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Copper-Catalyzed Electrophilic Amination of Organozinc Nucleophiles: Documentation of *O*-Benzoyl Hydroxylamines as Broadly Useful $R_2N(+)$ and $RHN(+)$ Synthons

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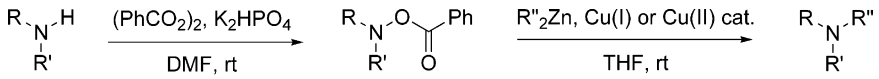

- simple access to 2° and 3° amines via electrophilic amination
- R' = H or alkyl

This paper details new copper-catalyzed electrophilic amination reactions of diorganozinc reagents using *O*-benzoyl hydroxylamines as electrophilic nitrogen sources that may be accessed in one step. Simple and functionalized aryl, heteroaryl-, benzyl, *n*-alkyl, *sec*-alkyl, and *tert*-alkyl nucleophiles couple with $R_2NOC(O)Ph$ and $RHNOC(O)Ph$ reagents in the presence of catalytic quantities of copper salts to provide tertiary and secondary amines, respectively, in generally good yields. In many cases, the product may be isolated analytically pure after a simple extractive workup. The amination process is shown to tolerate a significant degree of steric demand. The amination of nominally unreactive $C_{aryl}-H$ bonds via a sequential directed ortho metalation/transmetalation/catalytic amination reaction sequence is detailed. The direct Cu-catalyzed amination of Grignard reagents using cocatalysis by $ZnCl_2$ is described.

Introduction

The investigation of umpolung strategies in organic synthesis often produces reactions that are complementary to counterparts following normal polarity pathways.[1] In the context of amine synthesis, the effective application of the umpolung concept relies on the identification of useful electrophilic nitrogen synthons and reaction conditions that are sufficiently mild so as to tolerate functionality that might be required for subsequent manipulation. A large number of $R_2N(+)$ synthons have been developed for reactions with nucleophiles,[2] and recent advances from Erdik[3,4] and Narasaka[5,6,7] have demonstrated that transition-metal catalysts can potentiate the reactivity of Grignard reagents or zincates with oxime derivatives; however, in most instances electrophilic amination approaches are not currently competitive with catalytic nucleophilic amination strategies discovered and developed by Buchwald and Hartwig.[8,9]

Because of the central role of amine synthesis in organic chemistry, the electrophilic amination problem continues to attract considerable interest.[10−14] Hydroxylamine derivatives occupy a prominent position in the development of umpolung C−N bond constructions, with key advances relying on the use of appropriate activating groups to facilitate the amination. The use of sulfonyl[15] and phosphinyl[16,17] activation is representative,

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(2) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947−1980.
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(6) Tsutsui, H.; Ichikawa, T.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1869−1878.
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(10) Erdik, E. *Tetrahedron* **2004**, *60*, 8747−8782.
(11) Greck, C.; Drouillat, B.; Thomassigny, C. *Eur. J. Org. Chem.* **2004**, 1377−1385.
(12) Dembech, P.; Seconi, G.; Ricci, A. *Chem. Eur. J.* **2000**, *6*, 1281−1286.
(13) Greck, C.; Genêt, J. P. *Synlett* **1997**, 741−748.
(14) For recent examples of electrophilic amination reactions, see: (a) Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799−1801. (b) Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 897−900. (c) Kitamura, M.; Suga, T.; Chiba, S.; Narasaka, K. *Org. Lett.* **2004**, *6*, 4619−4621. (d) Saaby, S.; Bella, M.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120−8121. (e) Smulik, J. A.; Vedejs, E. *Org. Lett.* **2003**, *5*, 4187−4190. (f) Kitamura, M.; Chiba, S.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1063−1070. (g) Sapountzis, I.; Knochel, P. *J. Am. Chem. Soc.* **2002**, *124*, 9390−9391. (h) Niwa, Y.; Takayama, K.; Shimizu, M. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1819−1825.

