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Segregation of Separate Steps in Chromium-Catalyzed Reactions for Convenience and Mechanistic Analysis

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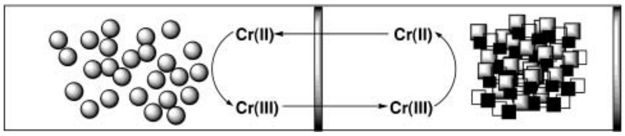
ABSTRACT



We have developed an apparatus for carrying out redox-coupled chromium–manganese or chromium–zinc reactions on solid-supported substrates which allows recycling of the stoichiometric reductant. In addition to providing a greatly simplified procedure for these reactions, we observe striking differences in the recyclability of Mn and Zn. A preliminary extension of the methodology to the catalytic coupling of allylchromium reagents with solid-supported aldehydes is also reported.

Nature has made full use of the advantages of compartmentalization in the construction of organismal biochemistry. By segregating various incompatible chemistries from one another, nature allows the acidic environment of the lysosome to coexist alongside other, less acidic cellular compartments, for example.

Solid-supported organic reactions are in a sense a compartmentalization strategy themselves, in which some combination of reagents, catalysts, and products are segregated by phase. The utility of *three-phase* systems in mechanistic analysis was recognized very early by Kautsky[1] and subsequently employed in a number of investigations by Rebek and co-workers.[2] Likewise, the ability of multipolymer systems to allow the use of otherwise incompatible reagents has been recognized.[3]

We recently disclosed[4] a method for the reduction of nitroarenes in solution or on a solid support which employs a Cr/Mn redox couple in a manner similar to that developed by Fürstner and co-workers[5] for the catalytic Nozaki−Hiyama−Kishi coupling[6] of allyl halides with aldehydes and used by Boeckman and Hudack[7] in the Takai−Utimoto reaction.[8] As a practical consideration, we found during the study that separation of the resin beads from unreacted manganese was not always a trivial process. Since our understanding of the mechanism of this reaction suggested that direct contact between the solid-supported substrate being reduced and the manganese surface was unnecessary, it occurred to us that we could accomplish several goals through the construction of an apparatus which would physically separate manganese from the resin. From a practical perspective, such a device would simplify purification of the resin and would potentially allow for recycling of the manganese. Ideally, one could simply keep cartridges of stoichiometric reductant on hand, reusing them as needed for reactions. Furthermore, it might also be possible to use other stoichiometric reductants which have proven difficult

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[1] (a) Kautsky, H.; Hirsch, A.; Flesch, W. *Chem. Ber.* **1935**, *68*, 152−162. (b) Kautsky, H. *Trans. Faraday Soc.* **1939**, *35*, 216−219.

[2] (a) Rebek, J., Jr.; Gaviña, F.; Navarro, C. *J. Am. Chem. Soc.* **1978**, *100*, 8113−8117. (b) Rebek, J., Jr. *Tetrahedron* **1979**, *35*, 723−731.

[3] Parlow, J. J. *Tetrahedron Lett.* **1995**, *36*, 1395−1396.

[4] Hari, A.; Miller, B. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2777−2779.

[5] (a) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349-12357. (b) Fürstner, A. *Chem. Eur. J.* **1998**, *4*, 567−570.

[6] (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179−3181. (b) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561−568. (c) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281−5284.

[7] Boeckman, R. K., Jr.; Hudack, R. A., Jr. *J. Org. Chem.* **1998**, *63*, 3524−3525.

[8] (a) Takai, K.; Nitta, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5263−5266. (b) Fujimura, O.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1990**, *55*, 1705−1706. (c) Takai, K.; Kataoka, Y.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 4389−4392.

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to employ under “normal” solution-phase conditions. Of more fundamental interest, we also were interested in the possibility of furthering our mechanistic understanding of the Cr/Mn redox couple through the spatial segregation of as many mechanistic steps as possible.

