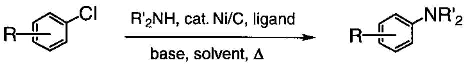
Aromatic Aminations by Heterogeneous Ni^0/C Catalysis**

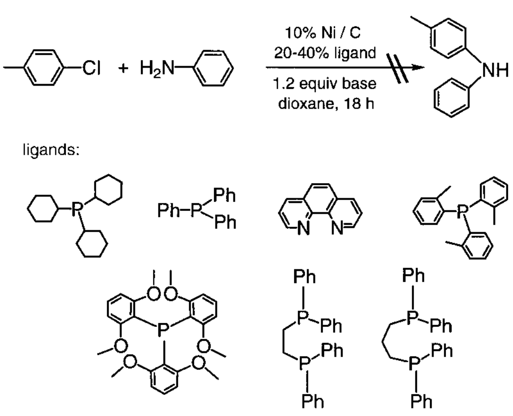
Bruce H. Lipshutz* and Hiroshi Ueda

Dedicated to Professor Harry H. Wasserman
on the occasion of his 80th birthday

Replacement of a leaving group on an aryl ring by nitrogen has been the focus of much research of late.[1] Most successful have been methods which rely on Pd^0 catalysis,[2] where a variety of primary and secondary amines can replace a bromide, iodide, or pseudo halide, including in some cases chlorides,[3] to afford the corresponding aniline compounds. Other approaches, which invoke Ni^0 catalysis[4] or titanium–nitrogen fixation,[5] are uniformly conducted under homogeneous conditions.[6] Given the importance of aryl amines in a variety of contexts (e.g., pharmaceuticals), a potentially scaleable *heterogeneous*[7] process which utilizes inexpensive precursor chlorides and nickel rather than palladium may provide a welcomed complement to existing protocols. Herein, we describe our initial work leading to an expedient method for effecting aminations of aryl chlorides using the heterogeneous catalyst[8] nickel-on-charcoal [Ni/C; Eq. (1)].



(1)



Scheme 1. Ligands shown to be unsuitable for displacement by amine.

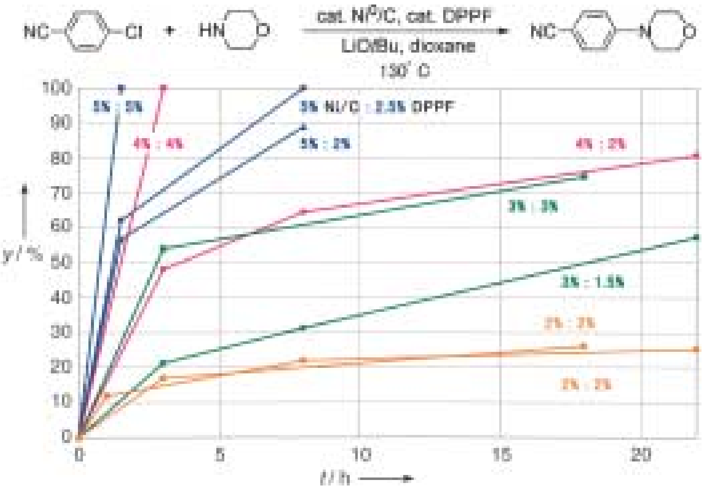
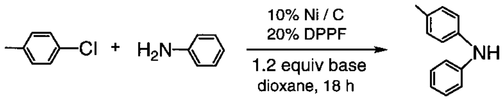
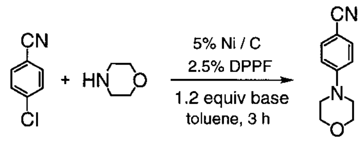


Figure 1. Reactivity of various % ratios of Ni/C:DPPF in aromatic amination reactions. $y(\%) = \%$ Conversion.

In our previous work carbon–carbon bond-forming reactions mediated by Ni/C (e.g., Negishi,[9a] Kumada,[9b] and Suzuki[9c] couplings) were usually best achieved in the presence of four equivalents of Ph_3P, relative to the percent loading of $Ni(NO_3)_2$ onto charcoal (ca. 5–10%). In the presence of Ph_3P, *n*BuLi (two equivalents relative to nickel) was introduced presumably generating the phosphane-ligated active Ni^0/C. However, this combination was not applicable to displacements by an amine (i.e., conversions were low or no reaction occurred), nor were alternatives based on a screening of several other phosphane ligands (Scheme 1). Eventually it was observed that not only did 1,1′-bis(diphenylphosphanyl)ferrocene (DPPF) lead to high yields of aminated aryl-ring products, but only one half of an equivalent (relative to nickel) of this bidentate ligand was necessary. In most cases, 5 mole% Ni/C was sufficient, which translated into the use of only 2.5% DPPF. While other ratios of Ni/C:DPPF could be employed (Figure 1), the 2:1 relationship was the best compromise. Either dioxane or toluene at reflux[10] appears to be suitable as solvent, whereas THF (with a lower boiling point) led to limited levels of educt consumption. Curiously, the base LiO*t*Bu consistently gave statistically significant greater rates of coupling and ultimately higher isolated yields than either the sodium[2a] or potassium analogues (Schemes 2 and 3). Other bases (e.g., Cs_2CO_3) were ineffective. The monodentate ligand **1**,[11] examined in place of DPPF,[12] was ineffective at the 2.5% or 10% level versus substrate (3% and 24% conversion, respectively).