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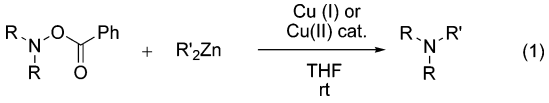
but surprisingly little had been done in the field employing acyl activation of the hydroxylamine moiety.[18]

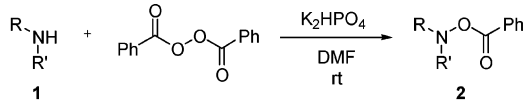
In an effort to address the technology gap between nucleophilic and electrophilic catalytic amination, we initiated a search for a useful electrophilic amination protocol that would employ readily accessible $R_2N(+)$ synthons and enjoy broad functional group compatibility. In this paper, we document the scope and limitations of a new copper-catalyzed C−N bond construction that couples *O*-benzoyl hydroxylamine derivatives and in situ generated diorganozinc reagents (eq 1). Salient features of the protocol that will be detailed in this article include the following: (i) remarkable tolerance of both steric hindrance at the reaction site and reactive functionality elsewhere in the molecules undergoing coupling; (ii) mild reaction conditions (rt, <1 h) and ease of product isolation/purification (acid−base extractive workup); (iii) broad scope with respect to the sp^3- and sp^2-hybridized nucleophiles; (iv) capacity of the reaction to facilitate direct amination of C_{aryl}−H bonds using directed ortho-metalation; and (v) direct amination of Grignard reagents using catalysis by Cu(II) and cocatalysis by Zn(II).[19]



Results and Discussion

Preparation of *O*-Benzoyl Hydroxylamines. The *O*-benzoyl hydroxylamines utilized in our earlier studies were prepared via the oxidation of secondary amines with benzoyl peroxide and an exogenous inorganic base in ethereal solvent, as originally reported by Ganem.[20] In the Ganem report, extended reaction times (>12 h) and refluxing conditions are necessary. While this method results in acceptable yields of desired product, competitive *N*-acylation of the amine was noted as a problematic side reaction. We discovered that these same oxidations, when conducted in a polar aprotic solvent, proceed to completion at room temperature with competitive *N*-acylation greatly suppressed. Utilizing this modified procedure, we were able to prepare a variety of *O*-benzoyl hydroxylamines, both from primary and secondary amines, in uniformly high yields (Table 1).[21] The reactions are typically run on a 50 mmol scale of the limiting reagent (benzoyl peroxide), and the products are easily purified by column chromatography. A number of these compounds are crystalline solids, and all show good stability (they can be stored indefinitely in the freezer without decomposition or loss of reactivity). Reaction times varied from 1 h for sterically unhindered primary and secondary amines (entries 1, 2, and 9) to 24 h for the most sterically demanding primary and secondary amines tested (entries 3, 6, and 7). In instances where the free hydroxylamine is readily available (e.g., Et_2-NOH is commercially available), benzoylation represents a simple alternate route to these compounds. In the case of Et_2N−OC(O)Ph (**2e**), acylation of the commercially available parent hydroxylamine resulted in clean formation of product (98% isolated yield), representing an alternative route to these compounds. While the reaction works uniformly well for *N*-alkylamines, heteroaromatic amines (e.g., imidazole) failed to undergo oxidation under the present reaction conditions. Attempted oxidation of methyl prolinate was likewise unsuccessful.

TABLE 1. Preparation of *O*-Benzoyl Hydroxylamines[a]



entry	R(R′)NH	R(R′)NOC(O)Ph	time (h)	% yield[c]
1	**1a**	**2a**	1	73
2	**1b**	**2b**	1	80
3[b]	**1c**	**2c**	24	68
4	**1d**	**2d**	4	92
5[b]	**1f**	**2f**	24	87
6[b]	**1g**	**2g**	24	91
7	**1h**	**2h**	6	89
8	**1i**	**2i**	1	61

[a] 1.2 equiv of the amine and 1.5 equiv of K_2HPO_4 were employed. [b] 2.5 equiv of the amine and 1.5 equiv of K_2HPO_4 were employed. [c] Isolated yield of product of purity ≥95% based on ^1H NMR spectroscopy (average of at least two experiments). Yield is based on the starting benzoyl peroxide.

