Transfer Catalysis Between Two Solids: Application to the Reduction of Nitroarenes**

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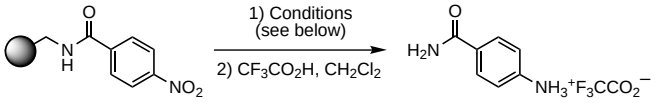
The need for new mild and selective methods for functional group transformations is a continuing driving force in synthetic organic chemistry. In addition, the rapidly growing field of combinatorial chemistry[1] has triggered a surge in the development of methods which are amenable to solid-supported synthesis.

As part of a larger effort directed towards the design and synthesis of novel peptidomimetics, we required methods for the mild and selective reduction of nitroarenes. By analogy to the description by Ohta et al.[2] of the ability of $CrCl_2$[3] to reduce nitroarenes in refluxing acidic methanol, we recently reported that $CrCl_2$ in dimethylformamide (DMF) can effect this reaction on the solid phase at room temperature.[4] However, the necessity of using a large excess of $CrCl_2$ (16 equiv) as a reducing agent is problematic with respect to preparative-scale reactions because of the cost and toxicity of the salt. The standard catalytic methods known for the solution-phase reduction of aromatic nitro compounds to anilines are hydrogenation reactions, which almost invariably employ a heterogeneous catalyst.[5] Such heterogeneous catalysts, while generally useful for solution-phase chemistry, are clearly inapplicable to solid-supported synthesis.[6] We sought a method that would be universally appropriate, and therefore began to explore methods under which our procedure could be rendered catalytic in chromium. Catalytic variants of the Nozaki–Hiyama–Kishi reaction involving the addition of organic halides to aldehydes[7] and the Takai–Utimoto reaction of acrolein acetals with aldehydes[8] have been reported.[9] These reactions make use of a redox couple between Cr^{II} and Mn^0, and employ trimethylsilyl chloride (TMSCl) as a proton surrogate. We now report the successful application and scope of the Cr^{II}/Mn^0/TMSCl system for the reduction of nitroarenes. As described below, this method is particularly advantageous when applied to solid-phase synthesis, since it involves a *homogeneous* reductant. However, it is also quite amenable to solution-phase synthesis.

Our experiments started with the attachment of a nitrobenzoic acid onto Rink amide resin under standard coupling conditions as reported previously.[4] As shown in Table 1, treatment of the resin-bound *p*-nitrobenzamide (**1**) with two equivalents of $CrCl_2$, 16 equivalents of Mn (up to 325 mesh powder), and 16 equivalents of TMSCl in DMF for 14 h at room temperature followed by trifluoroacetic acid mediated hydrolysis provided *p*-aminobenzamide as the trifluoroacetate salt (**2**, isolated in 70% yield, entry 3). Both Mn^0 and TMSCl are required for turnover of the chromium; leaving out either of these components prevents the reaction from occurring (entries 1 and 2). Substoichiometric quantities of $CrCl_2$ are equally successful, and we were able to run the reaction with as few as 0.25 equivalents of $CrCl_2$ without an increase in reaction time or diminishment of yield (entry 8). However, running the reaction with fewer than 0.25 equivalents of chromium results in lower conversion and longer reaction time (entries 9 and 10); since the solid-phase reactions were not run under anhydrous conditions, it is probable that turnover of the catalyst is reduced at longer reaction times because of hydrolysis of TMSCl. *N*-Methylpyrrolidone (NMP) is also a suitable solvent for this reaction (entry 11); however, the reduction does not proceed in THF or CH_2Cl_2.

Table 1. Catalytic reduction of solid-supported *p*-nitrobenzamide (**1**) and isolation of *p*-ammoniobenzamide trifluoroacetate (**2**).



