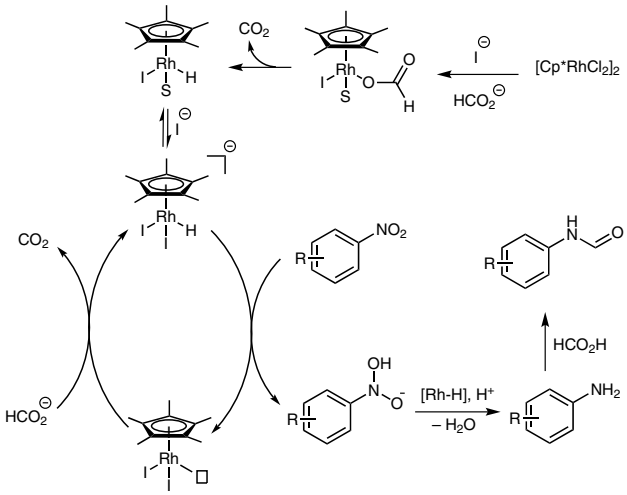
[a] Reaction conditions: substrate (1.6 mmol), $[Cp^*RhCl_2]_2$, KI (1.6 mmol), DMSO (2 mL), HCO_2H (32 mmol), Et_3N (10.7 mmol), 100 °C, 20 h, under argon.
[b] Isolated yield.
[c] HCO_2H (24 mmol) and Et_3N (9.6 mmol).

The reduction could be carried out at room temperature with a higher catalyst loading and a longer reaction time to give the corresponding amines **2** (Scheme 1). For example, reduction of 4-nitroanisole with 2 mol% of $[Cp^*RhCl_2]_2$ at 25 °C for 36 hours gave *p*-anisidine (**2a**) in 84% yield (Scheme 1).



Scheme 1 Transfer hydrogenation of 4-nitroanisole at room temperature. *Reagents and conditions*: 4-nitroanisole (0.5 mmol), $[Cp^*RhCl_2]_2$ (0.01mmol), KI (0.5 mmol), HCO_2H (12.5 mmol), Et_3N (12.5 mmol), 25 °C, 36 h.

A proposed mechanism is shown in Scheme 2. The potassium iodide additive might assist the formation of the anionic diiodo rhodium hydride, which is presumed to be the active catalyst for reduction. The stronger reducing ability of the diiodo rhodium hydride might stem from its anionic charge and the *trans*-effect of the iodide ligand.[6] The mechanism for the nitro reduction step requires further study. One possibility is direct transfer of the hydride to the nitro nitrogen atom by an ionic or outer-sphere mechanism, as in the reduction of ketones.[10]



Scheme 2 Proposed mechanism for N-formylation of nitro compounds by formic acid in the presence of the $[Cp^*RhCl_2]_2$–iodide system [S = solvent (DMSO)].

In conclusion, we have developed a simple and efficient protocol for chemoselective transfer hydrogenation of nitroarenes to amines or formanilides by using commercially available $[Cp^*RhCl_2]_2$ as the catalyst and formic acid as the hydrogen source. The addition of potassium iodide accelerated the transfer hydrogenation reaction, and the presence of a keto or halo group on the substrate was tolerated. At room temperature, the reduction gave the corresponding amines, providing a practical alternative method for the reduction of nitroarenes.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References

(1) (a) Downing, R. S.; Kunkeler, P. J.; van Bekkum, H. *Catal. Today* **1997**, *37*, 121. (b) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, **2001**.

(2) (a) Blaser, H. U. *Science* **2006**, *313*, 312. (b) Blaser, H. U.; Steiner, H.; Studer, M. *ChemCatChem* **2009**, *1*, 210. (c) Wang, X.; Liang, M.; Zhang, J.; Wang, Y. *Curr. Org. Chem.* **2007**, *11*, 299. (d) Chen, Y.; Qiu, J.; Wang, X.; Xiu, J. *J. Catal.* **2006**, *242*, 227. (e) Corma, A.; Serna, P. *Science* **2006**, *313*, 332. (f) Corma, A.; Serna, P.; Concepción, P.; Calvino, J. J. *J. Am. Chem. Soc.* **2008**, *130*, 8748. (g) Kantam, M. L.; Chakravarti, R.; Pal, U.; Sreedhar, B.; Bhargava, S. *Adv. Synth. Catal.* **2008**, *350*, 822. (h) Takasaki, M.; Motoyama, Y.; Higashi, K.; Yoon, S.-H.; Mochida, I.; Nagashima, H. *Org. Lett.* **2008**, *10*, 1601. (i) Corma, A.; González-Arellano, C.; Iglesias, M.; Sánchez, F. *Appl. Catal., A* **2009**, *356*, 99. (j) Fan, G. Y.; Zhang, L.; Fu, H. Y.; Yuan, M. L.; Li, R. X.; Chen, H.; Li, X. J. *Catal. Commun.* **2010**, *11*, 451.

