



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

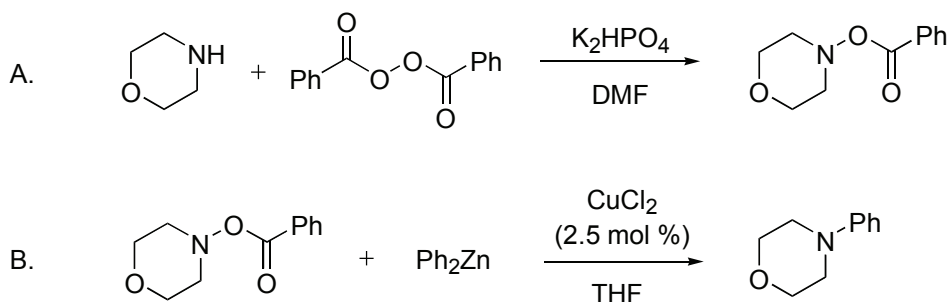
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

## COPPER-CATALYZED ELECTROPHILIC AMINATION OF DIORGANOZINC REAGENTS: 4-PHENYLMORPHOLINE



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Checked by George Nora and Marvin J. Miller.

### 1. Procedure

*A. 4-Benzoyloxymorpholine.* A 500-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar is 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 is stirred and morpholine (5.20 mL, 59.4 mmol) (Note 1) is added via syringe in one portion (Note 2). The flask is capped with a septum and the suspension is stirred at ambient temperature for 1 h, during which time a gradual discoloration of the reaction mixture from clear to yellow occurs. Deionized water (200 mL) is added and the contents are stirred vigorously for several min until all solid has dissolved. The reaction mixture is transferred to a 1-L separatory funnel and extracted with ethyl acetate (1 x 150 mL). The organic phase is collected and washed with saturated aqueous NaHCO<sub>3</sub> solution (2 x 100 mL). All of the aqueous fractions are combined and extracted with ethyl acetate (3 x 100 mL). All of the organic fractions are combined and washed with three 100-mL portions of deionized water, 100 mL of brine, dried over MgSO<sub>4</sub>, filtered, and concentrated by rotary evaporation. The resulting pale-yellow solid is purified by flash column chromatography (Note 3), to yield 7.28–8.03 g (70.3–77.5%) of 4-benzoyloxymorpholine as a white, crystalline solid (Note 4).

*B. 4-Phenylmorpholine.* An oven-dried 250-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar and a

septum is maintained under an inert atmosphere of argon and charged with zinc chloride (2.04 g, 15 mmol), and anhydrous tetrahydrofuran (27 mL) (Note 5). The solution is stirred and cooled in an ice-bath. Phenylmagnesium bromide (30 mL, 30 mmol) is added via syringe in one portion (Note 6). The resulting orange-colored solution is stirred for an additional 30 min in the ice-bath prior to use.

An oven-dried 1-L, two-necked, round-bottomed flask equipped with a thermometer, a septum, and a Teflon-coated magnetic stir bar is maintained under an inert atmosphere of argon and charged with 4-benzoyloxy-morpholine (5.18 g, 25 mmol), copper(II) chloride (0.084 g, 0.625 mmol), and anhydrous tetrahydrofuran (250 mL) (Note 7). The solution is stirred and cooled in an ice-bath. The previously generated diphenylzinc solution is added via cannula over the course of 5–10 min at a rate such that the internal temperature does not exceed 5 °C. The resulting light brown solution is stirred for 1.5 h in the ice-bath. Diethyl ether (250 mL) is added and the reaction mixture is transferred to a 1-L separatory funnel. The reaction mixture is washed with saturated aqueous NaHCO<sub>3</sub> solution (3 x 200 mL) (Note 8), brine (1 x 100 mL), and concentrated by rotary evaporation. The resulting yellow oil is dissolved in diethyl ether (100 mL) and the solution is extracted with 10 % aqueous HCl solution (3 x 50 mL). The aqueous extracts are basified with 10 % aqueous NaOH solution (200 mL) and extracted with dichloromethane (3 x 100 mL). The organic fraction is washed with 150-mL of brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated by rotary evaporation to yield 2.73 g (67%) of 4-phenylmorpholine as an off-white, crystalline solid (Note 9).

## 2. Notes

1. Benzoyl peroxide (97%) was purchased from Aldrich Chemical Company. Dipotassium hydrogen phosphate was purchased from Fisher Scientific. *N,N*-Dimethylformamide (99%) and morpholine (99%) (d = 0.996 g/mL @ 25 °C) were purchased from Acros. All reagents were used as received.

2. A slight exotherm develops approximately 30 seconds after the completion of addition of morpholine.

3. Flash column chromatography was performed on a silica gel column (20 cm length x 18 cm width, 180 g of silica gel) eluting with 50% EtOAc:hexanes. Collected fractions were analyzed by thin layer

chromatography (TLC), eluting with 50% EtOAc:hexanes ( $R_f = 0.35$  for 4-benzoyloxymorpholine). Visualization was accomplished with UV light and on spraying with aqueous ceric ammonium molybdate solution followed by heating.

