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Mechanistic Studies of the Copper-Catalyzed Electrophilic Amination of Diorganozinc Reagents and Development of a Zinc-Free Protocol

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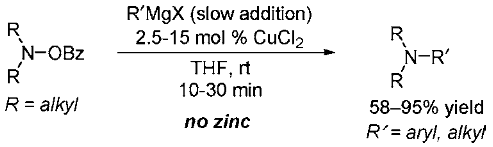
ABSTRACT



An S_N2 mechanism for the copper-catalyzed amination of diorganozinc reagents by *O*-benzoyl-*N*,*N*-dialkylhydroxylamines is supported by following stereochemically defined organometallics through the reaction and by employing the endocyclic restriction test. A copper-catalyzed electrophilic amination of organomagnesium compounds is also described in which the use of zinc halides has been eliminated.

The electrophilic amination of nonstabilized carbanions is a well-studied but underutilized method in synthetic chemistry.[1] Such aminations are classically conducted under relatively harsh conditions with variable yields, but a number of studies have provided improved protocols for the oxidative amination of myriad organometallics.[2] These reactions provide a valuable complement to the Buchwald−Hartwig coupling,[3] currently the state of the art in nucleophilic amination.

To better understand the Cu-catalyzed amination of diorganozinc reagents with *O*-acyl-*N*,*N*-dialkylhydroxylamines **1**,[2d−f] we wished to conduct experiments to elucidate the mechanism. This particular reaction lies at the crossroads of two well-understood scenarios. Various aminations of organolithium reagents have been reported to proceed through a substitution mechanism;[4,5] oxidative addition/reductive elimination is not possible for lithium. Conversely, it has been inferred that Cu mediates C−N bond formation by reductive elimination,[6] but several mechanisms can be invoked that lead to the formation of the necessary copper-amido bond.[7] In the reaction of interest, a copper complex could (i) diplace the benzoate leaving group through an S_N2 reaction, (ii) oxidatively add across the N−O bond in a non-S_N2 process, or (iii) add though a radical process (Figure 1).

We first sought to determine whether copper alone can effect the amination or if a synergistic effect with zinc is involved. The results of the amination of **1a** with stoichiometrically generated phenylcuprates are listed in Table 1.

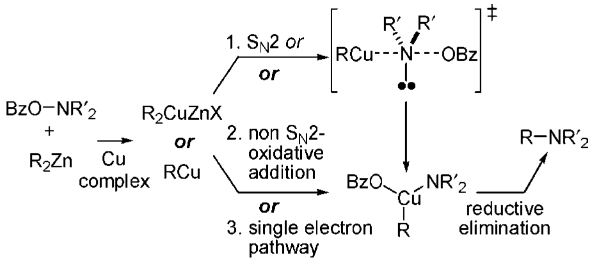


Figure 1. Possible mechanistic scenarios.

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(1) Reviews: (a) Dembech, P.; Seconi, G.; Ricci, A. *Chem. Eur. J.* **2000**, *6*, 1281−1286. (b) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947−1980. (c) Greck, C.; Genèt, J. P. *Synlett* **1997**, 741−748.

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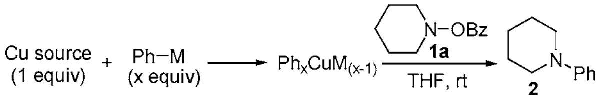
Table 1. Amination of 4-(Benzoyloxy)piperidine with Phenylcuprates[a]



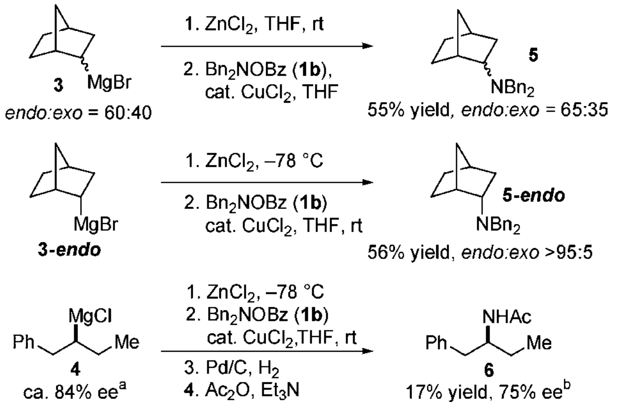
entry	Cu source	M	equiv of PhM	% yield[d]
1[b]	CuBr·SMe$_2$	Li	1	55
2[b]	CuBr·SMe$_2$	Li	2	68
3[b]	CuBr·SMe$_2$	MgBr	1	56
4[b]	CuBr·SMe$_2$	ZnBr[e]	2	68
5[c]	Li$_2$CuCl$_3$	Li	2	72
6[c]	Li$_2$CuCl$_3$	MgBr	1	68
7[c]	Li$_2$CuCl$_3$	ZnBr[e]	2	78
8	0.05 equiv of CuCl	ZnPh	1.1	88