Electrophilic Amination of Diorganozinc Reagents: Preparation of Secondary and Tertiary Amines. Our studies into the transition-metal-catalyzed electrophilic amination of weak carbon donors began with the discovery that copper salts catalyze the amination of R_2Zn reagents with *O*-benzoyl hydroxylamines under mild reaction conditions (rt, <1 h). With a convenient means of preparing our aminating reagents (vida supra), we next set out to test the generality of this newly discovered amination protocol. The reaction scope is quite broad, allowing for the facile preparation of a wide variety of both secondary and tertiary amines (Table 2). Aryl coupling proceeds in good to excellent yield for various *N*-monoalkyl- and *N*,*N*-dialkyl-*O*-benzoyl hydroxylamines (entries 1−3, 6−14, and 18−20), allowing for the preparation of diverse aniline derivatives. Heteroaryl coupling is also realized in good yield (entry 4). These results offer a complement to existing transition-metal-

(15) Boche, G.; Mayer, N.; Bernheim, M.; Wagner, K. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 687−688.
(16) Colvin, E. W.; Kirby, G. W.; Wilson, A. C. *Tetrahedron Lett.* **1982**, *23*, 3835−3836.
(17) Boche, G.; Bernheim, M.; Schrott, W. *Tetrahedron Lett.* **1982**, *23*, 5399−5402.
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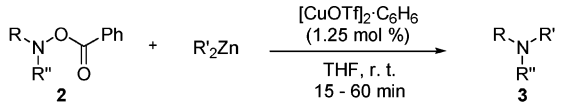
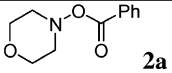
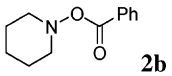
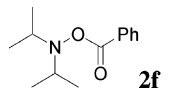
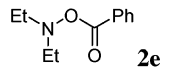
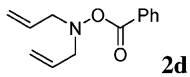
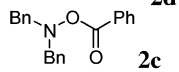
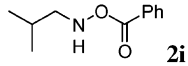
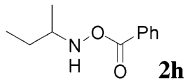
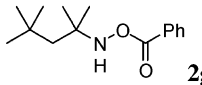
(19) A portion of this work has been previously communicated: (a) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680−5681. (b) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 364−366.
(20) Biloski, A. J.; Ganem, B. *Synthesis* **1983**, 537−538.
(21) (a) White, E. H.; Reefer, J.; Erickson, R. H.; Dzadzic, P. M. *J. Org. Chem.* **1984**, *49*, 4872−4876. (b) Zinner, G. *Arch. Pharm. (Weinheim, Ger.)* **1963**, *296*, 57−60.

TABLE 2. Scope of the Copper-Catalyzed Electrophilic Amination of Diorganozinc Reagents[a]



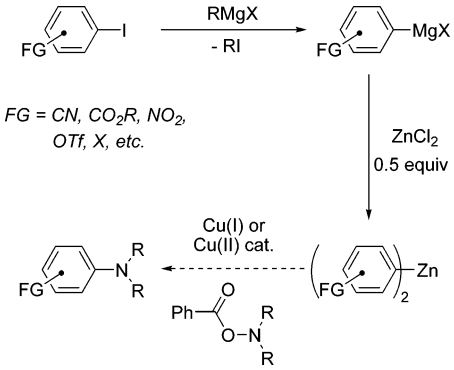
entry	R(R′′)N-OC(O)Ph	R′$_2$Zn (product)	% yield[c]
1	 **2a**	Ph (**3a**)	91
2	**2a**	2-MePh (**3b**)	94
3	**2a**	4-MeOPh (**3c**)	93
4	**2a**	2-pyridyl (**3d**)	71
5	**2a**	Bn (**3e**)	80
6	 **2b**	Ph (**3f**)	91
7	**2b**	4-MeOPh (**3g**)	95
8[b]	 **2f**	Ph (**3h**)	72
9[b]	**2f**	2-MePh (**3i**)	62
10[b]	**2f**	2,4,6-MePh (**3j**)	76
11	 **2e**	Ph (**3k**)	69
12	**2e**	2-MePh (**3l**)	70
13[b]	 **2d**	Ph (**3m**)	96
14	 **2c**	Ph (**3n**)	94
15	**2c**	Et (**3o**)	91
16	**2c**	^{i}Pr (**3p**)	77
17	**2c**	^{t}Bu (**3q**)	98
18[b]	 **2i**	Ph (**3r**)	71
19[b]	 **2h**	Ph (**3s**)	80
20[b]	 **2g**	Ph (**3t**)	74
21[b]	**2g**	^{t}Bu (**3u**)	43

