

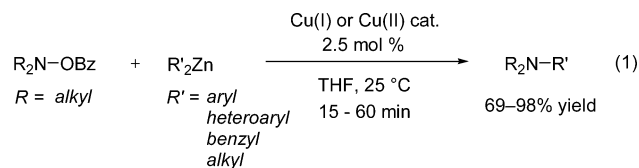
## Copper-Catalyzed Electrophilic Amination of Diorganozinc Reagents

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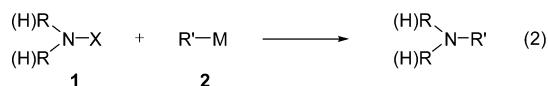
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Herein we report a useful new method for the preparation of a wide range of tertiary amines via the copper-catalyzed electrophilic amination of diorganozinc reagents with *O*-acyl hydroxylamine derivatives (eq 1).

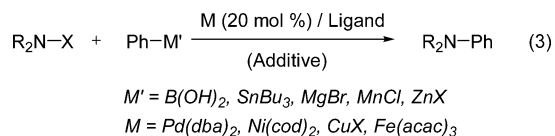


Amines are of fundamental interest in many fields of chemistry, as evidenced by the rapid increase in modern methods now available for their synthesis.<sup>1-3</sup> Electrophilic amination reactions of nonstabilized carbanions represent a valuable subset of C–N bond constructions,<sup>4-6</sup> and a wide range of R<sub>2</sub>N(+) synthons **1** are available for reaction with sp<sup>2</sup>- or sp<sup>3</sup>-hybridized carbon nucleophiles **2** (typically R'Li or R'MgX, eq 2).



While primary,<sup>7</sup> *N*-protected primary,<sup>8</sup> and secondary amines<sup>9</sup> are all accessible via such methods, the preparation of tertiary amines has received less attention.<sup>10</sup> An important early example from Boche that employed *N,N*-dialkyl *O*-sulfonyl hydroxylamine derivatives is representative: amination of organolithium and Grignard reagents occurs but is hampered by modest yields.<sup>11</sup> While catalysis may provide promise for a solution, literature precedent in this vein is limited. Reports from the laboratories of Erdik<sup>12</sup> and Narasaka<sup>13</sup> indicate that *N*-substituted imines are obtained upon treatment of *O*-sulfonyl oximes with RMgX or RZnX and a Cu(I) catalyst. Net delivery of the H<sub>2</sub>N(+) synthon is achieved by virtue of the hydrolytic workup that affords the resultant primary amines in variable yield. The analogous transition-metal-catalyzed amination of sp<sup>3</sup>-hybridized nitrogen electrophiles for the *direct* delivery of R<sub>2</sub>N(+) synthons has not been described.

With the aim of developing a convenient and general method for the preparation of tertiary amines, we evaluated conditions for the transition-metal-catalyzed amination of organometallic reagents (eq 3).



We initially employed *N,N*-dialkyl-*N*-chloroamines as our aminating agent. Such compounds have been used sparingly in electrophilic amination,<sup>6</sup> but their ease of synthesis renders them attractive starting materials. Results with PhB(OH)<sub>2</sub> and PhSnBu<sub>3</sub> proved disappointing under all conditions screened (transition-metal

**Table 1.** Evaluation of Conditions for the Copper-Catalyzed Amination of Organozinc Reagents<sup>a</sup>

entry	R <sub>2</sub> NOBz	R'ZnX	product	% yield <sup>b</sup>
1		PhZnCl		29
2		PhZnBr		25
3		PhZnI		18
4	Br <sub>2</sub> N-OBz	<sup>t</sup> BuZnCl	Br <sub>2</sub> N- <sup>t</sup> Bu	18
5		Ph <sub>2</sub> Zn		91

<sup>a</sup> 1.1 equiv of organozinc were employed. RZnX reagents were prepared via transmetalation of the corresponding RMgX reagent with 1.0 equiv of ZnX<sub>2</sub>. <sup>b</sup> Isolated yield of product of ≥95% purity as judged by <sup>1</sup>H NMR spectroscopy and GLC analysis. Yield is based on the starting R<sub>2</sub>N-OBz.

salt, supporting ligand, stoichiometric additive).<sup>14</sup> Other organometallic reagents tested (PhMgBr, PhMnCl, Ph<sub>2</sub>Mn, Ph<sub>2</sub>Zn) likewise proved ineffective. The results with PhZnX<sup>15</sup> proved promising, with yields of the desired tertiary amine reaching 10–20% for various transition metal/ligand combinations. In all cases, biphenyl formation was the major side reaction. All attempts to optimize conditions for the amination of PhZnX failed to provide substantial increases in yield, leading us to explore the use of a different aminating agent.

We next tested the hypothesis that *O*-acyl hydroxylamine derivatives might be effective reagents for the proposed C–N bond construction (Table 1). Despite their ease of synthesis and stability (*vide infra*), these compounds have not been employed extensively or effectively in the amination of organometallics.<sup>16</sup> In combination with a ligand-free CuOTf catalyst, these reagents proved promising in the amination of RZnX (entries 1–4).<sup>17</sup> A dramatic increase in yield was realized when R<sub>2</sub>Zn was employed as the organometallic reagent (entry 5), prompting us to explore the scope of electrophilic aminations with this family of nucleophile (Table 2).

