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Copper-Catalyzed Electrophilic Amination of Functionalized Diarylzinc Reagents

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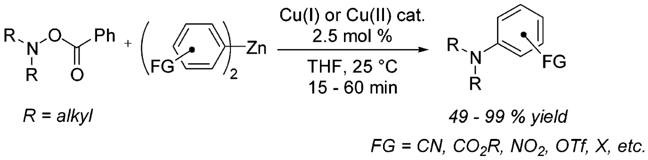
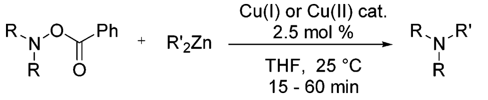


The copper-catalyzed electrophilic amination of functionalized diarylzinc reagents with *O*-acyl hydroxylamines allows for the preparation of functionalized tertiary arylamines in high yields, and is noteworthy for the mild reaction conditions employed. The functionalized diarylzinc reagents were prepared via an iodine/magnesium exchange of the corresponding aryl iodide followed by transmetalation of the resultant Grignard species with $ZnCl_2$.

The development of methodology for the expeditious preparation of amines continues to be an active area of research. Arylamines are particularly attractive targets, owing to the prominence of this structural motif in Nature, and many methods have been developed for the preparation of such compounds.[1] The Buchwald−Hartwig coupling has in particular gained increasing importance as a convenient route to functionally dense arylated amines and is the benchmark in catalyzed nucleophilic amination.[2,3] Electrophilic amination of nonstabilized carbanions represents an alternative approach, and is noteworthy in its use of the *umpolung* strategy for C−N bond construction.[4] Electrophilic amination of aryl carbanions has been successfully applied to arylamine synthesis, but with some exceptions (vide infra) harsh conditions (RMgX or RLi as the carbon donor) are needed and/or modest yields result.[5] Transition metal-catalyzed methods have recently been developed by Erdik and Narasaka that alleviate some of the problems associated with these earlier efforts; however, these methods are typically limited to the preparation of aniline derivatives lacking sensitive functionality.[6,7]

We have recently disclosed a copper-catalyzed electrophilic amination of diorganozinc reagents with *O*-acyl hydroxylamines, allowing for the preparation of tertiary amines under mild reaction conditions (eq 1).[8]



(1)

This reaction shows considerable latitude in the nucleophilic component, with both sp^2 (aryl, heteroaryl)- and sp^3 (alkyl, benzyl)-hybridized carbanions undergoing coupling in uniformly high yields. The *O*-acyl hydroxylamines employed are noteworthy in terms of both ease of preparation and stability, and represent a convenient source of sp^3-hybridized nitrogen electrophile for the direct delivery of $R_2N(+)$ synthons.[9] In our previous communication, the preparation of functionalized tertiary amines was not possible since many of the R'_2Zn nucleophiles were derived from organolithium reagents. As a new variant of this methodology, we now report the copper-catalyzed electrophilic amination of functionalized diarylzinc reagents, prepared via the I/Mg exchange of aryl iodides, as a general and mild route to functionalized tertiary arylamines.

Knochel and co-workers have recently described the I/Mg exchange reaction as an extremely useful route to functionalized aryl Grignard reagents.[10] Treatment of an electron -deficient aryl iodide with RMgX (typically ^{i}PrMgBr) at low temperatures results in rapid I/Mg exchange. Electron-rich aryl iodides can also be accommodated when elevated reaction temperatures (room temperature) are employed. The resultant Grignard reagents may be trapped with a number of electrophiles. Particularly topical examples involve reactions with aryl azosulfonates or nitroarenes to effect net delivery of a protected ArNH(+) synthon to the organometallic.[11,12]

The Grignard reagents derived from I/Mg exchange may also undergo transmetalation with 0.5 equiv of $ZnCl_2$ to give access to functionalized diarylzinc reagents. We envisaged employing these reagents in our copper-catalyzed electrophilic amination protocol, giving expeditious access to functionalized arylamine products (Scheme 1).

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(1) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449.

(2) (a) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578−5587. (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131−209. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818.

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(5) For instructive early examples, see: (a) Boche, G.; Mayer, N.; Bernheim, M.; Wagner, K. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 687−688. (b) Beak, P.; Kokko, B. J. *J. Org. Chem.* **1982**, *47*, 2822−2823. For a more thorough treatment of strategies employed, see ref 4.

(6) (a) Erdik, E.; Ay, M. *Synth. React. Inorg. Met. Org. Chem.* **1989**, *19*, 663−668. (b) Erdik, E.; Daskapan, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3139−3142. (c) Erdik, E.; Daskapan, T. *Synth. Commun.* **1999**, *29*, 3989−3997.

