Supporting Information

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

Ashley M. Berman and Jeffrey S. Johnson*

*Department of Chemistry, University of North Carolina at
Chapel Hill, Chapel Hill, North Carolina 27599-3290*

jsi@unc.edu

Experimental Section

Materials and Methods: General. Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon magnetic resonance spectra (1H NMR and ^{13}C NMR) were recorded on a Bruker model Avance 400 (1H NMR at 400 MHz and ^{13}C NMR at 100 MHz) spectrometer with tetramethylsilane or solvent resonance as the internal standard (1H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.24 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). 1H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, br t = broad triplet, q = quartet, sept = septet, m = multiplet), coupling constants (Hz), and integration. GLC analysis was performed on an Agilent 6890N Network GC System equipped with an HP-5 column (30 m x 0.316 mm, pressure = 10.0 psi, flow = 1.4 mL/min, detector = FID, 250°C) with helium gas as carrier. SFC analysis was performed on a Berger Supercritical Fluid Chromatograph model FCM 1100/1200 equipped with a Hypersil column (pressure = 150 bar, flow = 1.5 mL/min, detector = UV-vis). Samples were eluted with SFC grade CO_2 and 1.5% MeOH. Combustion analyses were performed by Atlantic Microlab Inc., Norcross, GA. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out either by acid/base extractive work-up or flash chromatography using Sorbent Technologies silica gel 60 (32-63 μm). All reactions were carried out under an inert atmosphere of argon or nitrogen in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments. Tetrahydrofuran was dried by passage through a column of neutral alumina

under nitrogen prior to use.¹ ZnCl₂ was dried under vacuum (0.1 mm Hg) at 150 °C for 12 hours prior to use. 4-Iodobenzonitrile and 4-iodobenzoic acid ethyl ester were prepared from the corresponding aryl bromides according to the method of Buchwald.² All other reagents were obtained from commercial sources and used without further purification.

I. Preparation of O-Benzoyl Hydroxylamines

General Procedure (A) for the preparation of O-benzoyl hydroxylamines. 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*-dimethyl formamide (125 mL). The suspension was stirred and the amine (60 - 125 mmol) was added via syringe in one portion. The suspension was stirred at ambient temperature for the indicated reaction time. 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. NaHCO₃ 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, 100-mL of brine, dried over MgSO₄, and concentrated by rotary evaporation. The resulting crude product mixture was purified by flash column chromatography, eluting with the indicated solvent system, to afford desired product of ≥95% purity as judged by ¹H NMR spectroscopy. The product was stored at sub-ambient temperature under anhydrous conditions.

4-Benzoyloxymorpholine (2a). The title compound was prepared according to General Procedure **A** using morpholine (5.20 mL, 60 mmol) with stirring for 1 h to yield 4-benzoyloxymorpholine (7.71 g, 37 mmol, 74 %) as a white solid following flash column chromatography with 50% EtOAc/hexanes. Analytical data for the title compound: **mp** (uncorrected) 82 – 84 °C. **IR** (Nujol, cm⁻¹) 2924, 2852, 1730, 1599, 1456; **¹H NMR** (400 MHz, CDCl₃) 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 $\text{C}_{11}\text{H}_{13}\text{NO}_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.96; H, 6.40; N, 6.67.

1-Benzoyloxypiperidine (2b). The title compound was prepared according to General Procedure **A** using piperidine (5.94 mL, 60 mmol) with stirring for 1 h to yield 1-benzoyloxypiperidine (8.23 g, 40 mmol, 80%) as a white solid following flash column chromatography with 25% EtOAc/hexanes. Analytical data for the title compound: **mp** (uncorrected) 55 - 59 °C. **IR** (Nujol, cm^{-1}) 2924, 2856, 1731, 1452; ^1H NMR (400 MHz, CDCl_3) δ 8.00 – 7.98 (m, 2H), 7.55 – 7.51 (m, 1H), 7.43 – 7.38 (m, 2H), 3.49 (br s, 2H), 2.76 (br s, 2H), 1.84 – 1.78 (m, 4H), 1.65 (br s, 1H), 1.28 – 1.26 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.7, 132.8, 129.7, 129.4, 128.3, 57.5, 25.0, 23.3.

O-Benzoyl-N,N-Diisopropylhydroxylamine (2f). The title compound was prepared according to General Procedure **A** using *N,N*-diisopropyl amine (17.5 mL, 125 mmol) with stirring for 24 h to yield *O*-benzoyl-*N,N*-diisopropylhydroxylamine (9.35 g, 42 mmol, 85%) as a clear, colorless oil following flash column chromatography with 15% EtOAc/hexanes. Analytical data for the title compound: **IR** (thin film, cm^{-1}) 3067, 2979, 2937, 2875, 1707, 1601, 1451; ^1H NMR (400 MHz, CDCl_3) δ 8.03 – 8.01 (m, 2H), 7.54 – 7.53 (m, 1H), 7.44 – 7.40 (m, 2H), 3.39 (sept, 2H, $J = 6.4$), 1.13 (d, 12H, $J = 6.4$); ^{13}C NMR (100 MHz, CDCl_3) δ 166.3, 132.9, 129.6, 129.4, 128.4, 53.5, 53.4.

O-Benzoyl-N-tert-Octylhydroxylamine (2g). The title compound was prepared according to General Procedure **A** using *tert*-octyl amine (20.1 mL, 125 mmol) with stirring for 24 h to yield *O*-benzoyl-*N-tert*-octylhydroxylamine (11.30 g, 45 mmol, 91 %) as a clear, colorless oil following flash column chromatography with 10%

EtOAc/hexanes. Analytical data for the title compound: **IR** (thin film, cm^{-1}) 3223, 3070, 2953, 2908, 2873, 1718, 1603, 1473, 1451; **^1H NMR** (400 MHz, CDCl_3) δ 8.02 – 8.00 (m, 2H), 7.65 (br s, 1H), 7.57 – 7.55 (m, 1H), 7.47 – 7.43 (m, 2H), 1.57 (s, 2H), 1.25 (s, 6H), 1.05 (s, 9H); **^{13}C NMR** (100 MHz, CDCl_3) δ 166.7, 133.1, 129.2, 128.6, 128.5, 59.9, 51.7, 31.7, 31.5, 26.7.

General Procedure (B) for the preparation of O-benzoyl hydroxylamines. A 50-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar was charged with benzoyl peroxide (1.21 g, 5.0 mmol), dipotassium hydrogen phosphate (1.31 g, 7.5 mmol), and *N,N*-dimethyl formamide (12.5 mL). The suspension was stirred and the amine (6.0 – 12.5 mmol) was added via syringe in one portion. The suspension was stirred at ambient temperature for the indicated reaction time. Deionized water (50 mL) was added and the contents were stirred vigorously for several minutes until all solids dissolved. The reaction mixture was transferred to a 125-mL separatory funnel and extracted with 25 mL of ethyl acetate. The organic phase was collected and washed with two 25-mL portions of saturated aq. NaHCO_3 solution. All of the aqueous fractions were combined and extracted with three 25-mL portions of ethyl acetate. All of the organic fractions were combined and washed with three 25-mL portions of deionized water, 25-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 the indicated solvent system, to afford desired product of $\geq 95\%$ purity as judged by ^1H NMR spectroscopy. The product was stored at sub-ambient temperature under anhydrous conditions.