[a] 1.1 equiv of diorganozinc was employed. With the exception of Et_2Zn (commercial solution), R_2Zn reagents were prepared via transmetalation of the corresponding RMgX or RLi reagent with 0.5 equiv of $ZnCl_2$. [b] 2.5 mol % of $CuCl_2$ was employed. [c] Isolated yield of product of purity ≥95% based on ^{1}H NMR spectroscopy and GLC analysis (average of at least two experiments). Yield is based on the starting $R_2NOC(O)Ph$.

catalyzed methods for the arylation of amines. The preparation of tertiary benzylamines is also possible using this methodology (entry 5). Likewise, alkyl coupling proceeds in good to excellent yield for primary, secondary, and tertiary dialkylzincs (entries 15−17 and 21).

A high level of steric tolerance is apparent in these reactions, as evidenced by the facile coupling of sterically hindered ^{i}Pr$_2$N−OC(O)Ph with both di(*o*-tolyl)- and di(mesityl)zinc reagents (entries 9 and 10). Sterically hindered secondary alkylamines are also accessible using this methodology. The synthesis of *N*,*N*-*tert*-octyl-*tert*-butylamine (**3u**), an immediate precursor to the useful lithio amide base LiN(^{t}Oct)^{t}Bu,[22] is exemplary; entry 21 reports the isolated yield (by distillation) for the preparation of **3u** on a 10 mmol scale. Although moderate compared to other entries in Table 2, the simplicity of the two-step process represents an attractive route to this useful secondary amine.

SCHEME 1. Strategy for the Preparation of Functionalized Arylamines



All reactions were complete within 15−60 min at room temperature, and simple acid−base extractive workup was sufficient to obtain analytically pure product in most instances. Both Cu(I) and Cu(II) salts catalyze the reaction with equal facility. Additives and/or supporting ligands for the metal are unnecessary. The aminations were generally performed on a <1 mmol scale. Upon scale up (25 mmol), we observed a slight decrease in yield (entry 1, 91%, 0.5 mmol scale; compared with 72%, 25 mmol scale). This may be attributed to a deleterious exotherm which becomes manifest on larger scale; the exotherm is easily managed by conducting the larger scale aminations at 0 °C.[23]

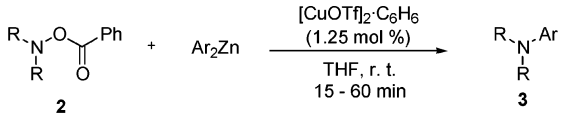
The use of 0.6 equiv of the diorganozinc reagent engenders a higher level of efficiency to the process. When **2b** was treated with 0.6 equiv of (*o*-MePh)$_2$Zn in the presence of 2.5 mol % of $CuCl_2$, *N*-*o*-tolylpiperidine was isolated in 86% yield.

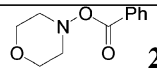
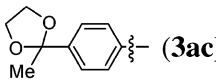
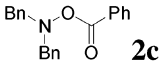
Preparation of Functionalized Arylamines. Knochel's recently described I/Mg exchange reaction offers a useful route to functionalized aryl Grignard reagents.[14] Treatment of an electron-deficient aryl iodide with RMgX (typically ^{i}PrMgBr) at low temperatures results in rapid I/Mg exchange. Electron-rich aryl iodides can also be accommodated when elevated reaction temperatures (room temperature) are employed. We envisioned utilizing such reagents in electrophilic amination processes, via an I/Mg exchange/transmetalation sequence, as a simple route to functionalized arylamines (Scheme 1).

The Grignard reagents derived from I/Mg exchange readily undergo transmetalation with 0.5 equiv of $ZnCl_2$, giving access to functionalized diarylzinc reagents that can be used without prior isolation and/or purification. We were successful in employing such reagents in our copper catalyzed electrophilic amination protocol, giving access to a wide array of functionalized arylamine products, which are readily purified in many cases by simple acid−base extractive workup (Table 3). The amination reaction shows broad functional group tolerance in

(22) Corey, E. J.; Gross, A. W. *Org. Synth.* **1987**, *65*, 166−172.
(23) Berman, A. M.; Johnson, J. S. *Org. Synth.*, in press. See the Supporting Information for details.