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(9) Biloski, A. J.; Ganem, B. *Synthesis* **1983**, 537−538.

(10) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302−4320.

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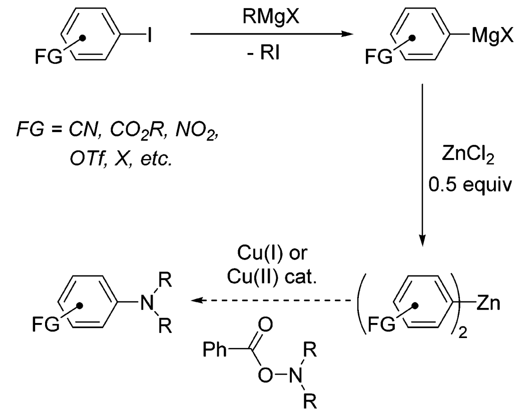
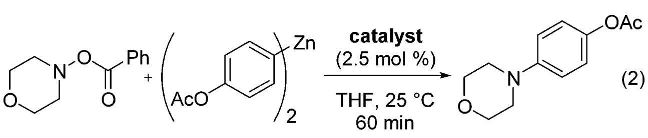
10.1021/jo048168g CCC: $30.25

SCHEME 1. Strategy for the Preparation of Functionalized Tertiary Arylamines



Employing Knochel's protocol for the preparation of functionalized Ar_2Zn reagents, we proceeded to test our hypothesis with a series of diverse aryl substrates. The requisite aryl iodides were either commercially available or easily prepared from the corresponding aryl bromides by the method of Buchwald.[13] The amination reaction showed broad functional group tolerance in the aryl component (Table 1). Various functional groups, including nitrile, ester, halide, triflate, and nitro, are tolerated under the reaction conditions. Those functional groups requiring prior protection were a phenol (as the derived acetate ester, entry 6) and a ketone (as the derived ketal, entry 9). Interestingly, the reaction proceeds equally well for both electron-deficient (entry 5) and electron-rich (entry 8) Ar_2Zn reagents. Heteroaromatic coupling is also accommodated under this general protocol (entry 12), albeit with somewhat diminished yields.

While most reactions were performed with CuOTf as catalyst, the use of other catalytic sources of copper is also feasible. Both CuI and $CuCl_2$ were found to catalyze the reaction with equal facility (eq 2; cf. Table 1, entry 6).

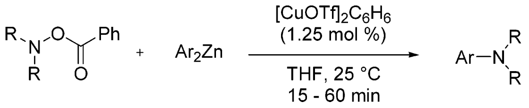


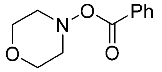
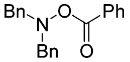
(2)

catalyst	yield
CuI	77%
$CuCl_2$	74%

Catalytic delivery of both aryl groups from the Ar_2Zn reagent is also possible (Table 2). While optimized conditions employ 1.1 equiv of the Ar_2Zn, the use of 0.6 equiv resulted in nearly identical (entries 1 and 2; cf. Table 1, entries 1 and 4) to slightly diminished yields (entries 3 and 4; cf. Table 1, entries 7 and 8) of product in the cases studied.

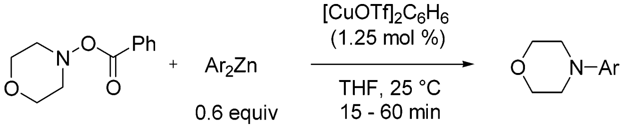
TABLE 1. Scope of the Copper-Catalyzed Electrophilic Amination of Functionalized Diarylzinc Reagents[a]



entry	R_2N-OC(O)Ph	Ar	% yield[d]
1		p-NCC$_6$H$_4$	76
2		p-EtO$_2$CC$_6$H$_4$	77
3		p-ClC$_6$H$_4$	93
4		p-FC$_6$H$_4$	71
5		m-F$_3$CC$_6$H$_4$	74
6		p-AcOC$_6$H$_4$	76
7		p-TfOC$_6$H$_4$	95
8		p-MeOC$_6$H$_4$^{b}	81
9		p-Me(OCH$_2$CH$_2$O)CC$_6$H$_4$^{b}	79
10		o-O$_2$NC$_6$H$_4$^{c}	83
11		2,4-(O$_2$N)$_2$C$_6$H$_3$^{c}	59
12		2-pyridyl	49
13		1-naphthyl^b	90
14		p-NCC$_6$H$_4$	95
15		p-EtO$_2$CC$_6$H$_4$	99
16		p-ClC$_6$H$_4$	88
17		p-MeOC$_6$H$_4$^{b}	87
18		o-O$_2$NC$_6$H$_4$^{c}	97