O-Benzoyl-*N,N*-Dibenzylhydroxylamine (2c). The title compound was prepared according to General Procedure **B** using dibenzylamine (2.7 mL, 12.5 mmol) with stirring for 24 h to yield *O*-benzoyl-*N,N*-dibenzylhydroxylamine (1.05 g, 3.3 mmol, 66%) as a white solid after flash chromatography with 1% EtOAc/hexanes. Analytical data for the title compound: **mp** (uncorrected) 96 – 98 °C. **IR** (Nujol, cm^{-1}) 2952, 2926, 2854, 1726, 1456; **^1H NMR** (400 MHz, CDCl_3) δ 7.82 – 7.80 (m, 2H), 7.50 – 7.46 (m, 1H), 7.44 – 7.42 (m, 4H), 7.36 – 7.23 (m, 8H), 4.19 (s, 4H); **^{13}C NMR** (100 MHz, CDCl_3) δ 164.9, 136.0,

132.8, 129.5, 129.4, 129.3, 128.3, 128.28, 127.6, 62.1.

O-Benzoyl-*N,N*-Diallylhydroxylamine (2d). The title compound was prepared according to General Procedure **B** using *N,N*-diallyl amine (0.74 mL, 6.0 mmol) with stirring for 4 h to yield *O*-benzoyl-*N,N*-diallylhydroxylamine (1.00 g, 4.6 mmol, 92 %) as a clear, colorless oil following flash column chromatography with 25% EtOAc/hexanes. Analytical data for the title compound: **IR** (thin film, cm^{-1}) 3081, 3015, 2983, 2838, 1750, 1647, 1602, 1451; **1H NMR** (400 MHz, $CDCl_3$) δ 7.97 – 7.94 (m, 2H), 7.55 – 7.51 (m, 1H), 7.42 – 7.38 (m, 2H), 6.04 – 5.94 (m, 2H), 5.27 – 5.15 (m, 4H), 3.65 – 3.63 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.3, 133.0, 132.6, 129.4, 129.2, 128.3, 119.5, 61.7.

O-Benzoyl-*N*-sec-Butylhydroxylamine (2h). The title compound was prepared according to General Procedure **B** using *N*-sec-butyl amine (0.61 mL, 6.0 mmol) with stirring for 6 h to yield *O*-benzoyl-*N*-sec-butylhydroxylamine (0.86 g, 4.5 mmol, 89 %) as a clear, colorless oil following flash column chromatography with 15% EtOAc/hexanes. Analytical data for the title compound: **IR** (thin film, cm^{-1}) 3239, 3068, 2969, 2936, 2878, 1720, 1602, 1452; **1H NMR** (400 MHz, $CDCl_3$) δ 8.02 – 8.00 (m, 2H), 7.76 (br s, 1H), 7.58 – 7.54 (m, 1H), 7.46 – 7.42 (m, 2H), 3.13 – 3.11 (m, 1H), 1.69 – 1.62 (m, 1H), 1.48 – 1.41 (m, 1H), 1.17 (d, 3H, $J = 6.4$), 0.97 (t, 3H, $J = 7.5$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.9, 133.2, 129.3, 128.6, 128.5, 58.2, 26.8, 17.5, 10.2.

O-Benzoyl-*N*-iso-Butylhydroxylamine (2i). The title compound was prepared according to General Procedure **B** using *N*-iso-butylamine (0.60 mL, 6.0 mmol) with stirring for 1 h to yield *O*-benzoyl-*N*-sec-butylhydroxylamine (0.59 g, 3.1 mmol, 61%) as a clear, colorless oil following flash column chromatography with 15% EtOAc/hexanes. Analytical data for the title compound: **IR** (thin film, cm^{-1}) 3245, 3069, 2960, 2929, 2872,

1720, 1602, 1470, 1452; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.01 – 7.98 (m, 3H), 7.56 – 7.54 (m, 1H), 7.45 – 7.41 (m, 2H), 2.94 (d, 2H, J = 6.7), 1.96 – 1.92 (m, 1H), 1.00 (d, 6H, J = 6.7); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 166.9, 133.3, 129.3, 128.5, 60.1, 26.4, 20.5.

O-Benzoyl-*N,N*-Diethylhydroxylamine (2e). An oven-dried round bottom flask equipped with magnetic stir bar and addition funnel was charged with *N,N*-diethylhydroxylamine (0.89 g, 1.0 mL, 10 mmol), freshly distilled triethylamine (1.0 g, 1.4 mL, 10 mmol), and anhydrous dichloromethane (10 mL). The addition funnel was charged with benzoyl chloride (1.4 g, 1.2 mL, 10 mmol) and anhydrous dichloromethane (5 mL). The benzoyl chloride solution was added drop wise over 10 minutes and reaction mixture stirred at room temperature an additional 30 minutes. The reaction mixture was diluted with water (25 mL) and the organic layer was separated, washed with water (1 x 25mL), dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography, eluting with 15% ethyl acetate/hexanes, to afford *O*-benzoyl-*N,N*-diethylhydroxylamine (1.89 g, 9.8 mmol, 98% yield) as a pale yellow oil. The product was stored at sub-ambient temperature under anhydrous conditions. Analytical data for the title compound: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.07 – 8.04 (m, 2H), 7.57 – 7.53 (m, 1H), 7.44 – 7.40 (m, 2H), 2.72 (q, J = 7.6 Hz, 4H), 0.73 (t, J = 7.6 Hz, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 165.8, 132.9, 129.4, 129.3, 128.3, 53.4, 11.8. For additional analytical data (IR spectrum), see Grinberg and Bittner.³

II. Electrophilic Amination of Diorganozinc Reagents: Preparation of Secondary and Tertiary Amines

General Procedure (C) for the copper catalyzed amination of diorganozinc reagents. 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 the RMgX or RLi (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 the *O*-benzoyl hydroxylamine (0.50 mmol), the copper salt (0.0125 mmol), and anhydrous tetrahydrofuran (5.0 mL). The solution was stirred and the previously generated diorganozinc 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. NaHCO₃ 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 Na₂SO₄, and concentrated by rotary evaporation, to afford the desired product of $\geq$ 95% purity as judged by ¹H NMR spectroscopy.