1 **2**

Entry	$CrCl_2$ [equiv]	Mn^0 [equiv][a]	TMSCl [equiv]	Solvent	Time [h]	Yield [%]
1	2	16	0	DMF	14	0
2	2	0	16	DMF/THF	14	0
3	2	16	16	DMF	14	70
4	2	16	16	CH_2Cl_2	14	0
5	2	16	16	THF	14	0
6	1	16	16	DMF	14	77
7	0.5	16	16	DMF	14	74
8	0.25	16	16	DMF	14	75
9	0.1	16	16	DMF	24	60[b]
10	0.05	16	16	DMF	192	33[b]
11	0.25	16	16	NMP	14	78

[a] Mn powder (up to 325 mesh). [b] Indicates percent conversion as measured by ^1H NMR spectroscopy of the cleaved product, rather than the yield of isolated product.

As in the stoichiometric case, the catalytic reduction of solid-supported nitroarenes by Cr^{II} tolerates a wide range of substitution on the aromatic ring (Table 2). Halogens are unaffected by these conditions (entries 5 and 6). The moderate yields observed in each case are most likely the result of difficulties encountered in separating the product from Mn powder; we found that substitution of Mn chips (ca. $7 \times 7 \times 1\ mm^3$) provided **2** from **1** in much higher purity and yield (88%). Likewise, other nitroarenes are uniformly reduced in higher yield and purity when Mn chips are employed. The use of Mn chips is particularly attractive since it suggests that reusable "catalytic converter"-type reaction chambers for a variety of Cr^{II}-catalyzed processes may be constructed; studies along such lines are in progress in our laboratory.

Similarly, we found that the Cr^{II}/Mn^0 redox system readily reduced a variety of nitroarenes in solution (Table 3). As in the solid-supported case, the reaction is exquisitely selective for the nitro group, even in the presence of other readily reducible functionality. Unlike the solid-phase reaction, the

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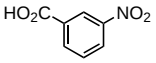
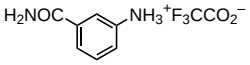
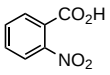
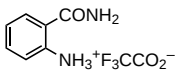
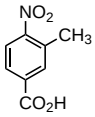
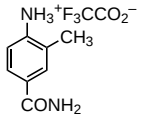
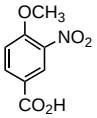
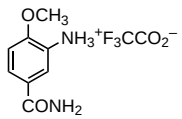
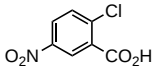
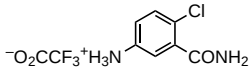
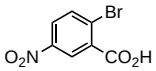
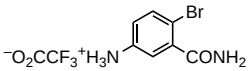
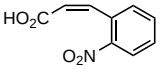
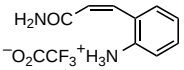
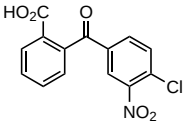
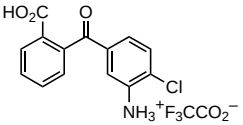
[**] We thank Professor Robert Boeckman for helpful discussions. This research was supported by a generous grant from the Eastman Kodak Company.

  1433-7851/99/3818-2777 $ 17.50+.50/0

Table 2. Catalytic reduction of nitrobenzoic and nitrocarboxylic acids to anilines on solid support.

Entry	Carboxylic acid	Product	Yield [%] method a[a]	Yield [%] method b[b]
1			60	
2			58	
3			72	84
4			67	
5			64	76
6			63	
7			n.d.[c]	86
8			n.d.[c]	82[d]

[a] Method a: Mn powder (up to 325 mesh, 16 equiv), TMSCl (16 equiv), $CrCl_2$ (0.25 equiv), DMF, 23 °C. [b] Method b: Mn chips (excess), TMSCl (16 equiv), $CrCl_2$ (0.25 equiv), DMF, 23 °C. [c] n.d. = not determined. [d] Wang resin (Advanced Chemtech).

reaction readily occurs in THF if Mn powder with up to 325 mesh is used.

