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An Ammonia Equivalent for the Palladium-Catalyzed Amination of Aryl Halides and Triflates

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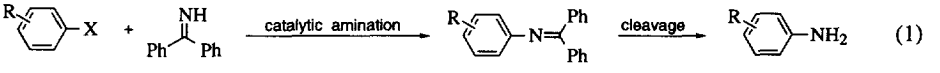
Abstract. Commercially available benzophenone imine serves as a convenient ammonia equivalent in the palladium-catalyzed amination of aryl halides and triflates. The benzophenone imine adducts can be cleaved directly to the corresponding primary anilines by catalytic hydrogenation or treatment with hydroxylamine hydrochloride or a catalytic amount of HCl in wet THF. © 1997 Elsevier Science Ltd.

A number of useful protocols for the palladium- and nickel-catalyzed conversion of aryl bromides,[1a, b] chlorides,[1c] iodides[1d] and triflates[1e, f] to the corresponding aniline derivatives have been recently reported. While these procedures are effective for the preparation of substituted anilines, no simple means for the preparation of the unsubstituted primary anilines has been described. We now have found that commercially available benzophenone imine serves as a convenient surrogate for ammonia in these coupling procedures (Eq 1). The benzophenone imines formed can be isolated in pure form or can be converted under a variety of conditions to the corresponding anilines in a straightforward manner.[2]

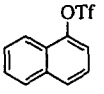
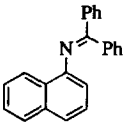
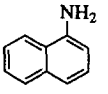
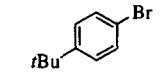
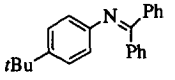
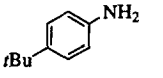
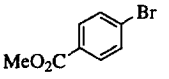
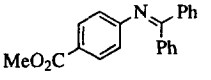
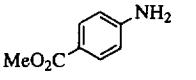
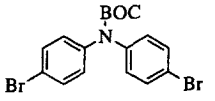
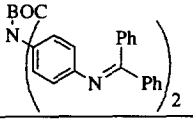
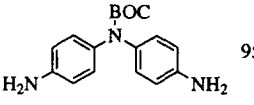


(1)

During the course of our work on the synthesis of oligoaniline derivatives for study as conducting and sensor materials we had reason to employ a protecting group for a primary aniline. We found that benzophenone imines served this role in a convenient manner; they were easily formed,[3] stable to base and mild acid, and cleaved under a variety of conditions. It occurred to us that the protected anilines might be directly accessible using our previously reported methods for the amination of aryl halides and triflates.

In general, we found that the coupling reactions with benzophenone imine were efficient. Shown in Table 1, are four examples of substrates which were converted to benzophenone imines.[4] The diphenyl ketimine moiety instilled or enhanced crystallinity in the products which allowed for facile purification by recrystallization from MeOH. Subsequent cleavage to the primary aniline was effected by acidic hydrolysis, hydrogenolysis, or

Table 1: Palladium-Catalyzed Amination of Aryl Bromides and Triflates

Entry	Substrate	Product	Yield (%)	Cleavage Conditions	Product	Yield (%)[e]
1			85%[a, ref. 5]	cat. HCl wet THF rt		98%
2			90%[b]	$NH_4^+ HCO_2^-$ cat Pd/C MeOH/60° C		84%
3			75%[c]	NH_2OH•HCl NaOAc MeOH/rt		88%
4			91%[d]	$NH_4^+ HCO_2^-$ cat Pd/C MeOH/60° C		95%