4-Phenylmorpholine (3a). The title compound was prepared according to General Procedure **C** using 4-benzoyloxymorpholine (0.103 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]₂·C₆H₆, 0.003 g, 0.0056 mmol), and a tetrahydrofuran solution of diphenylzinc to yield 4-phenylmorpholine (0.080 g, 0.49 mmol, 98%) as a white solid. The ¹H NMR spectrum was consistent with that reported in the literature.⁴

Procedure for 25 mmol scale: An oven-dried 250-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 (2.04 g, 15 mmol), and anhydrous tetrahydrofuran (27 mL). The solution was stirred and cooled in an ice-bath. Phenylmagnesium bromide (30 mL, 30 mmol) was added via syringe in one portion. The resulting orange colored solution was stirred for an additional 30 minutes in the ice-bath prior to use (*vida infra*). An oven-dried 1-L, two-necked, round-bottomed flask equipped with a thermometer and a Teflon-coated magnetic stirbar was maintained under an inert atmosphere of argon and charged with 4-benzoyloxymorpholine (5.18 g, 25 mmol), copper(II) chloride (0.084 g, 0.625 mmol), and anhydrous tetrahydrofuran (250 mL). The

solution was stirred and cooled in an ice-bath. The previously generated diphenylzinc solution (*vide supra*) was added via cannula over the course of 5-10 minutes at a rate such that the internal temperature does not exceed 5 °C. The resulting light brown solution was stirred for 1.5 hours in the ice-bath. Diethyl ether (250 mL) was added and the reaction mixture was transferred to a 1-L separatory funnel. The reaction mixture was washed with three 200-mL portions of saturated aq. NaHCO₃ solution (copious formation of a precipitate occurs in the initial wash), 100-mL of brine, and concentrated by rotary evaporation. The resulting yellow oil was dissolved in diethyl ether (100 mL) and extracted with three 50-mL portions of 10% aq. HCl solution. The aqueous extracts are basified with 200-mL of 10% aq. NaOH solution, and extracted with three 100-mL portions of dichloromethane. The organic fraction was washed with 150-mL of brine, dried over Na₂SO₄, and concentrated by rotary evaporation, to yield 2.87 – 3.01 g (70 – 74 %) of 4-phenylmorpholine as an off-white, crystalline solid: **mp** (uncorrected) 53 – 55 °C. **IR** (Nujol, cm⁻¹) 2922, 2854, 1601, 1458, 1377; **¹H NMR** (400 MHz, CDCl₃) 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); **¹³C NMR** (100 MHz, CDCl₃) δ 151.3, 129.2, 120.0, 115.7, 66.9, 49.4. **Anal.** Calcd for C₁₀H₁₃NO: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.71; H, 8.03; N, 8.52.

4-(2-Methylphenyl)morpholine (3b). The title compound was prepared according to General Procedure **C** using 4-benzoyloxymorpholine (0.104 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]₂·C₆H₆, 0.003 g, 0.0062 mmol), and a tetrahydrofuran solution of di-*o*-tolylzinc to yield 4-(2-methylphenyl)morpholine (0.086 g, 0.48 mmol, 97%) as a clear, pale yellow oil. The ¹H NMR spectrum was consistent with that reported in the literature.⁵

4-(4-Methoxyphenyl)morpholine (3c). The title compound was prepared according to General Procedure **C** using 4-benzoyloxymorpholine (0.104 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]₂·C₆H₆, 0.003 g, 0.0064 mmol), and

a tetrahydrofuran solution of bis-(4-methoxyphenyl)zinc to yield 4-(4-methoxyphenyl)morpholine (0.091 g, 0.47 mmol, 94%) as a white solid. The ^1H NMR spectrum was consistent with that reported in the literature.⁴

4-Pyridin-2-yl-morpholine (3d). The title compound was prepared according to General Procedure **C** using 4-benzoyloxymorpholine (0.103 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.003 g, 0.0060 mmol), and a tetrahydrofuran solution of bis-(2-pyridinyl)zinc to yield 4-pyridin-2-yl-morpholine (0.059 g, 0.36 mmol, 71%) as a yellow oil. The ^1H NMR spectrum was consistent with that reported in the literature.⁶

4-Benzylmorpholine (3e). The title compound was prepared according to General Procedure **C** using 4-benzoyloxymorpholine (0.104 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.003 g, 0.0062 mmol), and a diethyl ether solution of dibenzylzinc to yield 4-benzylmorpholine (0.070 g, 0.39 mmol, 78%) as a clear, colorless oil. The ^1H NMR spectrum was consistent with that reported in the literature.⁷

1-Phenylpiperidine (3f). The title compound was prepared according to General Procedure **C** using 1-benzoyloxypiperidine (0.103 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.003 g, 0.0066 mmol), and a tetrahydrofuran solution of diphenylzinc to yield 1-phenylpiperidine (0.074 g, 0.46 mmol, 92%) as a clear, pale yellow oil. The ^1H NMR spectrum was consistent with that reported in the literature.⁴

1-(4-Methoxyphenyl)piperidine (3g). The title compound was prepared according to General Procedure **C** using 1-benzoyloxy-piperidine (0.103 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.003 g, 0.0062 mmol), and a tetrahydrofuran solution of bis-(4-methoxyphenyl)zinc to yield 1-(4-methoxyphenyl)piperidine (0.094 g, 0.49 mmol, 98%) as a clear, pale yellow oil. The ^1H NMR spectrum was consistent with that reported in the literature.⁸

***N,N*-Diisopropylaniline (3h).** The title compound was prepared according to General Procedure **C** using *O*-benzoyl-*N,N*-diisopropylhydroxylamine (0.111 g, 0.50 mmol), copper(II) chloride (0.002 g, 0.0125 mmol), and a tetrahydrofuran solution of diphenylzinc to yield *N,N*-diisopropylaniline (0.072 g, 0.40 mmol, 81%) as a clear, colorless oil. The ^1H NMR spectrum was consistent with that reported in the literature.⁹

Diisopropyl-(2-Methylphenyl)amine (3i). The title compound was prepared according to General Procedure **C** using *O*-benzoyl-*N,N*-diisopropylhydroxylamine (0.111 g, 0.50 mmol), copper(II) chloride (0.002 g, 0.0125 mmol), and a tetrahydrofuran solution of di-*o*-tolylzinc to yield diisopropyl-(2-methylphenyl)amine (0.059 g, 0.31 mmol, 62 %) as a clear, colorless oil. The ^1H NMR spectrum was consistent with that reported in the literature.¹⁰

Diisopropyl-(2,4,6-Trimethylphenyl)amine (3j). The title compound was prepared according to General Procedure **C** using *O*-benzoyl-*N,N*-diisopropylhydroxylamine (0.111 g, 0.50 mmol), copper(II) chloride (0.002 g, 0.0125 mmol), and a tetrahydrofuran solution of di-mesitylzinc to yield diisopropyl-(2,4,6-trimethylphenyl)amine (0.084 g, 0.38 mmol,

77 %) as a clear, pale yellow colored oil. Analytical data for the title compound: **IR** (thin film, cm^{-1}) 2968, 2926, 2873, 1479, 1381; **^1H NMR** (400 MHz, CDCl_3) δ 6.78 (s, 2H), 3.53 (sept, 2H, $J = 6.4$), 2.22 (s, 9H), 0.99 (d, 12 H, $J = 6.4$); **^{13}C NMR** (100 MHz, CDCl_3) δ 143.7, 140.3, 134.0, 128.6, 49.7, 23.4, 20.8, 20.2. **Anal.** Calcd for $\text{C}_{15}\text{H}_{25}\text{N}$: C, 82.13; H, 11.49; N, 6.39. Found: C, 81.87; H, 11.47; N, 6.20.