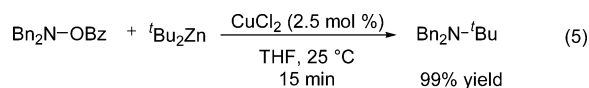
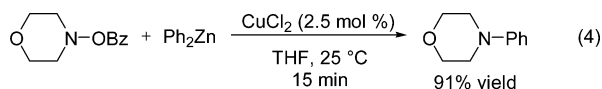
Copper-catalyzed coupling proceeds in good to excellent yield for various *N,N*-dialkyl-*O*-acyl hydroxylamine derivatives in combination with Ar<sub>2</sub>Zn reagents (entries 1–3, 6–8, 9, 14, 15). Heteroaryl coupling is also realized in good yield (entry 4). These results offer a complement to existing transition-metal-catalyzed methods for the arylation of amines. The preparation of tertiary benzylamines is also possible through the use of this method (entries 5, 10). Gratifyingly, alkyl coupling proceeds in good to excellent yield for primary, secondary, and tertiary dialkylzincs (entries 11–13). The current reaction also proceeds in the absence of catalyst, albeit with lower yields and longer reaction times (6–12 h).

**Table 2.** Scope of the Copper-Catalyzed Amination of Diorganozinc Reagents<sup>a</sup>

R <sub>2</sub> N-OBz + R' <sub>2</sub> Zn		$\xrightarrow[\text{THF, 25 } ^\circ\text{C}]{[\text{Cu}(\text{OTf})_2 \cdot \text{C}_6\text{H}_6 \text{ (1.25 mol \%)}]}$		R <sub>2</sub> N-R'		
		15 - 60 min				
entry	R <sub>2</sub> NOBz	R'	product	% yield <sup>b</sup>		
1		Ph		91		
2		2-MePh		94		
3		4-MeOPh		93		
4		2-pyridyl		71		
5		Bn		80		
6		Ph		91		
7		2-MePh		91		
8		4-MeOPh		95		
9	Bn <sub>2</sub> N-OBz	Ph	Bn <sub>2</sub> N-Ph	94		
10		Bn	Bn <sub>2</sub> N-Bn	91		
11		Et	Bn <sub>2</sub> N-Et	91		
12		<sup>t</sup> Pr	Bn <sub>2</sub> N- <sup>t</sup> Pr	77		
13		<sup>t</sup> Bu	Bn <sub>2</sub> N- <sup>t</sup> Bu	98		
14	Et <sub>2</sub> N-OBz	Ph	Et <sub>2</sub> N-Ph	69		
15		2-MePh		70		

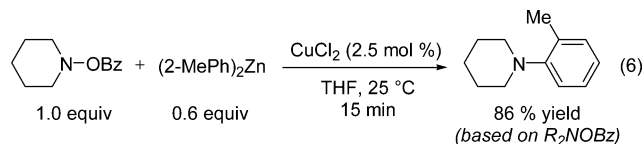
<sup>a</sup> 1.1 equiv of diorganozinc were employed. R<sub>2</sub>Zn reagents were prepared via transmetalation of the corresponding RLi or RMgX reagent with 0.5 equiv of ZnCl<sub>2</sub>. <sup>b</sup> Isolated yield of product of  $\geq 95\%$  purity as judged by <sup>1</sup>H NMR spectroscopy and GLC analysis (average of at least two experiments). Yield is based on the starting R<sub>2</sub>N-OBz.

The use of other copper salts is also feasible. Identical results are obtained when CuCl<sub>2</sub> is substituted for CuOTf under the standard reaction conditions (eqs 4 and 5; cf. Table 2, entries 1 and 13, respectively).



Preliminary results also indicate the feasibility of transferring both aryl groups of the diorganozinc reagent. *N*-(*o*-Tolyl)piperidine is obtained in 86% yield when Cu(II)-catalyzed arylation of *O*-benzoyl-*N*-hydroxypiperidine (1.0 equiv) is conducted with 0.6

equiv of (2-MePh)<sub>2</sub>Zn (eq 6) instead of the standard 1.1 equivalents (Table 2, entry 7).



From a preparative standpoint, this amination protocol has several attractive features. The reaction proceeds at ambient temperature in less than 1 h for all substrates tested. Isolation of analytically pure product via a simple acid/base extractive workup is suitable in most instances. The successful use of diorganozinc reagents generated in situ from the corresponding Grignard or organolithium obviates the need for isolation and distillation of R<sub>2</sub>Zn nucleophiles. The starting *N,N*-dialkyl *O*-acyl hydroxylamine electrophiles are easily prepared in one step by Ganem's method.<sup>18</sup> These materials are crystalline solids that show good stability: they can be purified via column chromatography and stored for months in a freezer with no evidence of decomposition or loss of reactivity.

The copper-catalyzed electrophilic amination of diorganozincs offers a general, convenient, and high-yielding means of preparing tertiary amines under mild conditions. Catalytic delivery of R<sub>2</sub>N-(+) synthons is a topic of continuing interest in our laboratory, and findings from this research will be the subject of future publications.

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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>.

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