[a] Conditions: 1 equiv of "Cu", 1 equiv of R$_2$NOC(O)Ph, 0.25 M THF. [b] Cuprate reacted at 0 °C for 30 min. [c] Cuprate reacted at −15 °C for 1 h. [d] Isolated yields (average of at least two experiments). Yield is based on the starting R$_2$NOC(O)Ph. [e] Prepared from Rieke zinc and bromobenzene.

The suitability of organolithium and -magnesium compounds in this reaction as precursors to the cuprate (entries 1−3, 5, 6) establishes that the Zn metal center is not integral for the C−N bond-forming event. Li$_2$CuCl$_3$ was used in addition to the CuBr·SMe$_2$ complex because its high solubility in THF rendered formation of the cuprate (especially monophenylcopper) more facile. Its use resulted in more consistent results and marginally higher yields (cf. entries 3 and 6). Under no set of conditions was the yield obtained in the Cu-catalyzed amination of Ph$_2$Zn matched (entry 8). In some reactions, a small amount of piperidine (<5%) was produced. In these reactions, we also observed the production of biphenyl; presumably, the N−O bond can serve as an oxidant that promotes biaryl coupling.

We next examined the fate of a stereodefined R*$_2$Zn reagent when subjected to the amination conditions. The Grignard reagents **3-*endo***[8] and **4** were chosen to conduct the study (Scheme 1). Though conveniently prepared, the use of **3-*endo*** is not completely unbiased, as the reaction of interest must proceed through diastereomeric transition states. This limitation has been overcome through the pioneering work of Hoffmann, who has developed the unbiased chiral Grignard reagent **4** and successfully used it to investigate various oxidations,[9] including electrophilic amination.[10]

Scheme 1. Amination of Stereodefined Grignard Reagents with *O*-Benzoyl-*N*,*N*-dibenzylhydroxylamine



[a] See footnote [13]. [b] Determined by GLC.

Transmetalation of an equilibrium mixture of **3** to zinc and further reaction with an excess of **1b** yielded a 65:35 *endo*:*exo* mixture of amine **5** in 55% yield (Scheme 1). This is similar to published ratios obtained for carbonation,[8a] mercuration,[8a] and amination.[11] After establishing that both isomers react similarly, we examined the resolved isomer. The use of **3-*endo*** provided amine **5-*endo*** (>95:5), supporting retention of configuration during the amination. Both isomers of **5** were assigned using NOESY spectroscopy.

Transmetalation of **4** (~84% ee) to zinc followed by amination with **1b** formed the corresponding tertiary amine. This amine was transformed via hydrogenolysis and subsequent acetylation to the acetamide (*S*)-**6** (75% ee, GLC). In a reaction of relevance reported by Hoffmann, sequential transmetalation of **4** to zinc and copper followed by conjugate addition to mesityl oxide resulted in 6% racemization.[12] The 9% racemization that we observe is comparable, and we conclude that this amination transfers chirality to the same extent as the conjugate addition of cuprates to enones. Taken

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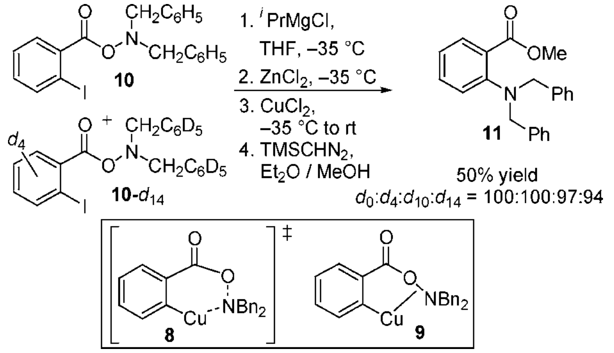
together with the retention observed in the norbornyl system, we conclude that a polar mechanism is at least dominant, if not exclusive. A radical mechanism can be eliminated, since considerable racemization would accompany such an intermediate.