***N,N*-Diethylaniline (3k).** The title compound was prepared according to General Procedure **C** using *N,N*-diethyl-*O*-benzoylhydroxylamine (0.096 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.003 g, 0.0068 mmol), and a tetrahydrofuran solution of diphenylzinc to yield *N,N*-diethylaniline (0.057 g, 0.39 mmol, 77%) as a clear, pale yellow oil. The ^1H NMR spectrum was consistent with that reported in the literature.¹¹

Diethyl-(2-methylphenyl)amine (3l). The title compound was prepared according to General Procedure **C** using *N,N*-diethyl-*O*-benzoylhydroxylamine (0.096 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.003 g, 0.0060 mmol), and a tetrahydrofuran solution of di-*o*-tolylzinc to yield diethyl-(2-methylphenyl)amine (0.065 g, 0.40 mmol, 80%) as a clear, pale yellow oil. The ^1H NMR spectrum was consistent with that reported in the literature.¹²

***N,N*-Diallylaniline (3m).** The title compound was prepared according to General Procedure **C** using *O*-benzoyl-*N,N*-diallylhydroxylamine (0.109 g, 0.50 mmol), copper(II) chloride (0.002 g, 0.0125 mmol), and a tetrahydrofuran solution of diphenylzinc to yield *N,N*-diallylaniline (0.083 g, 0.48 mmol, 96 %) as a clear, colorless oil. The ^1H NMR spectrum was consistent with that reported in the literature.¹³

***N*-iso-Butylaniline (3r).** The title compound was prepared according to General Procedure **C** using *O*-benzoyl-*N*-iso-butylhydroxylamine (0.097 g, 0.50 mmol), copper(II) chloride (0.002 g, 0.0125 mmol), and a tetrahydrofuran solution of diphenylzinc to yield *N*-sec-butylaniline (0.053 g, 0.35 mmol, 71%) as a clear, colorless oil. The ^1H NMR spectrum was consistent with that reported in the literature.¹⁴

***N*-sec-Butylaniline (3s).** The title compound was prepared according to General Procedure **C** using *O*-benzoyl-*N*-sec-butylhydroxylamine (0.097 g, 0.50 mmol), copper(II) chloride (0.002 g, 0.0125 mmol), and a tetrahydrofuran solution of diphenylzinc to yield *N*-sec-butylaniline (0.057 g, 0.38 mmol, 76 %) as a clear, pale brown colored oil. The ^1H NMR spectrum was consistent with that reported in the literature.¹⁵

General Procedure (D) for the copper catalyzed amination of diorganozinc reagents. 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 the RMgX or RLi (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 the *O*-benzoyl hydroxylamine (0.50 mmol), the copper salt (0.0125 mmol), and anhydrous tetrahydrofuran (5.0 mL). The solution was stirred and the previously generated diorganozinc 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, 10-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 the indicated solvent system, to afford desired product of $\geq 95\%$ purity as judged by ^1H NMR spectroscopy.

***N,N*-Dibenzylaniline (3n).** The title compound was prepared according to General Procedure **D** using *O*-benzoyl-*N,N*-dibenzylhydroxylamine (0.159 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.003 g, 0.0066 mmol), and a tetrahydrofuran solution of diphenylzinc to yield *N,N*-dibenzylaniline (0.129 g, 0.47 mmol, 94 %) as a white solid following flash column chromatography with 1% EtOAc/hexanes. The ^1H NMR spectrum was consistent with that reported in the literature.¹⁶

***N,N*-Dibenzylethylamine (3o).** The title compound was prepared according to General Procedure **D** using *O*-benzoyl-*N,N*-dibenzylhydroxylamine (0.159 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.003 g, 0.0062 mmol), and a hexanes solution of diethylzinc to yield *N,N*-dibenzylethylamine (0.102 g, 0.46 mmol, 91%) as a clear, pale yellow oil following flash column chromatography with 10% EtOAc/hexanes. The ^1H NMR spectrum was consistent with that reported in the literature.¹⁷

***N,N*-Dibenzylisopropylamine (3p).** The title compound was prepared according to General Procedure **D** using *O*-benzoyl-*N,N*-dibenzylhydroxylamine (0.159 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.003 g, 0.0058 mmol), and a tetrahydrofuran solution of diisopropylzinc to yield *N,N*-dibenzylisopropylamine (0.098 g, 0.41 mmol, 82%) as a clear, colorless oil following flash column chromatography with 2.5% EtOAc/hexanes. The ^1H NMR spectrum was

consistent with that reported in the literature.¹⁸

***N,N*-Dibenzyl-*tert*-butylamine (3q).** The title compound was prepared according to General Procedure **D** using *O*-benzoyl-*N,N*-dibenzylhydroxylamine (0.159 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.003 g, 0.0062 mmol), and a tetrahydrofuran solution of di-*tert*-butylzinc to yield *N,N*-dibenzyl-*tert*-butylamine (0.125 g, 0.495 mmol, 99 %) as a white solid with no purification necessary. The ^1H NMR spectrum was consistent with that reported in the literature.¹⁹

***N-tert*-Octylaniline (3t).** The title compound was prepared according to General Procedure **D** using *O*-benzoyl-*N-tert*-octylhydroxylamine (0.125 g, 0.50 mmol), copper(II) chloride (0.002 g, 0.0125 mmol), and a tetrahydrofuran solution of di-phenylzinc to yield *N-tert*-octylaniline (0.066 g, 0.32 mmol, 64 %) as a clear, colorless oil following flash column chromatography with 5% EtOAc/hexanes. Analytical data for the title compound: **IR** (thin film, cm^{-1}) 2954, 2907, 2871, 1601, 1497; **^1H NMR** (400 MHz, CDCl_3) δ 7.14 – 7.10 (m, 2H), 6.67 – 6.65 (m, 3H), 1.68 (s, 2H), 1.37 (s, 6 H), 1.01 (s, 9H); **^{13}C NMR** (100 MHz, CDCl_3) δ 146.9, 128.9, 117.3, 116.5, 55.2, 53.1, 31.8, 31.7, 30.5. **Anal.** Calcd for $\text{C}_{14}\text{H}_{23}\text{N}$: C, 81.89; H, 11.29; N, 6.82. Found: C, 82.08; H, 11.39; N, 6.66.

***N-tert*-Octyl-*N-tert*-Butylamine (3u).** An oven-dried 100-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 (1.50 g, 11 mmol) and anhydrous tetrahydrofuran (22 mL). The solution was stirred and cooled in an ice bath and a tetrahydrofuran solution of $^t\text{BuMgCl}$ (22 mL, 22 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 (vide infra). An oven-dried 100-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar was maintained under an

inert atmosphere of argon and charged with *O*-benzoyl-*N*-*tert*-octylhydroxylamine (2.49 g, 10 mmol), copper(II) chloride (0.0336 g, 0.25 mmol), and anhydrous tetrahydrofuran (25 mL). The solution was stirred and the previously generated di-*tert*-butylzinc solution (vida supra) was added via cannula in one portion. The resulting solution was stirred at ambient temperature for 1 h. Diethyl ether (100 mL) was added and the reaction mixture was transferred to a 500-mL separatory funnel. The reaction mixture was washed with three 100-mL portions of saturated aq. NaHCO₃ solution, 100-mL of brine, dried over MgSO₄, and concentrated by rotary evaporation. The resulting crude product mixture was purified by distillation under reduced pressure (50 mbar, bp 70 °C) to yield *N*-*tert*-octylaniline (0.791 g, 4.3 mmol, 43 %) as a clear, colorless oil. The ¹H NMR spectrum was consistent with that reported in the literature.²⁰

III. Preparation of Functionalized Aryl Amines

General Procedure (E) for the copper catalyzed amination of functionalized diarylzinc reagents. An oven-dried round bottom flask equipped with magnetic stir bar was charged with the aryl iodide (0.55 mmol), anhydrous tetrahydrofuran (3.0 mL), and the solution was cooled to -35 °C. A tetrahydrofuran solution of isopropyl magnesium 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 hour. 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 minutes. A second oven-dried round bottom flask equipped with magnetic stir bar was charged with the *N,N*-dialkyl *O*-benzoyl hydroxylamine derivative (0.25 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]₂·C₆H₆, 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 hour. The reaction mixture was diluted with diethyl ether (10 mL), the organic layer was washed with a saturated sodium bicarbonate solution (2 x 10 mL), and the aqueous layer was extracted with dichloromethane (2 x 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 1M hydrochloric acid solution (2 x 10 mL), the aqueous layer was basified with a 10% sodium hydroxide solution and extracted with dichloromethane (2 x 10 mL). The organic extracts were combined, dried over sodium sulfate, and the solvent was removed under reduced pressure, affording the desired product of ≥95% purity as judged by ¹H NMR

spectroscopy and GLC or SFC analysis.