For the sake of simplicity, it was also important to us that we be able to construct our devices from readily available commercial materials. After examining several reactor designs based on standard polypropylene chromatography columns, we found that a Bio-Rad Poly-Prep chromatography column (0.8 to 1.5 × 9 cm), equipped with two porous polymer frits (as shown in Figure 1), allowed the successful chromium-catalyzed reduction of resin-supported nitroarene to anilines.

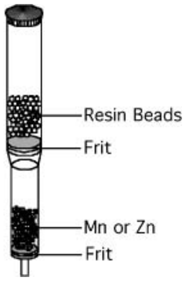
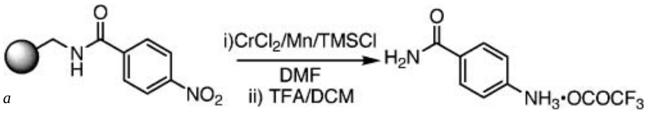


Figure 1. Recycling apparatus designs.

With an effective reactor design in hand, our next question was in regard to the recyclability of manganese used in the reaction. To explore this issue, we carried Mn through four to five cycles of reduction of resin-immobilized *p*-nitrobenzamide (Table 1).[9] Recyclability of the manganese was found to be strongly dependent on the particulate size of Mn employed in the reaction. Using Mn chips, the yield dropped steadily over four cycles. In contrast, Mn powder (−50 mesh) retained its ability to act as the stoichiometric reductant through three cycles and then lost essentially all activity. We were unable to examine whether this trend continued because of physical limitations of the device (i.e., −325 mesh powder passed through the frit).

Table 1. Recycling Mn in Apparatus “C”

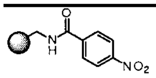
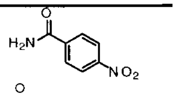
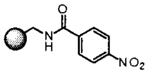
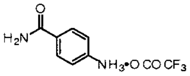
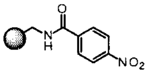
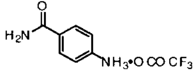
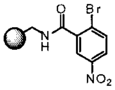
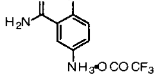
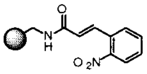
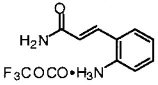


Mn chips		−50 mesh Mn powder	
cycle	yield (%)	cycle	yield (%)
1	88	1	90
2	82	2	88
3	72*	3	84
4	40*	4	15*
5	20*		

[a] An asterisk indicates conversion by NMR.

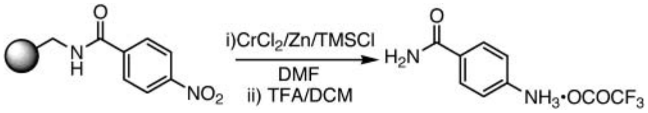
Given the success of this experimental setup in reducing nitroarenes cleanly, we became curious as to the possibility of employing other materials as stoichiometric reductants. For example, Fürstner and co-workers examined zinc as a potential reducing agent for chromium while developing their catalytic Nozaki−Hiyama−Kishi process, but found it problematic because of undesired side reactions (i.e., TMS-enol ether formation). Since our substrates are nonenolizable, we anticipated that zinc would be an effective stoichiometric reductant for the Cr-mediated catalytic reduction of nitroarenes. Indeed, yields using zinc as the stoichiometric reductant (Table 2) were at least as high as those employing manganese, and the recyclability of zinc was better (Table 3).[10] The superior ability of zinc to be recycled is most likely due to differences in solubility between zinc and manganese oxides in DMF. This is reflected qualitatively in the physical appearance of the metal surfaces following several cycles of reduction; manganese appears mottled or corroded, while zinc retains its metallic sheen.

Table 2. Applicability of Zn as a Stoichiometric Reductant in Cr-Mediated Nitroarene Reductions

Substrate	Cr equiv.	TMSCl equiv.	Product(a)
	0	16	
	0.25	2	 (15%)
	0.25	16	 (89%)
	0.25	16	 (72%)
	0.25	16	 (84%)

[a] Yield following TFA-mediated cleavage as described.