Scheme 2. Base: LiO*t*Bu (93% conversion); NaO*t*Bu (84% conversion); KO*t*Bu (0% conversion).



Scheme 3. Base: LiO*t*Bu (100% conversion); NaO*t*Bu (19% conversion); KO*t*Bu (18% conversion).

With LiO*t*Bu (1.2 equiv)[13] and the amine (2 equiv) in the presence of Ni/C, various aryl chlorides could be smoothly converted to their aniline derivatives (Table 1). The aryl chlorides

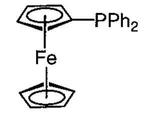


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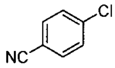
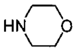
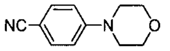
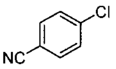
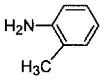
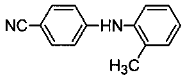
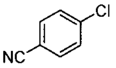
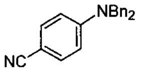
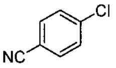
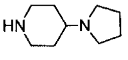
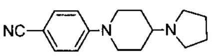
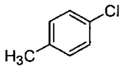
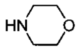
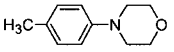
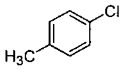
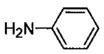
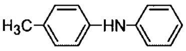
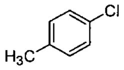
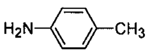
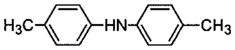
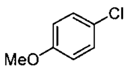
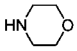
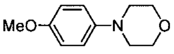
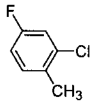
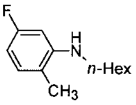
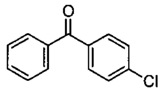
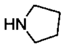
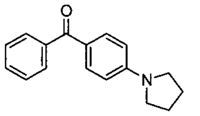
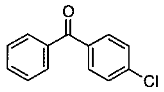
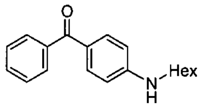
Table 1. Ni/C-catalyzed aminations of aryl chlorides.

Entry	Halide	Amine	Product[a]	Ni/DPPF loading [mol %]	Solvent[b]	Time [h]	Yield [%][c]
1				5/10 5/2.5 5/2.5	dioxane dioxane toluene	5 4.5 2.5	91 87 88
2				10/20	dioxane	6	78
3		Bn_2NH		5/2.5	toluene	7	79
4				5/2.5	toluene	3.5	92
5				10/20	dioxane	47	91
6				5/10	dioxane	20	93
7				10/20	dioxane	24	90
8				5/5	toluene	52	70
9		n-HexNH$_2$		5/2.5	toluene	46	76
10				5/2.5	toluene	16	87
11		n-HexNH$_2$		5/5	toluene	15	69

[a] Fully characterized by IR, NMR, and MS data. [b] Oil bath temperature was maintained at 130 °C. [c] Isolated, chromatographically pure material. Bn = benzyl, Hex = hexyl.

which reacted favorably range from the electron-poor to the electron-rich, and include a test case for steric effects of *ortho* substitution (entry 9). Several anilines could be used as nucleophiles, including an *ortho*-methylated example (entry 2). Pyrrolidyl (entry 10), morpholinyl (entries 1, 5 and 8), and a piperidinyl system (entry 4) all participated, as did primary (entries 9 and 11) and secondary amines (e.g., dibenzylamine, entry 3). No aryl amination reactions were noted with hexamethyldisilazane, imidazole, 13-aza-[15]crown-5,[14] and the sta base.[15]

In summary, a novel method for effecting aromatic aminations using aryl chlorides under heterogeneous conditions[16] is presented. Reliance on the combination of a Ni^{II} salt[17] supported on activated charcoal may be viewed as an experimentally appealing and economical alternative to existing protocols, in particular to those which utilize Pd^0 under homogeneous conditions.

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Herrmann, *Tetrahedron Lett.* **1997**, *38*, 2073–2074; f) N. P. Reddy, M. Tanaka, *Tetrahedron Lett.* **1997**, *38*, 4807–4810.

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[6] For aromatic aminations a) in the absence of solvent, see: L. Schio, G. Lemoine, M. Klich, *Synlett* **1999**, 1559–1562; b) under high pressure, see: H. Kotski, H. Sakai, T. Shinohara, *Synlett* **2000**, 116–118; c) by nucleophilic substitution, see: A. J. Belfield, G. R. Brown, A. J. Foubister, P. D. Ratcliffe, *Tetrahedron* **1999**, *55*, 13285–13300.