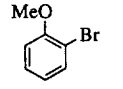
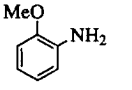
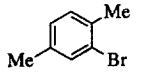
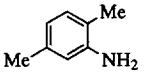
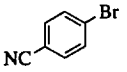
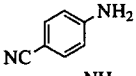
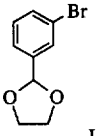
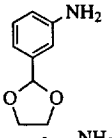
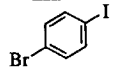
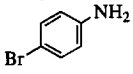
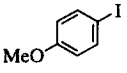
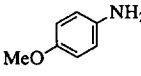
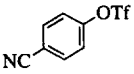
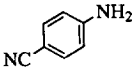
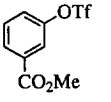
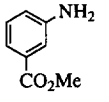
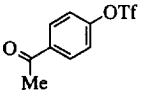
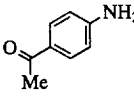
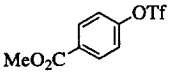
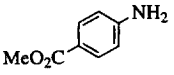
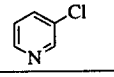
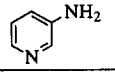
(a) 1 mol% $Pd(OAc)_2$, 1.5 mol% BINAP, 1.4 eq Cs_2CO_3, THF, 65 °C, 16 h. (b) 0.25 mol% $Pd_2(dba)_3$, 0.75 mol% BINAP, 1.4 eq NaO*t*Bu, toluene, 80 °C, 13 h. (c) 2 mol% $Pd(OAc)_2$, 3 mol% BINAP, 1.4 eq Cs_2CO_3, toluene, 100 °C, 5 h. (d) 0.25 mol% $Pd_2(dba)_3$, 0.75 mol% BINAP, 1.4 eq NaO*t*Bu, toluene, 80 °C, 6 h. (e) Isolated yields reported are an average of two runs.

transamination with hydroxylamine.[6] In many cases it may be advantageous to retain the imine moiety after coupling for use as a protecting group of the primary aniline because of its robust nature[7] and facile removal.[2]

Catalytic amination was carried out on additional substrates using benzophenone imine as shown in Table 2. The yields reported correspond to isolation of the primary aniline for the two step sequence of amination and imine cleavage. The methodology is effective with aryl chlorides, bromides, iodides and triflates. Couplings involving aryl triflates employed Cs_2CO_3 in place of NaO*t*Bu to avoid hydrolysis of the triflate.[1e, g] Benzophenone imine serves as an ideal coupling partner since it is relatively unhindered, the nitrogen is sp^2 hybridized,[8] and can not undergo palladium-catalyzed β-hydride elimination. Due to the variety of methods available for imine cleavage, conditions were found for selective diphenyl ketimine removal in products containing a benzylic acetal (entry 4), a methyl ester (entries 8 and 10), or a benzylic ketone (entry 9).

In summary, we have demonstrated the utility of employing benzophenone imine as a substitute for ammonia in the palladium-catalyzed amination of aryl halides and triflates. The couplings and subsequent deprotections proceed in uniformly high yields. When it is desirable to retain the imine as a means of masking the primary amine, the diphenyl ketimine adducts may be isolated as crystalline solids or purified by chromatography on silica gel in high yield.

Table 2: Palladium-Catalyzed Amination and Subsequent Imine Cleavage

Entry	Substrate	Product	Time	Cleavage[ref. 6]	Yield (%)[e]
1			5 h[a]	B	87
2			19 h[a]	B	77
3			1.5 h[a]	A	97
4			1.5 h[a]	A	89
5			48 h[b]	C	91
6			14 h[b]	A	88
7			4.5 h[c]	A	84
8			20 h[c]	A	80
9			4 h[c]	C	83
10			5 h[c]	A	89
11			16 h[d]	A	81

(a) 0.25 mol% $Pd_2(dba)_3$, 0.75 mol% BINAP, 1.4 eq NaO*t*Bu, toluene, 80 °C. (b) 1.0 mol% $Pd_2(dba)_3$, 3.0 mol% BINAP, 1.4 eq NaO*t*Bu, 1.4 eq 18-Crown-6, THF, rt. (c) 3 mol% $Pd(OAc)_2$, 4.5 mol% BINAP, 1.4 eq Cs_2CO_3, THF, 65 °C. (d) 5 mol% $Ni(COD)_2$, 10 mol% DPPF, 1.4 eq NaO*t*Bu, toluene, 100 °C.[ref. 1f] (e) Isolated yields reported are an average of two runs. All compounds were characterized by NMR (^1H, ^{13}C), and IR. All aniline products are commercially available except for entry 4 in Table 1 and entry 4 in Table 2.[ref. 9] Combustion analyses were obtained for all imine and aniline products which were not commercially available.