4-(Morpholin-4-yl)-benzonitrile (3v). The title compound was prepared according to General Procedure **E** using 4-iodobenzonitrile (0.126 g, 0.55 mmol), 4-(benzyloxymethyl)morpholine (0.052 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.002 g, 0.0031 mmol) to yield 4-(morpholin-4-yl)-benzonitrile (0.037 g, 0.20 mmol, 79%) as a white solid. The ^1H NMR spectrum was consistent with that reported in the literature.²¹

4-(Morpholin-4-yl)-benzoic acid ethyl ester (3w). The title compound was prepared according to General Procedure **E** using 4-iodobenzoic acid ethyl ester (0.152 g, 0.55 mmol), 4-(benzyloxymethyl)morpholine (0.052 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.002 g, 0.0031 mmol) to yield 4-(morpholin-4-yl)-benzoic acid ethyl ester (0.044 g, 0.19 mmol, 75%) as a white solid. The ^1H NMR spectrum was consistent with that reported in the literature.²²

4-(4-Chlorophenyl)-morpholine (3x). The title compound was prepared according to General Procedure **E** using 1-chloro-4-iodobenzene (0.131 g, 0.55 mmol), 4-(benzyloxymethyl)morpholine (0.052 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.002 g, 0.0031 mmol) to yield 4-(4-chlorophenyl)-morpholine (0.048 g, 0.24 mmol, 97%) as a white solid. The ^1H NMR spectrum was consistent with that reported in the literature.²³

4-(4-Fluorophenyl)-morpholine (3y). The title compound was prepared according to General Procedure **E** using 1-fluoro-4-iodo-benzene (0.122 g, 0.55 mmol), 4-(benzyloxymethyl)morpholine (0.052 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.002 g, 0.0031 mmol) to yield 4-(4-fluorophenyl)-morpholine (0.033 g, 0.18 mmol, 72%) as a pale yellow oil. Analytical data for the title compound: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.00 – 6.96 (m, 2H), 6.88 – 6.85 (m, 2H), 3.87 – 3.85 (m, 4H), 3.09 – 3.07 (m, 4H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 117.6, 117.5, 115.7, 115.5, 66.9, 50.4.

4-(3-Trifluoromethyl-phenyl)-morpholine (3z). The title compound was prepared according to General Procedure **E** using 1-iodo-3-trifluoromethyl-benzene (0.150 g, 0.55 mmol), 4-(benzyloxymethyl)morpholine (0.052 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.002 g, 0.0031 mmol) to yield 4-(3-trifluoromethyl-phenyl)-morpholine (0.042 g, 0.18 mmol, 72%) as a pale yellow oil. Analytical data for the title compound: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.37 – 7.35 (m, 1H), 7.12 – 7.05 (m, 3H), 3.88 – 3.86 (m, 4H), 3.21 – 3.19 (m, 4H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 151.5, 129.6, 125.7, 123.0, 118.4, 116.2, 111.9, 66.7, 48.9.

General Procedure (F) for the copper catalyzed amination of functionalized diarylzinc reagents. An oven-dried round bottom flask equipped with magnetic stir bar was charged with the aryl iodide (0.55 mmol), anhydrous tetrahydrofuran (3.0 mL), and the solution cooled to $-35\text{ }^{\circ}\text{C}$. A tetrahydrofuran solution of isopropyl magnesium bromide (0.60 mL, 1.0 M) was slowly added along the edges of the flask and the reaction mixture was stirred at $-35\text{ }^{\circ}\text{C}$ for 1 hour. 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 minutes. A second oven-dried round bottom flask equipped with magnetic stir bar was charged with the *N,N*-dialkyl *O*-benzoyl hydroxylamine derivative (0.25 mmol), copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 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 hour. The reaction mixture was diluted with diethyl ether (10 mL) and the organic layer was washed with a saturated sodium bicarbonate solution (2 x 10 mL), dried over magnesium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography, eluting with the indicated solvent system, to afford the desired product of $\geq 95\%$ purity as judged by ^1H NMR spectroscopy and GLC or SFC analysis.

4-(4-acetoxyphenyl)-morpholine (3aa). The title compound was prepared according to General Procedure **F** using 1-acetoxy-4-iodobenzene (0.144 g, 0.55 mmol), 4-(benzoyloxy)morpholine (0.052 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.002 g, 0.0031 mmol) to yield 4-(4-acetoxyphenyl)-morpholine (0.041 g, 0.18 mmol, 74%) as a white solid after flash chromatography with 30% ethyl acetate/hexanes. Analytical data for the title compound: **IR** (Nujol, cm^{-1}) 2924, 2854, 1761, 1514, 1460, 1377, 1201, 1120, 922, 834, 719; **^1H NMR** (400 MHz, CDCl_3) δ 7.00 – 6.98 (m, 2H), 6.90 – 6.88 (m, 2H), 3.86 – 3.84 (m, 4H), 3.13 – 3.11 (m, 4H), 2.27 (s, 3H); **^{13}C NMR** (100 MHz, CDCl_3) δ 169.8, 149.3, 144.0, 122.0, 116.6, 66.9, 49.8, 21.0. **Anal.** Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.12; H, 6.91; N, 6.15.

Trifluoromethanesulfonic acid 4-(morpholin-4-yl)-phenyl ester (3ab). The title compound was prepared according to General Procedure **F** using

trifluoromethanesulfonic acid 4-iodo-phenyl ester (0.194 g, 0.55 mmol) 4-(benzoyloxy)morpholine (0.052 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.002 g, 0.0031 mmol) to yield trifluoromethanesulfonic acid 4-(morpholin-4-yl)-phenyl ester (0.074 g, 0.24 mmol, 95%) as a clear oil after flash chromatography with 30% ethyl acetate/hexanes. The ^1H NMR spectrum was consistent with that reported in the literature.²⁴

4-Dibenzylamino-benzonitrile (3ag). The title compound was prepared according to General Procedure **F** using 4-iodobenzonitrile (0.126 g, 0.55 mmol), *O*-benzoyl-*N,N*-dibenzylhydroxylamine (0.079 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.002 g, 0.0031 mmol) to yield 4-dibenzylamino-benzonitrile (0.071 g, 0.24 mmol, 96%) as a white solid after flash chromatography with 15% ethyl acetate/hexanes. Analytical data for the title compound: ^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.18 (m, 12H), 6.72 – 6.70 (m, 2H), 4.71 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.9, 136.8, 133.6, 128.9, 127.4, 126.4, 120.3, 112.2, 98.7, 54.2.

