



# Mild and selective reductions of aryl halides catalyzed by low-valent nickel complexes

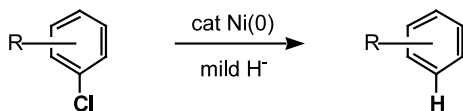
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**Abstract**—Treatment of aryl chlorides with catalytic amounts of  $(\text{PPh}_3)_2\text{NiCl}_2 + \text{PPh}_3$  in the presence of an equivalent of  $\text{Me}_2\text{NH}\cdot\text{BH}_3$  and either  $\text{K}_2\text{CO}_3$  or  $\text{Cs}_2\text{CO}_3$  in  $\text{CH}_3\text{CN}$  under mild conditions leads to the corresponding product of reduction. Aryl bromides and iodides can also be reduced, selectively, using this reagent combination. © 2001 Elsevier Science Ltd. All rights reserved.

For the past few years, there has been a considerable effort aimed at devising methods by which aryl chlorides can be effectively used as substrates in several palladium- and nickel-catalyzed displacement reactions.<sup>1</sup> While most are carried out under homogeneous conditions, alternatives involving both  $\text{Pd/C}$ <sup>2</sup> and more recently,  $\text{Ni/C}$ ,<sup>3</sup> offer benefits usually ascribed to heterogeneous catalysis.<sup>4</sup> While both  $\text{C}-\text{C}$ <sup>5</sup> and  $\text{C}-\text{N}$ <sup>6</sup> bond constructions have been documented under the influence of  $\text{Ni/C}$ , more recently this easily prepared and inexpensive catalyst has been found to mediate the corresponding reductions of aromatic  $\text{C}-\text{Cl}$  bonds when in the presence of an equivalent of  $\text{Me}_2\text{NH}\cdot\text{BH}_3/\text{K}_2\text{CO}_3$ .<sup>7</sup> Although highly effective in most situations, the process requires refluxing acetonitrile, temperatures at which certain valued functionalities such as ketones and olefins are unfortunately reduced competitively with that occurring at the  $\text{C}-\text{Cl}$  site. Moreover, for small scale experiments, it may be simpler to effect such reductions in solution, rather than first preparing  $\text{Ni(II)/C}$ .<sup>8</sup> We now report that by conducting these reactions using an in-situ derived nickel catalyst, conversion of aryl  $\text{C}-\text{Cl}$  bonds to the corresponding  $\text{C}-\text{H}$  derivatives can be accomplished under mild conditions without affecting most common functional groups. The method is also applicable to reductions of both aryl bromides and iodides.



**Keywords:** dehalogenation; nickel catalyst; aryl halides; amine-boranes.

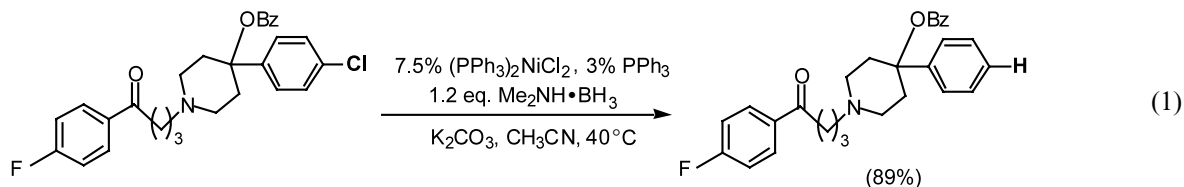
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A standard set of conditions was established which calls for 3 mole%  $(\text{Ph}_3\text{P})_2\text{NiCl}_2$  relative to substrate and an equal amount of  $\text{Ph}_3\text{P}$  (thus, 3 equiv. of  $\text{Ph}_3\text{P}$  per nickel), along with 1.1 equiv. of  $\text{Me}_2\text{NH}\cdot\text{BH}_3/\text{K}_2\text{CO}_3$  (1:1) in  $\text{CH}_3\text{CN}$ . The 10% excess amine borane–base combination was employed to provide sufficient reducing agent for the  $\text{Ni(II)}$  salt. Reactions were conducted at  $40^\circ\text{C}$  mainly to increase solubility of the reductant, which is limited at room temperature.<sup>9</sup> In those cases where preformed  $\text{Ni(0)}$  is needed so as to avoid, e.g. hydroboration of an isolated olefin,  $\text{Cs}_2\text{CO}_3$  was found to be the base of choice. Perhaps due to enhanced solubility, the cesiated amide borane is far faster at reducing the initially green  $\text{Ni(II)}$  to arrive at red solutions usually indicative of  $\text{Ni(0)}$ .  $\text{Cs}_2\text{CO}_3$  also prevents the occasionally observed (when using  $\text{K}_2\text{CO}_3$ ) formation of off-white–yellow complex  $\text{NiCl}_2\cdot(\text{CH}_3\text{CN})_2$ ,<sup>10</sup> which ties up nickel and prevents active catalyst formation. Upon addition of substrate, the mixture turns from red–orange to yellow and eventually dark as the reaction progresses. Attempts to replace  $\text{CH}_3\text{CN}$  with several alternative solvents, including THF, glyme, diglyme, DMF, and DMA, invariably led to inferior yields.