TABLE 3. Copper-Catalyzed Electrophilic Amination of Functionalized Diarylzinc Reagents[a]



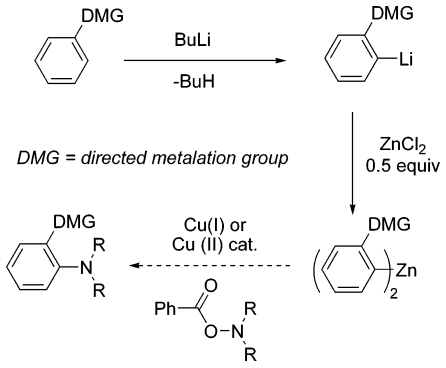
entry	R_2N-OC(O)Ph	Ar_2Zn (product)	% yield[d]
1	 **2a**	*p*-NCPh (**3v**)	76
2	**2a**	*p*-EtO_2CPh (**3w**)	77
3	**2a**	*p*-ClPh (**3x**)	93
4	**2a**	*p*-FPh (**3y**)	71
5	**2a**	*m*-F_3CPh (**3z**)	74
6	**2a**	*p*-AcOPh (**3aa**)	76
7	**2a**	*p*-TfOPh (**3ab**)	95
8[b]	**2a**	*p*-MeOPh (**3c**)	81
9[b]	**2a**	 (**3ac**)	79
10[c]	**2a**	*o*-O_2NPh (**3ad**)	83
11[c]	**2a**	2,4-$(O_2N)_2$Ph (**3ae**)	59
12[b]	**2a**	1-naphthyl (**3af**)	90
13	 **2c**	*p*-CNPh (**3ag**)	95
14	**2c**	*p*-EtO_2CPh (**3ah**)	99
15	**2c**	*p*-ClPh (**3ai**)	88
16[b]	**2c**	*p*-MeOPh (**3aj**)	87
17[c]	**2c**	*o*-O_2NPh (**3ak**)	97

[a] 1.1 equiv of diarylzinc was 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 $R_2NOC(O)Ph$.

the nucleophilic component. Diverse functional groups, including nitrile, ester, halide, triflate, and nitro, are all tolerated under the reaction conditions. Those functional groups requiring prior protection were a phenol (as the derived acetate ester, entry 6) and 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.

As was true for the unfunctionalized diorganozinc reagents, the use of 0.6 equiv of Ar_2Zn is feasible as demonstrated by the obtention of **3v** (74%), **3y** (74%), **3ab** (83%), and **3c** (71%) in yields comparable to those reported in Table 3.

SCHEME 2. Strategy for the Directed Ortho Metalation/Amination Sequence



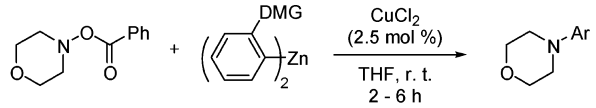
Directed Ortho Lithiation/Amination Sequence. Directed ortho lithiation has been utilized extensively as a reliable tool for the functionalization of poorly reactive C_{aryl}−H bonds.[24] Most work in this area has focused on the utility of this methodology toward the construction of new C−C bonds.[25] Fewer studies have addressed the aspects of C−N bond construction. Seminal examples by Snieckus illustrate the potential utility of this methodology for the formation of new C−N bonds.[26,27] We envisaged employing a directed ortho lithiation/transmetalation sequence to obtain Ar_2Zn reagents in situ. These reagents could then be used (without isolation and/or purification) in the title copper-catalyzed electrophilic amination protocol, allowing for the facile, selective oxidation of C_{aryl}−H bonds (Scheme 2).

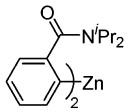
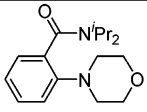
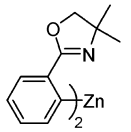
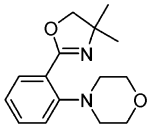
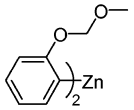
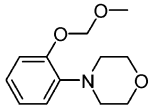
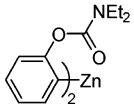
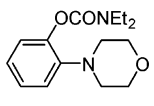
We tested this hypothesis with four arenes, employing the most commonly used directing groups in similar directed ortho lithiation protocols (Table 4). The reaction works well for both *N*,*N*-dialkylamide and methoxymethyl ether directing groups (entries 1 and 3). Somewhat less effective are the commonly employed *O*-aryl carbamate and oxazoline directing groups under the current reaction conditions (entries 2 and 4). A noticeable reduction in reaction rate is apparent for all substrates tested, presumably a result of the enhanced coordination in the derived diorganozinc reagents. The directed ortho metalation/amination sequence allows for the preparation of diverse amine products not readily accessible using previous methodology.