[a] 1.1 equiv of diarylzinc were employed. Ar_2Zn reagents were prepared from the corresponding ArI as follows: (1) ^{i}PrMgBr, −35 °C, 1 h, (2) $ZnCl_2$, −35 °C, 10 min. [b] Ar_2Zn prepared from the corresponding ArI as follows: (1) ^{i}PrMgBr, rt, 1 h, (2) $ZnCl_2$, rt, 10 min. [c] Ar_2Zn prepared from the corresponding ArI as follows: (1) PhMgBr, −35 °C, 10 min, (2) $ZnCl_2$, −35 °C, 10 min. [d] Isolated yield of product of ≥95% purity as judged by ^{1}H NMR spectroscopy and GLC analysis (average of at least two experiments). Yield is based on the starting R_2N-OC(O)Ph.

TABLE 2. Copper-Catalyzed Electrophilic Amination of Functionalized Diarylzinc Reagents[a]



entry	Ar	% yield[c]
1	p-NCC$_6$H$_4$	74
2	p-FC$_6$H$_4$	74
3	p-TfOC$_6$H$_4$	83
4	p-MeOC$_6$H$_4$^{b}	71

[a] 0.6 equiv of diarylzinc were employed. Ar_2Zn reagents were prepared from the corresponding ArI as follows: (1) ^{i}PrMgBr, −35 °C, 1 h, (2) $ZnCl_2$, −35 °C, 10 min. [b] Ar_2Zn prepared from the corresponding ArI as follows: (1) ^{i}PrMgBr, rt, 1 h, (2) $ZnCl_2$, rt, 10 min. [c] Isolated yield of product of ≥95% purity as judged by ^{1}H NMR spectroscopy and GLC analysis (average of at least two experiments). Yield is based on the starting R_2N-OC(O)Ph.

In summary, we have developed an efficient protocol for the expeditious preparation of functionalized tertiary arylamines under mild conditions. The reactions are conducted at room temperature and are complete in 1 h or less for all substrates tested. Simple acid/base extractive workup is suitable in most instances to obtain analytically pure material. The reaction is noteworthy in its use of Knochel's I/Mg exchange protocol to generate functionalized diarylzinc reagents from the corresponding aryl iodides in situ, thus obviating the need for isolation and/or purification of Ar_2Zn. The *O*-acyl hydroxylamines employed are easily prepared by the method of Ganem and show excellent long-term stability. We are currently examining ways to extend the scope and utility of this

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[13] Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844−14845.

electrophilic amination protocol. Results from these studies will be the topic of future publications.

Experimental Section

4-(Morpholin-4-yl)benzonitrile (Table 1, entry 1): Representative Procedure for the Copper-Catalyzed Amination of Functionalized Diarylzinc Reagents. An oven-dried round-bottom flask equipped with a magnetic stir bar was charged with 4-iodobenzonitrile (0.1258 g, 0.55 mmol) and anhydrous tetrahydrofuran (3.0 mL); the solution was cooled to −35 °C. A tetrahydrofuran solution of isopropylmagnesium bromide (0.60 mL, 1.0 M) was slowly added along the edges of the flask and the reaction mixture was stirred at −35 °C for 1 h. A tetrahydrofuran solution of zinc(II) chloride (1.0 mL, 0.28 M) was slowly added along the edges of the flask and the reaction mixture was stirred at −35 °C for 10 min. A second oven-dried round-bottom flask equipped with a magnetic stir bar was charged with 4-(benzoyloxy)morpholine (0.0520 g, 0.25 mmol), copper(I) trifluoromethanesulfonate benzene complex ($[CuOTf]_2 \cdot C_6H_6$, 0.0016 g, 0.0031 mmol), and anhydrous tetrahydrofuran (2.0 mL). The contents of the first flask were added to this second flask and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with diethyl ether (10 mL), the organic layer was washed with a saturated sodium bicarbonate solution (2 × 10 mL), and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The organic layers were combined and the solvent was removed under reduced pressure. The resulting residue was taken up in diethyl ether (10 mL) and washed with a 1 M hydrochloric acid solution (2 × 10 mL), and the aqueous layer was basified with a 10% sodium hydroxide solution and extracted with dichloromethane (2 × 10 mL). The organic extracts were combined and dried over sodium sulfate, and the solvent was removed under reduced pressure to yield 4-(morpholin-4-yl)benzonitrile (0.0370 g, 0.20 mmol, 79% yield) as a white solid of ≥95% purity as judged by ^1H NMR spectroscopy and GLC analysis. The ^1H NMR spectrum was consistent with that reported in the literature.[14]

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Supporting Information Available: Experimental procedures for electrophilic amination reactions and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048168G

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