We used the endocyclic restriction test[5,14] to differentiate between an S_N2 displacement at nitrogen and non-S_N2 oxidative addition/reductive elimination of the N−O/C−N bond. This test allows one to obtain a general picture of the transition state geometry. When the system is a six-membered ring, an intramolecular S_N2 process is forbidden because the 6-*endo-tet* transition structure **8** is prohibitively strained (Scheme 2). A non-S_N2 oxidative addition process into the pendent N−O bond would proceed to give an oxametalacyclopentane. This intermediate is geometrically attainable because the precursor σ-bond complex **9** is not strained; the intramolecular cross-coupling is therefore feasible via this mechanism.

Scheme 2. Endocyclic Restriction Test



We selected iodide **10** as the organocopper precursor. The deuterated analog **10**-d_{14} is easily prepared from benzene-d_6.[15] This system provides **11**-d_0 and **11**-d_{14} as non-crossover products and **11**-d_4 and **11**-d_{10} as crossover products, analyzed easily by mass spectrometry (MS). Low-temperature iodine/magnesium exchange[16] of an equivalent mixture of **10** and **10**-d_{14} provided the functionalized Grignard reagents that were converted to the corresponding diorganozincs. The addition of catalytic $CuCl_2$ and warming to room temperature provided amino acids that were converted to the methyl esters **11** using $TMSCHN_2$.[17] Deiodinated starting material could be recovered by hydrolyzing the intermediate diorganozinc with no detectable amination prior to the addition of $CuCl_2$.

Analysis of the products by MS revealed a near statistical mixture of the four isotopomers, meaning the amination is occurring intermolecularly. This supports a transition state that has a large Cu−N−OBz bond angle (e.g., ∼180°).

We then reinitiated our previous efforts toward devising a procedure that would reduce or eliminate completely the need for pregenerating the diorganozinc.[2f] Eliminating stoichiometric amounts of an anhydrous zinc salt would be beneficial for large-scale reactions.

The dominant side reaction when Grignard reagents react with *O*-acylhydroxylamines is C-acylation to form ketones. With the hope that acylation could be slowed enough to permit amination, several analogs of **12** were prepared that contain either electron-rich or sterically bulky substituents on the acyl moiety. Table 2 displays the relevant experiments that were conducted using 3 mol % $CuCl_2$ with or without catalytic $ZnCl_2$. PhMgBr was added by syringe pump over 7 min to ensure reproducibility. Higher yields were realized when $ZnCl_2$ was omitted altogether. The use of 2.2 equiv of the Grignard was not necessary (entry 7). All analogs except carbonate **12g** were equally capable of providing amine **13** (entry 13).

Table 2. Amination of *O*-Acyl-*N*,*N*-diethylhydroxylamines with Phenylmagnesium Bromide Catalyzed by $ZnCl_2$ and $CuCl_2$[a]

$$\underset{\textbf{12a-g}}{Et_2NO_2CR} + \underset{\text{(slow addition)}}{PhMgBr} \xrightarrow[\text{THF, rt}]{\text{3 mol \% CuCl}_2\text{, cat. ZnCl}_2} \underset{\textbf{13}}{Et_2N{-}Ph}$$

entry	R	equiv of PhMgBr	equiv of $ZnCl_2$	% yield[b]
1	Ph (**12a**)	2.2	0.1	84
2	4-MeOPh (**12b**)	2.2	0.1	62
3	4-Me_2NPh (**12c**)	2.2	0.1	81
4	2-MePh (**12d**)	2.2	0.1	74
5	2,4,6-Me_3Ph (**12e**)	2.2	0.1	75
6	Ph (**12a**)	2.2		87
7	Ph (**12a**)	1.1		89
8	4-MeOPh (**12b**)	2.2		79
9	4-Me_2NPh (**12c**)	2.2		79
10	2-MePh (**12d**)	2.2		89
11	2,4,6-Me_3Ph (**12e**)	2.2		82
12	^{t}Bu (**12f**)	2.2		83
13	EtO (**12g**)	2.2		27

[a] Conditions: PhMgBr added via syringe pump (0.15 mmol/min), 1 equiv of $R_2NOC(O)Ph$, 0.03 equiv of $CuCl_2$, 0.16 M **12** in THF. [b] Yields determined by GLC vs internal standard. Yield is based on the starting $Et_2NOC(O)R$.