Table 1 illustrates a broad sampling of aryl chlorides, which are cleanly reduced using this methodology.<sup>11</sup> Most notably, aryl ketones (entry 6, and Eq. (1) below) are untouched, while the outcome with isolated double bonds (e.g. entry 4) may be dependent upon substitution pattern and surrounding functionality.<sup>12</sup> Dialkyl ketones, unfortunately, are slowly reduced at a rate competitive with that of aryl chlorides. Both activated (entries 1, 4) and electron-rich substrates (entry 2) participated with equal efficiency. Heteroaromatics (entries 3, 5–7) behaved similarly. Both free and pro-

tected amines did not complicate the reduction (entries 5 and 6, respectively). Acidic protons, such as in a secondary amide (entry 8) are of no consequence; in fact, use of 2% aqueous  $\text{CH}_3\text{CN}$  does not alter the reactions' outcome (entry 7). A free alcohol (entry 2),

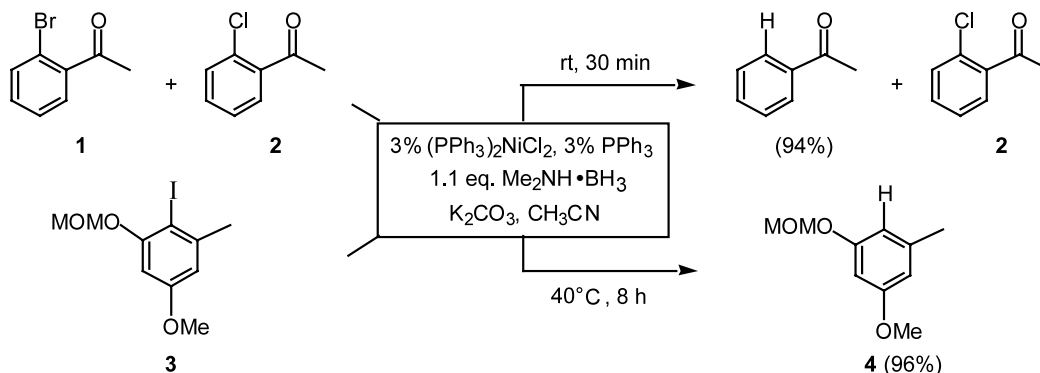
not surprisingly, therefore, does not require protection. Noteworthy is the clean reduction of the benzoate derivative of densely functionalized haloperidol (Eq. (1)),<sup>11</sup> further attesting to the functional group compatibility offered by this combination of reagents.



**Table 1.** Ni(0)-catalyzed reductions of aromatic and heteroaromatic chlorides

Aryl chloride $\xrightarrow[1.1 \text{ equiv. Me}_2\text{NH}\cdot\text{BH}_3, \text{ base, CH}_3\text{CN}]{3\% (\text{PPh}_3)_2\text{NiCl}_2, 3\% \text{PPh}_3}$ reduced aromatic <sup>15</sup>						
entry	aryl chloride	base	temp (°C)	time (h)	yield (%)	
1		R = CN $\text{K}_2\text{CO}_3$	40	18	quant <sup>a</sup>	
		R = CN $\text{Cs}_2\text{CO}_3$	40	12	quant <sup>a</sup>	
		R = $\text{CF}_3$ $\text{Cs}_2\text{CO}_3$	50	12	quant <sup>a</sup>	
2		R = $\text{CO}_2\text{Me}$ $\text{Cs}_2\text{CO}_3$	40	48	84 <sup>b,c</sup>	
		R = $\text{CH}_2\text{OH}$ $\text{Cs}_2\text{CO}_3$	40	32	88	
3		$\text{K}_2\text{CO}_3$	40	6	90	
4		$\text{Cs}_2\text{CO}_3$	50	6	87 <sup>b,d,e</sup>	
5		$\text{K}_2\text{CO}_3$	50	16	quant	
6		$\text{Cs}_2\text{CO}_3$	25	12	89 <sup>b</sup>	
7		$\text{K}_2\text{CO}_3$	40	8	92 <sup>f</sup>	
8		$\text{K}_2\text{CO}_3$	40	12	91 <sup>c</sup>	