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References and Footnotes

§ Wallenberg Foundation Postdoctoral Fellow

(1) (a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217. (c) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.*, in press. (d) Wolfe, J. P.; Buchwald, S. L. Manuscript submitted. (e) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264 and references cited therein. (f) Louie, J.; Driver, M. S.; Hamann, B.C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268 and references cited therein. (g) Åhman, J.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, accompanying paper in this issue.

(2) (a) Wessjohann, L.; McGaffin, G.; de Meijere, A. *Synthesis*, **1989**, 359. (b) Fasth, K.-J.; Antoni, G.; Långström, B. *J. Chem. Soc., Perkin Trans. I* **1988**, 3081. (c) O'Donnell, M. J.; Boniece, J. M.; Earp, S. E. *Tetrahedron Lett.* **1978**, 2641.

(3) Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* **1971**, *36*, 1570.

(4) Representative Procedure: An oven-dried Schlenk tube was charged with $Pd_2(dba)_3$ (0.00125 mmol) and BINAP (0.00375 mmol), and purged with argon. To the flask was added 4-*t*-butylbromobenzene (1.00 mmol), benzophenone imine (1.20 mmol), NaO*t*Bu (1.40 mmol) and toluene (4 mL), and the mixture was heated to 80 °C with stirring until the starting material had been consumed as judged by GC analysis. The mixture was cooled to room temperature, diluted with ether (10 x volume of toluene), filtered, and concentrated. The crude product was then recrystallized from MeOH. Yellow crystals of the diphenyl ketimine adduct were isolated in 90% yield.

(5) The imine product has been previously prepared: Seno, M.; Shirashi, S.; Suzuki, Y.; Asahara, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1413. It was found that DBU could be used in place of Cs_2CO_3 to carry out the Pd-catalyzed (3 mol%) coupling of α-naphthyltriflate and benzophenone imine in 82% yield at 110 °C in toluene (24 h). Utilizing DBU as a base has not been found to be general in scope.

(6) General Procedures for Imine Cleavage:

Method A (Transamination with Hydroxylamine) To a solution of the imine adduct in MeOH (0.1 M) at rt was added NaOAc (2.4 eq) and hydroxylamine hydrochloride (1.8 eq). Oxime formation was usually complete in 15 to 30 minutes. The solution was then partitioned between 0.1 M NaOH and CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The product was purified by chromatography on silica gel.

Method B (Hydrogenolysis) A solution of the imine adduct, ammonium formate (15 eq) and 5% Pd/C (10 mol%) were heated to 60 °C in MeOH (0.2 M in imine). After 2 h reduction was usually complete. The solution was cooled to rt and diluted with CH_2Cl_2 (5 x volume MeOH) to be passed through a plug of celite. The organic solution was washed with 0.1 M NaOH, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The product was purified by chromatography on silica gel.

Method C (Acidic Hydrolysis) To a solution of the imine adduct in THF (0.3 M) was added aqueous 2.0 M HCl (added 5% by volume of THF). After 5-20 minutes hydrolysis was complete and the reaction mixture was partitioned between 0.5 M HCl and 2:1 hexane/EtOAc. The aqueous layer was separated and made alkaline. The product aniline was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*.

(7) The imine adducts are stable to purification by chromatography on silica gel. As a further demonstration of the stability of the diphenyl ketimine, we have found that it was possible to carry out halogen metal exchange (*n*-BuLi, THF, –78 °C) on the benzophenone imine protected 4-bromoaniline without substantial (<5 %) addition to the imine.

(8) Reductive elimination from palladium should be more facile (electronically) for an imine than an amine.

(9) Manecke, G.; Vogt, H. G. *J. Solid-Phase Biochem.* **1979**, *4*, 233.

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