4-Dibenzylamino-benzoic acid ethyl ester (3ah). The title compound was prepared according to General Procedure **F** using 4-iodobenzoic acid ethyl ester (0.152 g, 0.55 mmol), *O*-benzoyl-*N,N*-dibenzylhydroxylamine (0.079 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.002 g, 0.0031 mmol) to yield 4-dibenzylamino-benzoic acid ethyl ester (0.086 g, 0.25 mmol, 100%) as a white solid after flash chromatography with 5% ethyl acetate/hexanes. Analytical data for the title compound: ^1H NMR (400 MHz, CDCl_3) δ 7.87 – 7.84 (m, 2H), 7.35 – 7.20 (m, 10H), 6.72 – 6.70 (m, 2H), 4.71 (s, 4H), 4.30 (q, 2H, $J = 7.1$), 1.33 (t, 3H, $J = 7.1$); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 152.4, 137.4, 131.4, 128.8, 127.2, 126.4, 118.3, 111.2, 60.1, 54.0, 14.4.

***N*-(4-Chloro-phenyl)-dibenzylamine (3ai).** The title compound was prepared according to General Procedure **F** using 1-chloro-4-iodo-benzene (0.131 g, 0.55 mmol), *O*-benzoyl-*N,N*-dibenzylhydroxylamine (0.079 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.002 g, 0.0031 mmol) to yield *N*-(4-chloro-phenyl)-dibenzylamine (0.071 g, 0.23 mmol, 92%) as a white solid after flash chromatography with 1% ethyl acetate/hexanes. The ^1H NMR spectrum was consistent with that reported in the literature.²⁵

General Procedure (G) for the copper catalyzed amination of functionalized diarylzinc reagents. An oven-dried round bottom flask equipped with magnetic stir bar was charged with the aryl iodide (0.55 mmol), anhydrous tetrahydrofuran (3.0 mL), and the solution cooled to $-35\text{ }^{\circ}\text{C}$. A tetrahydrofuran solution of phenyl magnesium bromide (0.60 mL, 1.0 M) was slowly added along the edges of the flask and the reaction mixture was stirred at $-35\text{ }^{\circ}\text{C}$ for 10 minutes. 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 $-35\text{ }^{\circ}\text{C}$ for 10 minutes. A second oven-dried round bottom flask equipped with magnetic stir bar was charged with the *N,N*-dialkyl *O*-benzoyl hydroxylamine derivative (0.25 mmol), copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 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 hour. The reaction mixture was diluted with diethyl ether (10 mL) and the organic layer was washed with a saturated sodium bicarbonate solution (2 x 10 mL), dried over magnesium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography, eluting with the indicated solvent system, to afford the desired product of $\geq 95\%$ purity as judged by ^1H NMR spectroscopy and GLC or SFC analysis.

4-(2-Nitrophenyl)-morpholine (3ad). The title compound was prepared according to General Procedure **G** using 1-iodo-2-nitrobenzene (0.137 g, 0.55 mmol), 4-(benzyloxymethyl)morpholine (0.052 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.002 g, 0.0031 mmol) to yield 4-(2-nitro-phenyl)-morpholine (0.052 g, 0.25 mmol, 100%) as a yellow, viscous oil after flash chromatography with 15% ethyl acetate/hexanes. The ^1H NMR spectrum was consistent with that reported in the literature.⁹

4-(2,4-Dinitrophenyl)-morpholine (3ae). The title compound was prepared according to General Procedure **G** using 1-iodo-2,4-dinitrobenzene (0.162 g, 0.55 mmol), 4-(benzyloxymethyl)morpholine (0.052 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.002 g, 0.0031 mmol) to yield 4-(2,4-dinitro-phenyl)-morpholine (0.037 g, 0.15 mmol, 59%) as a yellow solid after flash chromatography with 30% ethyl acetate/hexanes. The ^1H NMR spectrum was consistent with that reported in the literature.²⁶

N-(2-nitrophenyl)-dibenzylamine (3ak). The title compound was prepared according to General Procedure **G** using 1-iodo-2-nitrobenzene (0.137 g, 0.55 mmol), O-benzoyl-N,N-dibenzylhydroxylamine (0.079 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.002 g, 0.0031 mmol) to yield N-(2-nitro-phenyl)-dibenzylamine (0.076 g, 0.24 mmol, 96%) as a yellow, viscous oil after flash chromatography with 15% ethyl acetate/hexanes. Analytical data for the title compound:

¹H NMR (400 MHz, CDCl₃) δ 7.74 – 7.71 (m, 1H), 7.34 – 7.21 (m, 11H), 7.08 – 7.06 (m, 1H), 6.99 – 6.97 (m, 1H), 4.20 (s, 4H); **¹³C NMR** (100 MHz, CDCl₃) δ 145.1, 144.6, 137.5, 133.1, 128.9, 128.8, 127.8, 126.1, 123.9, 122.0, 57.1.

General Procedure (H) for the copper catalyzed amination of functionalized diarylzinc reagents. An oven-dried round bottom flask equipped with magnetic stir bar was charged with the aryl iodide (0.55 mmol) and anhydrous tetrahydrofuran (3.0 mL). A tetrahydrofuran solution of isopropyl magnesium bromide (0.60 mL, 1.0 M) was slowly added and the reaction mixture was stirred at room temperature for 1 hour. A tetrahydrofuran solution of zinc(II) chloride (1.0 mL, 0.28 M) was slowly added and the reaction mixture was stirred at room temperature for 10 minutes. A second oven-dried round bottom flask equipped with magnetic stir bar was charged with the *N,N*-dialkyl *O*-benzoyl hydroxylamine derivative (0.25 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]₂·C₆H₆, 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 hour. The reaction mixture was diluted with diethyl ether (10 mL) and the organic layer was washed with a saturated sodium bicarbonate solution (2 x 10 mL), dried over magnesium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography, eluting with the indicated solvent system, to afford the desired product of ≥95 % purity as judged by ¹H NMR spectroscopy and GLC or SFC analysis.

2-(4-Morpholin-4-yl-phenyl)-2-methyl-1,3-dioxolane (3ac). The title compound was prepared according to General Procedure H using 2-(4-iodophenyl)-2-methyl-1,3-dioxolane (0.159 g, 0.55 mmol), 4-(benzoyloxy)morpholine (0.052 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]₂·C₆H₆, 0.002 g, 0.0031 mmol) to yield 2-(4-morpholin-4-yl-phenyl)-2-methyl-1,3-dioxolane (0.051 g, 0.21 mmol, 82%) as a white solid after flash chromatography with 30% ethyl acetate/hexanes. Analytical data for the title compound: **IR** (Nujol, cm⁻¹) 2923, 2854, 1610, 1514, 1460, 1377, 1265, 1225, 1200, 1192, 1126, 1041, 926, 877, 818, 723; **¹H NMR** (400 MHz,

CDCl₃) δ 7.39 – 7.37 (m, 2H), 6.89 – 6.87 (m, 2H), 4.04 – 4.00 (m, 2H), 3.87 – 3.85 (m, 4H), 3.80 – 3.76 (m, 2H), 3.18 – 3.15 (m, 4H), 1.64 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 150.8, 134.6, 126.2, 115.1, 108.8, 66.9, 64.4, 49.2, 27.5. **Anal.** Calcd for C₁₄H₁₉NO₃: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.33; H, 7.77; N, 5.61.