<sup>a</sup> by GC. <sup>b</sup> Used 5%  $(\text{PPh}_3)_2\text{NiCl}_2$ , and 5%  $\text{PPh}_3$ . <sup>c</sup> 1.5 equiv  $\text{Me}_2\text{NH}\cdot\text{BH}_3$ /base. <sup>d</sup> Including <1% olefin reduced product (by GC & NMR). <sup>e</sup> Used pre-formed Ni(0).<sup>16</sup> <sup>f</sup> 96% yield in the presence of 2%  $\text{H}_2\text{O}$ .



**Scheme 1.** Competitive reduction of an aryl bromide versus aryl chloride, and reduction of an electron-rich iodide.

Based on the above results, it is perhaps not unexpected that an aryl bromide (e.g. **1**) rapidly reduced as well, even at room temperature, conditions under which the corresponding chloride (**2**) is unreactive (Scheme 1). Aryl iodides, which are commonly reduced using  $\text{Bu}_3\text{SnH}$  (AIBN, benzene,  $\Delta$ ),<sup>13</sup> are also prone toward reduction under these conditions, as illustrated by conversion of the highly electron-rich species **3** to **4** (Scheme 1).

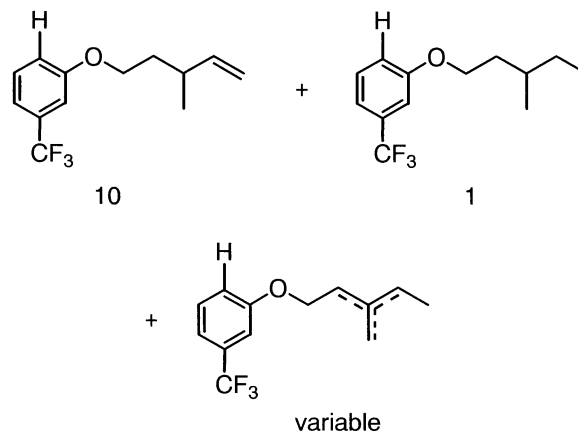
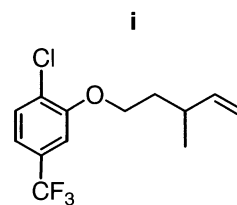
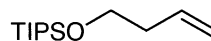
In summary, a mild and operationally simple method is described for reductions of aryl halides, in particular, relatively stable and inexpensive aryl chlorides.<sup>14</sup> Many functional groups are tolerated by the combination of reagents: catalytic  $\text{NiCl}_2(\text{Ph}_2\text{P})_2/\text{Ph}_3\text{P}+\text{Me}_2\text{NH}\cdot\text{BH}_3/\text{K}_2\text{CO}_3$  in  $\text{CH}_3\text{CN}$ . Both bromides and iodides are more readily and selectively reduced over the corresponding aryl chlorides under these conditions. Further applications of this nickel-catalyzed reductive chemistry (e.g. to protecting group chemistry) will be reported shortly.

### Acknowledgements

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### References

1. Sturmer, R. *Angew. Chem., Int. Ed.* **1999**, 38, 3307. For some representative recent examples, see: Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, 123, 2719; Bohm, V. P. W.; Weskamp, T.; Gstottmayr, C. W. K.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2000**, 39, 1602.
2. For one very recent report, see: Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2001**, 42, 429.
3. Lipshutz, B. H. *Adv. Synth. Catal.* **2001**, 343, 313.
4. Smith, G. V.; Notheisz, F. *Heterogeneous Catalysis in Organic Chemistry*; Academic Press: San Diego, 1999.
5. (a) Lipshutz, B. H.; Blomgren, P. A. *J. Am. Chem. Soc.* **1999**, 121, 5819; (b) Lipshutz, B. H.; Tomioka, T.; Blomgren, P. A.; Sclafani, J. *Inorg. Chim. Acta* **1999**, 296, 164; (c) Lipshutz, B. H.; Sclafani, J. A.; Blomgren, P. A. *Tetrahedron* **2000**, 56, 2139.
6. Lipshutz, B. H.; Ueda, H. *Angew. Chem., Int. Ed.* **2000**, 39, 4492.
7. Lipshutz, B. H.; Tomioka, T.; Sato, K. *Synlett* **2001**, 970.
8. Lipshutz, B. H.; Tasler, S. *Adv. Synth. Catal.* **2001**, 343, 327.
9. Nonetheless, at room temperature, the reduction may take place (cf. Table 1, entry 6). Using  $\text{Ni/C}$  for this substrate, which required refluxing  $\text{CH}_3\text{CN}$ , the corresponding carbinol was obtained.
10. Suzuki, H.; Ishiguro, S. *Bull. Chem. Soc. Jpn.* **1993**, 66, 83.
11. All products were compared spectroscopically with authentic samples, or if new, were fully characterized by IR, NMR, MS, and HRMS data.
12. Although a simple *mono*-substituted olefin (e.g. **i**) appears to be unresponsive to these reductive conditions, this course may be substrate-dependent. For example, we have observed the potential for both significant amounts of alkene hydrogenation as well as olefin isomerization, as in the case of **ii**.