In conclusion, a Cr^{II}/Mn^0 redox couple has been successfully applied for the first time to the reduction of aromatic nitro compounds to anilines. The reaction proceeds cleanly at room temperature on the solid phase, and tolerates a wide range of additional substitution on the aromatic ring. We presume that the reaction proceeds by a catalytic cycle analogous to those proposed by Fürstner et al. and Boeckman et al.;[9] efforts are underway to verify if this is indeed the case. As applied to the solid-phase reduction of nitroarenes, this methodology represents a rare example of the preparative use of transfer catalysis between two solid phases.[10]

Experimental Section

General: All starting materials were purchased from commercial sources and used as received. Rink amide resin (100 – 200 mesh copoly(styrene-1 % divinylbenzene)) was purchased from Novabiochem. TMSCl and solvents used for catalytic reaction were distilled over an appropriate drying agent prior to use. All solid-phase reactions were performed in a 2-mL Bio-Rad BioSpin polypropylene chromatography column equipped with a glass frit, and the mixtures were shaken on a Burrell wrist-action shaker.

Catalytic reduction of arylnitro compounds on Rink amide resin: Resin **1**, obtained as reported[2] from Rink amide resin (50 mg, 0.66 mmol g^{-1}), was thoroughly washed and dried. To this resin in dry DMF were added $CrCl_2$ (1 mg, 0.25 equiv) and manganese (29 mg, 16 equiv). TMSCl (57.2 mg, 16 equiv) was then added, and the reaction mixture was shaken overnight. The resin (which settles at the top of the manganese) was then carefully transferred to another polypropylene tube and thoroughly washed with DMF, MeOH, and CH_2Cl_2. The amine was cleaved from the resin by treatment with trifluoroacetic acid/CH_2Cl_2 (95/5). After draining off the resin was washed with CH_2Cl_2. The combined organic layers were collected and evaporated to give the desired compound **2** (6.2 mg, 75 %).

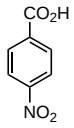
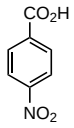
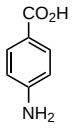
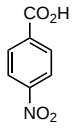
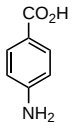
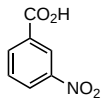
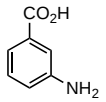
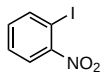
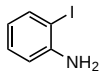
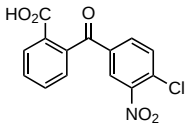
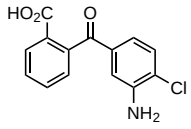
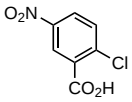
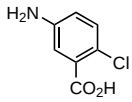
Catalytic reduction of arylnitro compounds in THF: To a mixture of 4-nitrobenzoic acid (42 mg, 0.25 mmol), manganese powder (220 mg, 4 mmol, 16 equiv), and $CrCl_2$ (1.5 mg, 0.0125 mmol, 0.05 equiv) stirring in THF at room temperature under N_2 was added TMSCl (0.25 mL, 2 mmol, 8 equiv). After 18 h the reaction mixture was filtered, and the solvent removed by rotary evaporation. Water (6 mL) was then added to the solid material remaining; after 3 h of stirring this mixture was filtered. The solid material remaining on the filter paper and the filtrate were extracted with ethyl acetate (5 × 10 mL). The combined extracts were dried over Na_2SO_4, filtered, and evaporated. The material remaining following evaporation of the solvent was purifed by chromatography on silica (elution with hexane/ethyl acetate 1/3) to provide 4-aminobenzoic acid (29 mg, 85 %).

Received: February 16, 1999
Revised version: May 27, 1999 [Z 13042 IE]
German version: *Angew. Chem.* **1999**, *111*, 2938 – 2941

Keywords: chromium · manganese · reductions · solid-phase synthesis

  1433-7851/99/3818-2778 $ 17.50+.50/0

Table 3. Catalytic solution-phase reduction of nitroarenes.[a]

Entry	Nitroarene	$CrCl_2$ [equiv]	Mn source (equiv)[b]	Product	Yield [%]
1		0.2	chips (excess)	n.r.[c]	0
2		0.2	powder (16)		83
3		0.05	powder (16)		85
4		0.2	powder (16)		80
5		0.2	powder (16)		55
6		0.2	powder (16)		70
7		0.2	powder (16)		73

[a] Entries 1–4 were conducted in THF, and employed eight equivalents of TMSCl. Entry 5 was carried out in DMF, and required treatment with tetrabutylammonium fluoride (TBAF) on workup. [b] Powder with up to 325 mesh. [c] n.r. = no reaction.

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