***N*-(4-Methoxyphenyl)-dibenzylamine (3aj).** The title compound was prepared according to General Procedure **H** using 4-iodoanisole (0.129 g, 0.55 mmol), *O*-benzoyl-*N,N*-dibenzylhydroxylamine (0.079 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]₂·C₆H₆, 0.002 g, 0.0031 mmol) to yield *N*-(4-methoxyphenyl)-dibenzylamine (0.068 g, 0.22 mmol, 90%) as a white solid after flash chromatography with 5% ethyl acetate/hexanes. The ¹H NMR spectrum was consistent with that reported in the literature.²⁵

General Procedure (I) for the copper catalyzed amination of functionalized diarylzinc reagents. An oven-dried round bottom flask equipped with magnetic stir bar was charged with the aryl iodide (0.55 mmol) and anhydrous tetrahydrofuran (3.0 mL). A tetrahydrofuran solution of isopropyl magnesium bromide (0.60 mL, 1.0 M) was slowly added and the reaction mixture was stirred at room temperature for 1 hour. A tetrahydrofuran solution of zinc(II) chloride (1.0 mL, 0.28 M) was slowly added and the reaction mixture was stirred at room temperature for 10 minutes. A second oven-dried round bottom flask equipped with magnetic stir bar was charged with the *N,N*-dialkyl *O*-benzoyl hydroxylamine derivative (0.25 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]₂·C₆H₆, 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 hour. The reaction mixture was diluted with diethyl ether (10 mL), the organic layer was washed with a saturated sodium bicarbonate solution (2 x 10 mL), and the aqueous layer was extracted with dichloromethane (2 x 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 1M hydrochloric acid solution (2 x 10 mL), the aqueous layer was basified with a 10%

sodium hydroxide solution and extracted with dichloromethane (2 x 10 mL). The organic extracts were combined, dried over sodium sulfate, and the solvent was removed under reduced pressure, affording the desired product of $\geq 95\%$ purity as judged by ^1H NMR spectroscopy and GLC or SFC analysis.

4-(Naphthalen-1-yl)-morpholine (3af). The title compound was prepared according to General Procedure I using 1-iodo-naphthalene (0.140 g, 0.55 mmol), 4-(benzyloxymethyl)morpholine (0.052 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.002 g, 0.0031 mmol) to yield 4-(naphthalen-1-yl)-morpholine (0.048 g, 0.23 mmol, 90%) as a white solid. The ^1H NMR spectrum was consistent with that reported in the literature.²⁷

4-(4-Methoxyphenyl)-morpholine (3c). The title compound was prepared according to General Procedure I using 4-iodoanisole (0.129 g, 0.55 mmol), 4-(benzyloxymethyl)morpholine (0.052 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ($[\text{CuOTf}]_2 \cdot \text{C}_6\text{H}_6$, 0.002 g, 0.0031 mmol) to yield 4-(4-methoxyphenyl)-morpholine (0.040 g, 0.21 mmol, 83%) as a white solid. The ^1H NMR spectrum was consistent with that reported in the literature.²²

IV. Directed Ortho Lithiation/Amination Sequence

General Procedure (J) for the copper catalyzed amination of diorganozinc reagents. 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 tetramethylethylene diamine (0.070 g, 0.61 mmol) and anhydrous tetrahydrofuran (2.5 mL). The solution was stirred and cooled in a CO_2 /acetone bath and a cyclohexane solution of sec-BuLi (0.47 mL, 0.61 mmol, 1.3 M) was added via syringe

along edges of flask. The resulting solution was stirred for 10 min at $-78\text{ }^{\circ}\text{C}$ and a tetrahydrofuran solution of the functionalized arene (1.5 mL, 0.55 mmol, 0.4M) was added via syringe gradually along edges of flask. The solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. A tetrahydrofuran solution of ZnCl_2 (1.0 mL, 0.038 g, 0.28 mmol, 0.3M) was added via syringe along edges of flask and the solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 min. The cold bath was removed and the solution was allowed to gradually warm to ambient temperature over the course of 15 min prior to use (*vide 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 4-benzoyloxymorpholine (0.052 g, 0.25 mmol), copper(II) chloride (0.0008 g, 0.0063 mmol), and anhydrous tetrahydrofuran (2.5 mL). The solution was stirred and the previously generated diarylzinc solution (*vide supra*) was added via cannula in one portion. The resulting solution was stirred at ambient temperature for the indicated reaction time. 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, 10-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 the indicated solvent system, to afford desired product of $\geq 95\%$ purity as judged by ^1H NMR spectroscopy.

2-Morpholino-*N,N*-Diisopropylbenzamide (3al). The title compound was prepared according to General Procedure **J** using *N,N*-diisopropylbenzamide (0.113 g, 0.55 mmol) with stirring for 12 h to yield 2-morpholino-*N,N*-diisopropylbenzamide (0.064 g, 0.22 mmol, 88 %) as a clear, pale yellow oil following flash column chromatography with 30% EtOAc/hexanes. Analytical data for the title compound: **IR** (thin film, cm^{-1}) 2963, 2856, 2822, 1625, 1490, 1450, 1377, 1339; **^1H NMR** (400 MHz, CDCl_3) δ 7.30 – 7.26 (m, 1H), 7.12 – 7.01 (m, 3H), 3.84 – 3.70 (m, 4H), 3.52 – 3.34 (m, 4H), 2.77 – 2.72 (m, 2H), 1.55 – 1.53 (m, 6H), 1.20 – 1.18 (m, 3H), 0.97 – 0.95 (m, 3H); **^{13}C NMR** (100 MHz, CDCl_3) δ 170.3, 148.5, 135.0, 129.1, 126.9, 123.7, 118.9, 67.2, 52.8, 50.6, 45.5, 20.7, 20.5, 20.4, 20.3.

***N,N*-Diethylcarbamic acid 2-Morpholinophenyl ester (3ao).** The title compound was prepared according to General Procedure J using *N,N*-diethylcarbamic acid phenyl ester (0.107 g, 0.55 mmol) with stirring for 12 h to yield *N,N*-diethylcarbamic acid 2-morpholinophenyl ester (0.044 g, 0.16 mmol, 62%) as a white solid following flash column chromatography with 30% EtOAc/hexanes. Analytical data for the title compound: **IR** (thin film, cm^{-1}) 2969, 2854, 2817, 1721, 1604, 1497, 1419; **^1H NMR** (400 MHz, CDCl_3) δ 7.17 – 7.03 (m, 4H), 3.82 – 3.77 (m, 4H), 3.50 – 3.37 (m, 4H), 3.00 – 2.96 (m, 4H), 1.27 – 1.19 (m, 6H); **^{13}C NMR** (100 MHz, CDCl_3) δ 153.9, 145.4, 144.8, 126.1, 123.7, 120.1, 67.4, 51.8, 42.1, 41.7, 14.3, 13.5.