The Mg → Cu transmetalation and resulting amination evidently occurs much faster than C-acylation regardless of the relative reactivity of the carbonyl toward nucleophilic attack ($k_{\text{transmetalation}} \cdot k_{\text{amination}} \gg k_{\text{acylation}}$). This observation parallels the copper-catalyzed conjugate addition of Grignard reagents to α,β-unsaturated ketones. To gauge the relative reactivity of the two electrophilic sites, aminations were then examined in the absence of $CuCl_2$ (Table 3).

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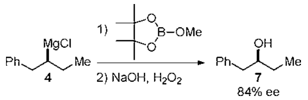
(13) We established this value by preparing known alcohol **7** (from ref 9) in 84% ee, which is slightly lower than that published (ca. 91% ee).



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(15) See Supporting Information for preparation of **10** and **10**-d_{14}.

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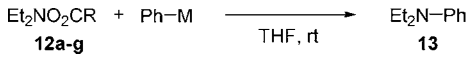
Table 3. Uncatalyzed Amination of *O*-Acyl-*N*,*N*-diethylhydroxylamines with Phenylmagnesium Bromide[a]


$$\underset{\textbf{12a-g}}{Et_2NO_2CR} + Ph{-}M \xrightarrow[\text{THF, rt}]{} \underset{\textbf{13}}{Et_2N{-}Ph}$$

entry	R	PhM (equiv)	temp	% yield[b]
1	Ph (**12a**)	PhMgBr (1.1)	rt	9
2	4-MeOPh (**12b**)	PhMgBr (1.1)	rt	17
3	4-Me$_2$NPh (**12c**)	PhMgBr (1.1)	rt	21
4	2-MePh (**12d**)	PhMgBr (1.1)	rt	18
5	2,4,6-Me$_3$Ph (**12e**)	PhMgBr (1.1)	rt	85
6	2,4,6-Me$_3$Ph (**12e**)	PhLi (2.2)	rt	36
7	2,4,6-Me$_3$Ph (**12e**)	PhLi (2.2)	−30 °C	50
8	2,4,6-Me$_3$Ph (**12e**)	PhLi (2.2)	0 °C	46
9	^{t}Bu (**12f**)	PhMgBr (2.2)	rt	54
10	^{t}Bu (**12f**)	PhMgBr (2.2)	0 °C	37
11	^{t}Bu (**12f**)	PhMgBr (2.2)	44 °C	57
12	EtO (**12g**)	PhMgBr (2.2)	rt	14

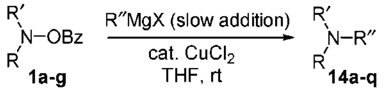
[a] Conditions: 1 equiv of R$_2$NOC(O)Ph, 0.16 M **12** in THF. [b] Yields determined by GLC vs internal standard. Yield is based on the starting Et$_2$NOC(O)R.

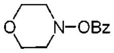
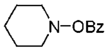
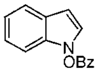
In the absence of Cu, the predominant products were benzophenone, benzhydrol, and triphenylmethanol. Electron-rich and moderately sterically encumbered substrates provided a slight improvement over **12a** (entries 2−4, compare to 1); however, it was not until large acyl groups were used that **13** became the major product (entries 5, 9). Attempts to increase the yield using **12f** by varying the temperature were unsuccessful. PhLi reacts with **12e** to give modest yields that increased as the temperature was decreased (entries 6−8).