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[10] It was important to maintain a strong reflux, which was accomplished by setting the oil bath temperature to 130°C.

[11] D. Guillaneux, H. B. Kagan, *J. Org. Chem.* **1995**, *60*, 2502–2505.

[12] A similar observation has been made in the case of 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (BINAP) and its monodentate analogue.[2a] By contrast, in refluxing dioxane (5% Ni/C, LiO*t*Bu, 18 h), use of 2.5% DPPF led to 95% conversion.

[13] M. Prashad, B. Hu, Y. Lu, R. Draper, D. Har, O. Repic, T. J. Blacklock, *J. Org. Chem.* **2000**, *65*, 2612–2614.

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[16] Representative procedure for the amination of aryl chlorides (Table 1, entry 1): Ni^{II}/C (50.5 mg, 0.038 mmol, 0.74 mmol g^{-1}), DPPF (10.7 mg, 0.019 mmol), and lithium *tert*-butoxide (74.3 mg, 0.90 mmol) were added to a flame-dried 5 mL round-bottomed flask under a blanket of argon at room temperature. Dry toluene (0.5 mL) was added by syringe and the slurry allowed to stir for 90 min. *n*-Butyllithium (31 μL, 2.42 M in hexanes, 0.075 mmol) was added dropwise with swirling. After 30 min, 4-chlorobenzonitrile (104.2 mg, 0.75 mmol), which was dissolved in dry toluene (0.5 mL), and morpholine (132 μL, 1.50 mmol) were added, followed by heating to reflux for 2.5 h (the oil bath temperature was set to 130°C). After cooling to room temperature, the crude reaction mixture was then filtered through a glass filter and the filter cake further washed with methanol and dichloromethane. The filtrate was collected, solvents were removed on a rotary evaporator and the crude product was then purified by flash chromatography with cyclohexane/EtOH (7/3) to give 123.8 mg (0.66 mmol; 88%) *N*-(4-cyanophenyl)-morpholine as a pale yellow solid.[4c]

[17] The extent of nickel bleed from the charcoal was quantitatively assessed to be 2.3–2.9% of the 5% Ni/C (i.e., 0.15% relative to substrate) using inductively coupled plasma (ICP) atomic emission spectrometry. For an overview of this technique, see: *Inductively Coupled Plasma Mass Spectrometry* (Ed.: A. Montaser), Wiley-VCH, New York, **1998**.

Application of a Spin-Labeled Spin-Trap to the Detection of Nitric Oxide (NO)**

Lucien Marx and André Rassat*

When a dilute monoradical reacts to give diamagnetic products, its EPR signal decays without major changes, while when a diradical is transformed into a monoradical, a new EPR spectrum is generally observed. In the case of a diradical with strong dipolar interaction,[1] the single broad line is replaced by three narrow lines, and there is a very large increase of the monoradical signal. A narrow-line monoradical in very low concentration and a broad-line diradical in much higher concentration display peaks of similar height,[2] as shown in Figure 1 where the EPR spectra of synthetic mixtures of tempone (2,2,6,6-tetramethyl-4-oxo-1-oxypiperidine (radical); line width $\Delta H = 0.18$ mT) and of diradical **1**[3] ($\Delta H = 4.2$ mT) are presented: even when the monoradical constitutes only 0.1% of the total paramagnetic species, its signal can be detected.

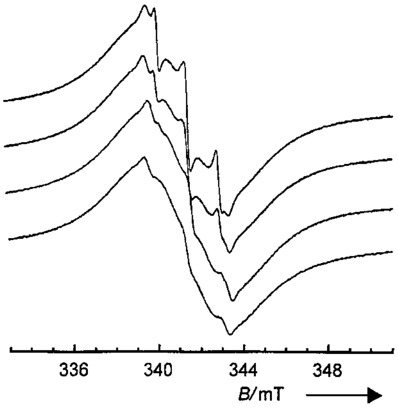

Figure 1. EPR spectra of ethanol solutions of synthetic mixtures containing (from top to bottom) 0, 0.1, 0.5, and 1 mole% of tempone relative to 10^{-3} M diradical **1**.

This suggests a new use of diradicals as *spin-labeled spin-traps*. These reagents would combine a stable radical (R_T), designed to trap selectively the radical to be detected and to yield diamagnetic products, and another radical (R_L), unreactive during this reaction, at a distance such that the diradical EPR spectrum would be a single line.[4] In this way, as R_T reacts, the signal of the R_L moiety would be detected at the very beginning of the reaction, with both the concentration of spin trap and of spin adduct being monitored on the same spectrum. Furthermore, the rate of the trapping reaction (usually bimolecular) could easily be increased by increasing the biradical concentration.

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