4. Analytical data for 4-benzoyloxymorpholine: mp 82–84 °C, lit mp 81–82 °C;<sup>2</sup> IR (Nujol,  $\text{cm}^{-1}$ ) 2924, 2852, 1730, 1599, 1456, 1377, 1315, 1269, 1248, 1178, 1165, 1101, 1084, 1066, 1049, 1007, 922, 858, 712;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.03 (br t,  $J = 9.4$  Hz, 2 H), 3.43 (br d,  $J = 9.3$  Hz, 2 H), 3.85 (br t,  $J = 11.2$  Hz, 2 H), 3.96 (br d,  $J = 10.7$  Hz, 2 H), 7.45–7.41 (m, 2 H), 7.58–7.53 (m, 1 H), 8.00–7.98 (m, 2 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 57.0, 65.8, 128.4, 129.2, 129.4, 133.1, 164.6. Anal. Calcd for  $\text{C}_{11}\text{H}_{13}\text{NO}_3$ : C, 63.76; H, 6.32; N, 6.76. Found: C, 63.96; H, 6.40; N, 6.67. The checkers noted that storage of this compound in the freezer (-10 °C) or at room temperature resulted in discoloration. The checkers recommend that it be used immediately upon formation.

5. Zinc chloride (98%) was purchased from Riedel-de-Haën and because it is very hygroscopic, it was dried under vacuum (0.1 mmHg) at 150 °C for 12 h prior to use. Tetrahydrofuran was dried by passage through a column of neutral alumina under nitrogen prior to use.

6. Phenylmagnesium bromide was purchased from Aldrich Chemical Company as a 1.0 M solution in tetrahydrofuran, and was used as received. The checkers noted that if the color does not change upon addition of the Grignard reagent, then the reaction does not proceed.

7. Copper(II) chloride (97%) was purchased from Aldrich Chemical Company and was used as received. Upon addition of the copper (II) chloride the solution turned a light green.

8. Copious formation of a white precipitate accompanied the initial wash with saturated aqueous  $\text{NaHCO}_3$  solution.

9. Analytical data for 4-phenylmorpholine: mp 50–52 °C, (lit mp 53–54 °C);<sup>3</sup> IR (Nujol,  $\text{cm}^{-1}$ ) 2922, 2854, 1601, 1498, 1458, 1377, 1231, 1126, 928, 771, 758, 690;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.16–3.13 (m, 4 H), 3.86–3.84 (m, 4 H), 6.92–6.85 (m, 3 H), 7.30–7.24 (m, 2 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 49.4, 66.9, 115.7, 120.0, 129.2, 151.3. Anal. Calcd for  $\text{C}_{10}\text{H}_{13}\text{NO}$ : C, 73.59; H, 8.03; N, 8.58. Found: C, 73.71; H, 8.03; N, 8.52. The checkers report that the procedure, when checked at half-scale, provided a 71% yield.

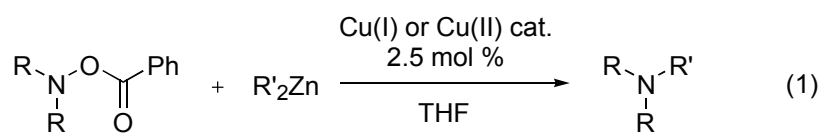
## Waste Disposal Information

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### 3. Discussion

Amines are of fundamental interest in many areas of chemistry. Consequently, the development of methodology for the facile preparation of these compounds continues to be a topical area of research.<sup>4</sup> Among the modern methods for the preparation of amines, the Buchwald-Hartwig coupling is a convenient and general route to aryl amines, and represents the benchmark in catalyzed nucleophilic amination.<sup>5,6</sup> Electrophilic amination of nonstabilized carbanions is an alternative approach, and is noteworthy for its use of the *umpolung* strategy for C-N bond construction.<sup>7,8</sup> Generally, electrophilic amination has been limited to only the most reactive carbon donors (RLi and RMgX reagents), and yields of amine products are modest. Reports of transition-metal catalyzed methods present a possible solution to these problems, but have as yet been limited to the preparation of primary aniline derivatives.<sup>9,10</sup>

The copper-catalyzed electrophilic amination of diorganozinc reagents presented here allows for the expeditious preparation of tertiary amines under mild reaction conditions (eq 1).<sup>11</sup>