The use of other *O*-2,4,6-trimethylbenzoyl hydroxylamines was not extensively evaluated because they are not as easily accessed as the demethylated derivatives. Instead, we investigated the scope of the copper-catalyzed amination of organomagnesium compounds (Table 4). The yields for tertiary amines **14a**−**q** were moderate to excellent for the majority of cases investigated. For a number of cases, it was necessary to increase the catalyst loading to achieve synthetically useful yields. The benefit of this increase was substrate-dependent (compare entries 5 and 6 to entries 11 and 12), and high catalyst loadings were ultimately detrimental (entries 17−20). Secondary amines were not sucessfully prepared. Instead, deprotonation to the Mg-amide occurred (entry 22). As predicted by an S$_N$2 pathway, **1g**[18] was unable to provide *N*-phenylindole by this methodology (entry 23).[19]

In summary, we can support an S$_N$2 pathway for the Cu-catalyzed amination of dialkylzinc reagents by (i) demonstrating that zinc is not essential in the C−N bond-forming step, (ii) showing that the configuration at the reacting carbon is retained through the reaction, and (iii) employing the endocyclic restriction test. We were able to develop a Cu-catalyzed amination of Grignard reagents after realizing the relative rates of O-acylation, transmetalation, and C−N bond formation were favorable. This reaction does not possess the scope of our previous protocol employing diorganozinc compounds but in some cases can be operationally superior as a result of the absence of anhydrous zinc salts.

Table 4. Copper-Catalyzed Amination of *O*-Acyl-*N*,*N*-dialkylhydroxylamines with Grignard Reagents[a]


$$\underset{\textbf{1a-g}}{R(R')N{-}OBz} \xrightarrow[\text{cat. CuCl}_2\text{, THF, rt}]{\text{R}''\text{MgX (slow addition)}} \underset{\textbf{14a-q}}{R(R')N{-}R''}$$

entry	R(R′)NOBz	R″MgX (equiv) (product)	mol % CuCl$_2$	% yield[b]
1	Bn$_2$N−OBz **1b**	Et (1.1) (**14a**)	2.5	95
2	**1b**	^{c}Hex (1.1) (**14b**)	2.5	88
3	**1b**	^{t}Bu (1.1) (**14c**)	2.5	88
4	**1b**	^{c}Pr (1.5) (**14d**)	15	59
5	**1b**	Ph (1.6) (**14e**)	5	20[c]
6	**1b**	Ph (1.6) (**14e**)	10	92
7	**1b**	4-FPh (2.2) (**14f**)	10	58
8	 **1c**	Ph (1.6) (**14g**)	2.5	37
9	**1c**	Ph (1.6) (**14g**)	10	68
10	**1c**	2-MePh (1.1) (**14h**)	2.5	7
11	 **1a**	Ph (1.1) (**14i**)	2.5	52
12	**1a**	Ph (1.1) (**14i**)	10	64
13	**1a**	2-MePh (1.1) (**14j**)	2.5	75
14	**1a**	2,4,6-Me$_3$Ph (1.2) (**14k**)	2.5	61
15	Et$_2$N−OBz **1d**	2-MePh (1.1) (**14l**)	2.5	61
16	**1d**	2,4,6-Me$_3$Ph (1.2) (**14m**)	2.5	80
17	**1d**	4-MeOPh (1.7) (**14n**)	5	65[d]
18	**1d**	4-MeOPh (1.7) (**14n**)	10	75
19	**1d**	4-MeOPh (1.7) (**14n**)	25	26[d]
20	**1d**	4-MeOPh (1.7) (**14n**)	50	8[d]
21	(allyl)$_2$N−OBz **1e**	^{c}Hex (1.1) (**14o**)	2.5	84
22	^{s}BuHN−OBz **1f**	Ph (2.2) (**14p**)	5	trace
23	 **1g**	Ph (2.2) (**14q**)	2.5	0

[a] Conditions: RMgX added via syringe pump (0.15 mmol/min), 1 equiv of R$_2$NOC(O)Ph. [b] Isolated yields of product of purity ≥95% based on ^{1}H NMR spectroscopy (average of at least two experiments) unless noted.[c] Yield determined by ^{1}H NMR spectroscopy vs internal standard. [d] Yield determined by GLC vs internal standard. Yield is based on the starting R$_2$NOC(O)Ph.

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

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[18] Acheson, R. M.; Benn, M. H.; Jacyno, J.; Wallis, J. D. *J. Chem. Soc., Perkins Trans. 2* **1983**, 497−500.

[19] The copper-catalyzed amination ofdiphenylzinc with **1g** was also unsuccessfull.