Double-Metal-Catalyzed Electrophilic Amination. The organozinc reagents employed in these studies were generally prepared from the corresponding RMgX or RLi reagent via transmetalation with 0.5 equiv of $ZnCl_2$. The resultant R_2Zn solution was subsequently added to the remaining reaction components and amination allowed to proceed under normal reaction conditions. Recent reports in the literature suggest that in situ generation of organozinc reagents from RMgX is also possible using a catalytic quantities of a Zn(II) salt.[28] This method obviates the use of large quantities of anhydrous zinc salts, which could present processing concerns on scale. We tested the feasibility of this protocol for our electrophilic amination reaction.

(24) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933.
(25) Anctil, E. J. G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150−160.
(26) Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1983**, *24*, 3795−3798.
(27) Iwao, M.; Reed, J. N.; Snieckus, V. *J. Am. Chem. Soc.* **1982**, *104*, 5531−5533.
(28) Miller, J.; Farrell, R. P. *Tetrahedron Lett.* **1998**, *39*, 7275−7278.

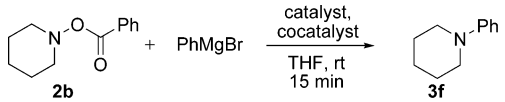
TABLE 4. Directed Ortho Metalation/Amination Reactions[a]



entry	Ar_2Zn	product	% yield[c]
1		 (**3al**)	88
2		 (**3am**)	55
3[b]		 (**3an**)	95
4		 (**3ao**)	62

[a] 1.1 equiv of diarylzinc was employed. Ar_2Zn reagents were prepared from the corresponding arene as follows: (1) ^{s}BuLi, TMEDA, −78 °C, 30 min; (2) $ZnCl_2$, −78 °C to rt, 30 min. [b] Ar_2Zn prepared from the corresponding arene as follows: (1) ^{t}BuLi, 0 °C, 1 h; (2) $ZnCl_2$, 0 °C to rt, 30 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 $R_2NOC(O)Ph$.

Studies early in this project illustrated the apparent incompatibility of $R_2NO-C(O)Ph$ reagents with RMgX nucleophiles: rapid acylation (ketone formation) of the Grignard reagent under standard reaction conditions was the predominant reaction pathway. Thus, for the proposed "catalytic-in-zinc" protocol to be successful, the projected transmetalation/amination must be faster than direct acylation. Gratifyingly, this is the case, and we observed good yields of the desired amination product when catalytic quantities of $ZnCl_2$ were employed (eq 2). An analogous experiment using morpholine-derived **2a**, 2.5 mol % of $CuCl_2$, and 10 mol % of $ZnCl_2$ gave *N*-phenylmorpholine (**3a**) in 69% isolated yield.



(2)

catalyst	cocatalyst	yield
none	none	4%
CuOTf (2.5%)	none	13%
CuOTf (2.5%)	$ZnCl_2$ (10%)	65%

Our studies suggest that the rate of addition of the Grignard reagent is important, with both rapid (<1 min) and exceedingly slow (>60 min) additions resulting in lower product yield. Dropwise addition over the course of 5 min results in optimal yields. Reaction temperature is likewise crucial, with subambient temperatures resulting in diminished yields and/or incomplete reaction.

Conclusion

In conclusion, we have developed a mild and broadly applicable method for the preparation of a wide variety of secondary and tertiary amines via the copper-catalyzed electrophilic amination of R_2Zn reagents. The *O*-benzoyl hydroxylamine aminating reagents employed are easily prepared in one step from the corresponding primary or secondary amine and show good stability. The R_2Zn reagents are generated from the corresponding RMgX or RLi, and are used without prior isolation and/or purification. Isolation of analytically pure material is possible in most instances via a simple acid/base extractive workup, thus making these reactions operationally convenient. The reaction shows good substrate scope, both in terms of the functional groups tolerated on the nucleophilic component and the sterics of the coupling partners. Work is continuing in our laboratory on the development of new methods of $R_2N(+)$ delivery and results from these studies will be reported in future publications.