(3) (a) Lauwiner, M.; Rys, P.; Wissmann, J. *Appl. Catal., A* **1998**, *172*, 141. (b) Rahaim, R. J.; Maleczka, R. E. *Org. Lett.* **2005**, *7*, 5087. (c) Junge, K.; Wendt, B.; Shaikh, N.; Beller, M. *Chem. Commun.* **2010**, *46*, 1769. (d) Sharma, U.; Kumar, P.; Kumar, N.; Kumar, V.; Singh, B. *Adv. Synth. Catal.* **2010**, *352*, 1834. (e) Kadam, H. K.; Tilve, S. G. *RSC Adv.* **2012**, *2*, 6057. (f) Layek, K.; Kantam, M. L.; Shirai, M.; Nishio-Hamane, D.; Sasaki, T.; Maheswaran, H. *Green Chem.* **2012**, *14*, 3164. (g) Luo, P.; Xu, K.; Zhang, R.; Huang, L.; Wang, J.; Xing, W.; Huang, J. *Catal. Sci. Technol.* **2012**, *2*, 301. (h) Kelly, S. M.; Lipshutz, B. H. *Org. Lett.* **2013**, *16*, 98. (i) Park, S.; Lee, I. S.; Park, J. *Org. Biomol. Chem.* **2013**, *11*, 395.

(4) (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (c) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045. (d) Wills, M.; Palmer, M.; Smith, A.; Kenny, J.; Walsgrove, T. *Molecules* **2000**, *5*, 4. (e) Everaere, K.; Mortreux, A.; Carpentier, J. F. *Adv. Synth. Catal.* **2003**, *345*, 67. (f) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2201. (g) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226. (h) Samec, J. S. M.; Backvall, J. E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237. (i) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300. (j) Wu, X.; Xiao, J. *Chem. Commun.* **2007**, 2449. (k) Wang, C.; Wu, X.; Xiao, J. *Chem. Asian J.* **2008**, *3*, 1750. (l) Wu, X. F.; Wang, C.; Xiao, J. L. *Platinum Met. Rev.* **2010**, *54*, 3.

(5) (a) Sharf, V. Z.; Freidlin, L. K.; Savchenko, B. M.; Krutii, V. N. *Russ. Chem. Bull.* **1979**, *28*, 1061. (b) Jagadeesh, R. V.; Wienhöfer, G.; Westerhaus, F. A.; Surkus, A.-E.; Junge, H.; Junge, K.; Beller, M. *Chem. Eur. J.* **2011**, *17*, 14375. (c) Imai, H.; Nishiguchi, T.; Fukuzumi, K. *Chem. Lett.* **1976**, *5*, 655. (d) Watanabe, Y.; Ohta, T.; Tsuji, Y.; Hiyoshi, T.; Tsuji, Y. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2440. (e) The Khai, B.; Arcelli, A. *J. Organomet. Chem.* **1986**, *309*, C63. (f) Wienhöfer, G.; Sorribes, I.; Boddien, A.; Westerhaus, F.; Junge, K.; Junge, H.; Llusar, R.; Beller, M. *J. Am. Chem. Soc.* **2011**, *133*, 12875. (g) Sorribes, I.; Wienhöfer, G.; Vicent, C.; Junge, K.; Llusar, R.; Beller, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 7794.

(6) Wu, J.; Wang, C.; Tang, W.; Pettman, A.; Xiao, J. *Chem. Eur. J.* **2012**, *18*, 9525.

(7) (a) Pratap, T. V.; Baskaran, S. *Tetrahedron Lett.* **2001**, *42*, 1983. (b) Kamal, A.; Srinivasa Reddy, K.; Rajendra Prasad, B.; Hari Babu, A.; Ramana, A. V. *Tetrahedron Lett.* **2004**, *45*, 6517. (c) Rahman, M.; Kundu, D.; Hajra, A.; Majee, A. *Tetrahedron Lett.* **2010**, *51*, 2896. (d) Lou, X. B.; He, L.; Qian, Y.; Liu, Y. M.; Cao, Y.; Fan, K. N. *Adv. Synth. Catal.* **2011**, *353*, 281.

(8) (a) Pettit, G.; Kalnins, M.; Liu, T.; Thomas, E.; Parent, K. *J. Org. Chem.* **1961**, *26*, 2563. (b) Kotachi, S.; Tsuji, Y.; Kondo, T.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 549. (c) Jackson, A.; Meth-Cohn, O. *J. Chem. Soc., Chem. Commun.* **1995**, 1319.

(9) **Arylformamides 3a–n; General Procedure**
Nitroarene **1** (1.6 mmol), KI (1.6 mmol), $[Cp^*RhCl_2]_2$ (0.0016 mmol), and a magnetic stirrer bar were placed in a carousel tube, and DMSO, HCO_2H (32 mmol), and Et_3N (10.7 mmol) were added by injection. The mixture was bubbled with argon for 15 min at r.t. then stirred under argon at 100 °C for 20 h. The mixture was cooled to r.t., basified with sat. aq NaOH, and extracted with CH_2Cl_2 (5 × 3 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (PE–EtOAc).

(10) Wei, Y. W.; Xue, D.; Lei, Q.; Wang, C.; Xiao, J. L. *Green Chem.* **2013**, *15*, 629.