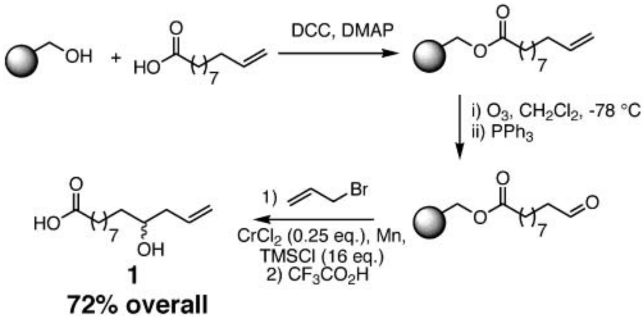
Table 3. Recycling Zinc



cycle	yield (%)
1	89
2	85
3	85
4	81

Our success with this reactor in the Cr-catalyzed reduction of nitroarenes led us to explore the possibility of also using it in solid-supported catalytic Nozaki−Hiyama−Kishi couplings. We prepared a Wang resin-bound aldehyde as shown in Scheme 1.

Scheme 1



Following coupling of 10-undecenoic acid to Wang resin under standard conditions, the resin was subjected to ozonolysis and reductive workup by analogy to a literature procedure[11] to provide a resin-bound aldehyde. Subsequent treatment of this aldehyde with allyl bromide, catalytic chromium chloride, and excess Mn and TMSCl[12] followed by cleavage with trifluoroacetic acid provided the expected product **1** in 72% overall yield from starting Wang resin.

In summary, we have presented a simple procedure for segregating and recycling the stoichiometric reductant (Mn or Zn) during chromium-catalyzed reductions of nitroarenes and resin-supported Nozaki−Hiyama−Kishi couplings. We anticipate that this procedure should be applicable to a variety of chromium-catalyzed reactions, and efforts to examine its scope are in progress in our laboratory.[13] In addition to improving the practicality with which these reactions may be carried out, the method of mechanistic segregation described herein extends the “three phase test” method of mechanistic analysis.

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(9) **Typical procedure for each cycle:** A reactor was loaded with 1.8 g (33 mmol) of manganese. After adding the second porous polymer frit at the center of the column, the resin-bound *p*-nitrobenzamide (50 mg, 0.033 mmol) was added, followed by dry DMF (5 mL), chromium chloride (1 mg, 0.008 mmol), and TMS-Cl (67 μL, 0.528 mmol). The reactor tube was then capped, and the mixture was shaken overnight at room temperature on a Burrell wrist-action shaker. The resin was then carefully transferred to another polypropylene tube and thoroughly washed with DMF, MeOH, and CH$_2$Cl$_2$. Product was cleaved from the resin and analyzed as described in ref 4. Prior to reusing the reactor in the next cycle, the manganese was washed with DMF and CH$_2$Cl$_2$.

(10) The procedure for the reduction employing Zn was essentially identical to the recycle test employing Mn; the reactor was charged with 2.1 g (33 mmol) of Zn prior to the first reduction cycle.

(11) Sylvain, C.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **1997**, *38*, 1043−1044.

(12) A reactor (Figure 1) containing 1.9 g (35 mmol) of Mn was prepared as described previously. The Wang resin-bound aldehyde (50 mg, initial resin loading 0.7 mmol/g) was introduced to the reactor, followed by dry DMF, chromium chloride (1 mg, 0.008 mmol, 0.25 equiv), and TMS-Cl (67 μL, 0.528 mmol, 16 equiv). Allyl bromide (16.9 mg, 0.132 mmol, 4 equiv) was then added, and the reaction was shaken overnight at room temperature on a Burrell wrist-action shaker. Cleavage of the product was as described previously.

(13) For reviews of applications of chromium in organic synthesis, see: (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991−1045. (b) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1−36. (c) Ho, T.-L. *Synthesis* **1979**, 1−20. (d) Hanson, J. R.; Premuzic, E. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 247−252.