Experimental Section

4-Benzoyloxymorpholine (2a). Representive Oxidation. A 500-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar was charged with benzoyl peroxide (12.11 g, 50 mmol), dipotassium hydrogen phosphate (13.06 g, 75 mmol), and *N*,*N*-dimethylformamide (125 mL). The suspension was stirred, and morpholine (5.20 mL, 60 mmol) was added via syringe in one portion. The suspension was stirred at ambient temperature for 1 h. Deionized water (200 mL) was added, and the contents were stirred vigorously for several minutes until all solids dissolved. The reaction mixture was transferred to a 1-L separatory funnel and extracted with 150 mL of ethyl acetate. The organic phase was collected and washed with two 100-mL portions of saturated aq $NaHCO_3$ solution. All of the aqueous fractions were combined and extracted with three 100-mL portions of ethyl acetate. All of the organic fractions were combined and washed with three 100-mL portions of deionized water and 100 mL of brine, dried over $MgSO_4$, and concentrated by rotary evaporation. The resulting crude product mixture was purified by flash column chromatography, eluting with 50% EtOAc/hexanes to afford the title compound (7.71 g, 37 mmol, 74%) of ≥95% purity as judged by ^{1}H NMR spectroscopy. The product was stored at subambient temperature under anhydrous conditions. Analytical data **2a**: mp (uncorrected) 82−84 °C; IR (Nujol, cm^{-1}) 2924, 2852, 1730, 1599, 1456; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.98 (m, 2H), 7.58−7.53 (m, 1H), 7.45−7.41 (m, 2H), 3.96 (br d, J = 10.7 Hz, 2H), 3.85 (br t, J = 11.2 Hz, 2H), 3.43 (br d, 9.3 Hz, 2H), 3.03 (br t, 9.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 133.1, 129.4, 129.2, 128.4, 65.8, 57.0. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.96; H, 6.40; N, 6.67.

4-Phenylmorpholine (3a). Representative Amination. An oven-dried 10-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar was maintained under an inert atmosphere of argon and charged with zinc chloride (0.075 g, 0.55 mmol) and anhydrous tetrahydrofuran (2.0 mL). The solution was stirred at ambient temperature, and an ethereal solution of PhMgBr (1.1 mL, 1.1 mmol, 1.0 M) was added via cannula in one portion. The resulting solution was stirred for 20 min at ambient temperature prior to use (vida infra). An oven-dried 25-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar was maintained under an inert atmosphere of argon and charged with **2a** (0.103 g, 0.50 mmol), the copper(I) trifluoromethanesulfonate benzene complex ($[CuOTf]_2 \cdot C_6H_6$, 0.003 g, 0.0056 mmol), and anhydrous tetrahydrofuran (5.0 mL). The solution was stirred, and the previously generated diphenylzinc solution (vida supra) was added via cannula in one portion. The resulting solution was stirred

at ambient temperature for 1 h. Diethyl ether (10 mL) was added, and the reaction mixture was transferred to a 125-mL separatory funnel. The reaction mixture was washed with three 10-mL portions of saturated aq $NaHCO_3$ solution and extracted with three 10-mL portions of 10% aq HCl solution. The aqueous extracts were basified with 10% aq NaOH solution and extracted with three 10-mL portions of dichloromethane. The organic fraction was washed with 10 mL of brine, dried over Na_2SO_4, and concentrated by rotary evaporation to afford the title compound as a white solid (0.080 g, 0.49 mmol, 98%) of ≥95% purity as judged by ^{1}H NMR spectroscopy. This yield is for a specific experiment and differs slightly from that in Table 2, which is an average of multiple experiments. Analytical data for **3a**: mp (uncorrected) 53−55 °C; IR (Nujol, cm^{-1}) 2922, 2854, 1601, 1458, 1377; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.24 (m, 2H), 6.92−6.85 (m, 3H), 3.86−3.84 (m, 4H), 3.16−3.13 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 129.2, 120.0, 115.7, 66.9, 49.4. Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.71; H, 8.03; N, 8.52.

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

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