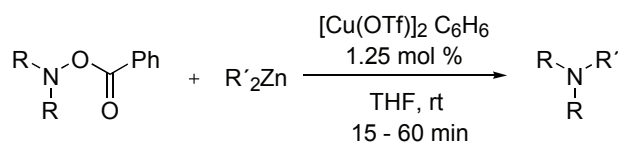


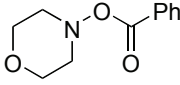
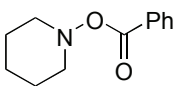
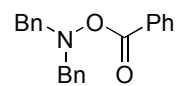
The *O*-benzoyl hydroxylamines employed are easily prepared from the corresponding secondary amines upon treatment with benzoyl peroxide, and show good stability: they are crystalline solids which can be purified via column chromatography and stored indefinitely in a freezer without decomposition or loss of reactivity. These reagents consequently represent a convenient source of sp<sup>3</sup>-hybridized nitrogen electrophiles for the direct delivery of R<sub>2</sub>N<sup>+</sup> synthons. The secondary amine oxidation that is used here is a modification of a protocol originally reported by Ganem.<sup>2</sup> Elevated temperatures were found to be unnecessary and the use of DMF as reaction solvent provided higher yields than diethyl ether.

The amination reaction is quite general in the nucleophilic component, with both  $sp^2$ - (aryl, heteroaryl) and  $sp^3$ -hybridized (alkyl, benzyl) carbanions undergoing coupling in uniformly high yields (Table 1). On a scale of <1 mmol, it is convenient to conduct the reaction at ambient temperature; however, the 25-mmol preparation conducted in this procedure should be performed in an ice bath to minimize a deleterious exotherm.

The  $R_2Zn$  reagents employed are prepared via transmetallation from the corresponding  $RMgX$  or  $RLi$  with 0.5 equivalents of  $ZnCl_2$ , and are used *in situ* without isolation or purification.

**Table 1.** Scope of the Copper-Catalyzed Amination of Diorganozinc Reagents<sup>a</sup>



entry	$R_2N-OC(O)Ph$	$R'$	% yield <sup>b</sup>
1		<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	93
2		<i>o</i> -MeC <sub>6</sub> H <sub>4</sub>	94
3		2-pyridyl	71
4		Bn	80
5		Ph	91
6		Ph	94
7		Bn	91
8		Et	91
9		<i>t</i> -Bu	98

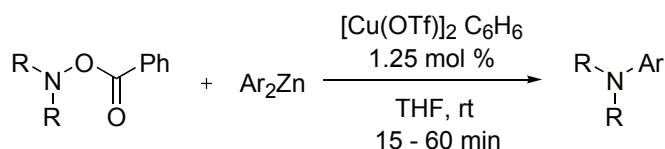
<sup>a</sup> Unless otherwise noted, 1.1 equiv of  $R_2Zn$  were employed. Reactions were run on a 0.50 mmol scale of the starting  $R_2N-OC(O)Ph$ . <sup>b</sup> Isolated yield of product (average of at least two experiments). Yield is based on the starting  $R_2N-OC(O)Ph$ .

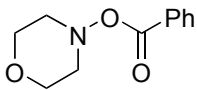
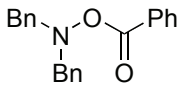
Functionalized tertiary aryl amines can also be prepared when functionalized  $Ar_2Zn$  reagents are employed.<sup>12</sup> The latter are generated *in situ* from the corresponding aryl iodides via a simple Mg/I exchange/transmetallation sequence.<sup>13</sup> The reaction shows good functional

group tolerance, with nitrile, ester, halide, triflate, and nitro functionalities all accommodated (Table 2).

In conclusion, the copper-catalyzed amination of diorganozinc reagents represents a convenient and general route to tertiary amines. The reaction is noteworthy for the mild reaction conditions employed and ease of product purification (acid/base extractive workup). The catalyst is cheap and requires no exogenous supporting ligand. Such procedures may find utility as a complement to Buchwald-Hartwig coupling reactions.

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



entry	R <sub>2</sub> N-OC(O)Ph	Ar	% yield <sup>b</sup>
1		<i>p</i> -NCC <sub>6</sub> H <sub>4</sub>	76
2		<i>p</i> -EtO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	77
3		<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	93
4		<i>p</i> -TfOC <sub>6</sub> H <sub>4</sub>	95
5		<i>o</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	83
6		<i>p</i> -NCC <sub>6</sub> H <sub>4</sub>	95
7		<i>p</i> -EtO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	99
8		<i>o</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	97

<sup>a</sup> 1.1equiv of Ar<sub>2</sub>Zn were employed. Reactions were run on a 0.25 mmol scale of the starting R<sub>2</sub>N-OC(O)Ph. <sup>b</sup> Isolated yield of product (average of at least two experiments). Yield is based on the starting R<sub>2</sub>N-OC(O)Ph.

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## Appendix

### Chemical Abstracts Nomenclature (Registry Number)

Benzoyl peroxide: Dibenzoyl peroxide; (94-36-0)

Phenylmagnesium bromide: Magnesium, bromophenyl-; (100-58-3)

4-Benzoyloxymorpholine; (5765-65-1)

4-Phenylmorpholine: (92-53-5)