13. Neumann, W. P. *Synthesis* **1987**, 665.
14. The following procedure is representative (Table 1, entry 3). Into a flame-dried 10 mL round-bottomed flask equipped with a stir bar and septum were added aryl chloride (293 mg, 1.0 mmol),  $(\text{PPh}_3)_2\text{NiCl}_2$  (20 mg, 0.03 mmol, 3 mol%),  $\text{PPh}_3$  (8 mg, 0.03 mmol), 98% borane–dimethylamine complex (66 mg, 1.1 mmol), and  $\text{K}_2\text{CO}_3$  (152 mg, 1.1 mmol) under argon. Dry, deoxygenated acetonitrile (2 mL) was added via syringe and the slurry was allowed to stir for 6 h at 40°C. Upon completion, the mixture was cooled to room temperature and filtered through Celite, the filter cake being further washed with ether. The solvents were then removed on a rotary evaporator. The crude material was purified by column chromatography on silica gel (4% diethyl ether in pet ether) to give 232 mg (90%) of the reduced product.
15. Products for all entries in Table 1 and Scheme 1 were either compared with known data in the literature, or if new, were fully characterized by IR, NMR,  $^{13}\text{C}$  NMR, MS, and HRMS data (below).
- Peridol derivative* (Eq. (1)):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.06 (d,  $J=6.8$  Hz, 2H), 8.01 (dd,  $J=8.8$  Hz, 1H), 7.58 (t,  $J=7.6$  Hz, 1H), 7.46 (t,  $J=7.6$  Hz, 2H), 7.39 (d,  $J=7.6$  Hz, 2H), 7.33 (t,  $J=7.6$  Hz, 2H), 7.28–7.24 (m, 2H), 7.13 (t,  $J=7.6$  Hz, 2H), 3.01 (t,  $J=7.0$  Hz, 2H), 2.94 (d,  $J=10.4$  Hz, 2H), 2.67 (d,  $J=12.8$  Hz, 2H), 2.53–2.40 (m, 4H), 2.13 (t,  $J=12$  Hz, 2H), 2.01 (p,  $J=7.0$  Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  198.51, 164.86, 133.77, 133.10, 131.35, 130.91, 130.81, 129.78, 128.67, 128.63, 127.60, 124.68, 115.94, 115.73, 81.17, 57.83, 49.59, 36.38, 35.80, 21.93. IR (neat) 2926, 2851, 2815, 1718, 1684, 1104. HRMS-ESI  $(\text{M}+\text{H})^+$  calcd for  $\text{C}_{28}\text{H}_{29}\text{NO}_3\text{F}$  446.2131, obsd 446.2148.
- Methyl 4-(2-methylphenoxy)butyrate*:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.17–7.13 (m, 2H), 6.89–6.80 (m, 2H), 4.02 (t,  $J=6.0$  Hz, 2H), 3.70 (s, 3H), 2.58 (t,  $J=7.4$  Hz, 2H), 2.23 (s, 3H), 2.19–2.12 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  173.69, 156.92, 130.66, 126.81, 126.73, 120.38, 110.80, 66.53, 51.60, 30.67, 24.78, 16.24. IR (neat) 1739, 1245. HRMS-ESI  $(\text{M}+\text{H})^+$  calcd for  $\text{C}_{12}\text{H}_{16}\text{O}_3$  208.10995, obsd 208.10995.
16. Premixing  $(\text{PPh}_3)_2\text{NiCl}_2$ ,  $\text{PPh}_3$ ,  $\text{Me}_2\text{NH}\cdot\text{BH}_3$ , and  $\text{Cs}_2\text{CO}_3$  in  $\text{CH}_3\text{CN}$  (ca. 0.5 M in stoichiometric reagents) is necessary to prevent olefin reduction. Usually ca. 2 h are needed for the mixture to turn to a red–brown solution, to which is added the substrate (neat).