2-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-1-Morpholinobenzene (3am). The title compound was prepared according to General Procedure J using 4,4-dimethyl-2-phenyl-4,5-dihydro-oxazole (0.096 g, 0.55 mmol) with stirring for 4 h to yield 2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-1-morpholinobenzene (0.036 g, 0.14 mmol, 55%) as a clear, pale yellow colored oil following flash column chromatography with 50% EtOAc/hexanes. Analytical data for the title compound: **IR** (thin film, cm^{-1}) 2964, 2927, 2893, 2858, 2818, 1723, 1646, 1598, 1492, 1448; **^1H NMR** (400 MHz, CDCl_3) δ 7.63 – 7.61 (m, 1H), 7.36 – 7.34 (m, 1H), 7.00 – 6.96 (m, 2H), 4.05 (s, 1H), 3.84 – 3.82 (m, 4H), 3.05 – 3.03 (m, 4H), 1.36 (s, 6H); **^{13}C NMR** (100 MHz, CDCl_3) δ 163.0, 151.4, 131.7, 131.6, 121.8, 121.7, 118.1, 78.9, 67.4, 67.1, 52.3, 28.3.

1-Methoxymethyloxy-2-Morpholinobenzene (3an). 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 methoxymethyl phenyl ether (0.076 g, 0.55 mmol) and anhydrous diethyl ether (2.0 mL). The solution was stirred and cooled in an ice bath and a pentane solution of *t*-BuLi (0.40 mL, 0.61 mmol, 1.5 M) was added via syringe along edges of flask. The resulting solution was stirred for 1 h at 0 °C and a tetrahydrofuran solution of ZnCl₂ (1.0 mL, 0.038 g, 0.28 mmol, 0.3 M) was added via syringe along edges of flask and the solution was stirred at 0 °C for 15 min. The cold bath was removed and the solution was allowed to gradually warm to ambient temperature over the course of 15 min prior to use (*vide 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 4-benzoyloxymorpholine (0.052 g, 0.25 mmol), copper(II) chloride (0.0008 g, 0.0063 mmol), and anhydrous tetrahydrofuran (2.5 mL). The solution was stirred and the previously generated diarylzinc solution (*vide supra*) was added via cannula in one portion. The resulting solution was stirred at ambient temperature for 6 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. NaHCO₃ solution, 10-mL of brine, dried over MgSO₄, and concentrated by rotary evaporation. The resulting crude product mixture was purified by flash column chromatography with 30% EtOAc/hexanes to yield 1-methoxymethyloxy-2-morpholinobenzene (0.055 g, 0.25 mmol, 100%) as a clear, colorless oil. Analytical data for the title compound: Analytical data for the title compound: **IR** (thin film, cm⁻¹) 2953, 2852, 2822, 1597, 1498, 1447, 1235; **¹H NMR** (400 MHz, CDCl₃) δ 7.10 – 7.07 (m, 1H), 6.99 – 6.93 (m, 3H), 5.22 (s, 2H), 3.87 – 3.85 (m, 4H), 3.50 (s, 3H), 3.09 – 3.06 (m, 4H); **¹³C NMR** (100 MHz, CDCl₃) δ 150.0, 142.2, 123.1, 122.8, 118.4, 116.6, 95.2, 67.3, 56.3, 51.2.

¹H NMR Spectra

Diisopropyl-(2,4,6-Trimethylphenyl)amine (3j)

N-tert-Octylaniline (3t)

2-Morpholino-*N,N*-Diisopropylbenzamide (3a)

***N,N*-Diethylcarbamic acid 2-Morpholinophenyl ester (3ao)**

Current Data Parameters
 NAME AMBIV217
 EXPNO 2
 PROCNO 1
 F2 - Acquisition Parameters
 Date_ 20050827
 Time 13.14
 INSTRUM spect
 PROBHD 5 mm HR 13C/31
 PULPROG zgpg30
 TO 32768
 SOLVENT CDCl3
 NS 16
 DS 2
 SWH 5995.204 Hz
 FIDRES 0.182595 Hz
 AQ 2.7329011 sec
 RG 71.8
 DW 83.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec
 ***** CHANNEL f1 *****
 NUC1 1H
 P1 9.30 usec
 PL1 -3.00 dB
 SFO1 399.802388 MHz
 F2 - Processing parameters
 SI 32768
 SF 399.8000199 MHz
 SW 0 Hz
 SSB no
 LB 0.00 Hz
 GB 0
 PC 1.00
 1D NMR plot parameters
 CX 23.00 cm
 CY 12.50 cm
 F1P 13.405 ppm
 F1 5379.50 Hz
 F2P 1.540 ppm
 F2 5617.00 Hz
 PRACH 0.55109 Hz/cm
 HZCN 260.55104 Hz/cm

473.89
 480.69
 488.09
 491.85
 498.88
 505.77
 1181.70
 1186.25
 1190.88
 1340.54
 1346.97
 1353.90
 1360.65
 1367.62
 1374.59
 1381.49
 1506.49
 1511.12
 1515.64
 2894.78
 2863.70
 2861.37
 2857.33
 2854.83
 2853.54
 2849.26
 2846.85
 2823.82
 2815.75
 2808.73
 2801.45

HZ

Integral

1.0000

1.0284

1.0574

1.0326

1.6797

2-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-1-Morpholinobenzene (3am)

1-Methoxymethoxy-2-Morpholinobenzene (3an)

References

- (1) Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001**, 78, 64.
- (2) Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, 124, 14844-14845.
- (3) Bittner, S.; Grinberg, S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1708-11.
- (4) Ishikawa, T.; Uedo, E.; Tani, R.; Saito, S. *J. Org. Chem.* **2001**, 66, 186-91.
- (5) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, 64, 5575-5580.
- (6) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, 61, 7240-7241.
- (7) Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* **2001**, 2002, 523-528.
- (8) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, 55, 12829-12842.
- (9) Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Org. Lett.* **2003**, 5, 3515-3517.
- (10) Wickham, P. P.; Hazen, K. H.; Guo, H.; Jones, G.; Reuter, K. H.; Scott, W. J. *J. Org. Chem.* **1991**, 56, 2045-50.
- (11) Djakovitch, L.; Wagner, M.; Kohler, K. *J. Organomet. Chem.* **1999**, 592, 225-234.
- (12) Yoder, C. H.; Kaduk, B. A. *Tetrahedron Lett.* **1970**, 3711-14.
- (13) Kayaki, Y.; Koda, T.; Ikariya, T. *J. Org. Chem.* **2004**, 69, 2595-2597.
- (14) Brown, D. S.; Elliott, M. C.; Moody, C. J.; Mowlem, T. J.; Marino, J. P., Jr.; Padwa, A. J. *J. Org. Chem.* **1994**, 59, 2447-55.
- (15) Micovic, I. V.; Ivanovic, M. D.; Piatak, D. M.; Bojic, V. D. *Synthesis* **1991**, 1043-5.
- (16) Beller, M.; Breindl, C.; Riermeier, T. H.; Tillack, A. *J. Org. Chem.* **2001**, 66, 1403-1412.
- (17) Katritzky, A. R.; Yannakopoulou, K.; Lue, P.; Rasala, D.; Urogdi, L. *J. Chem. Soc., Perkin Trans. 1* **1989**, 225-32.
- (18) Brown, J. H.; Bushweller, C. H. *J. Am. Chem. Soc.* **1995**, 117, 12567-77.
- (19) Suzuki, K.; Okano, K.; Nakai, K.; Terao, Y.; Sekiya, M. *Synthesis* **1983**, 723-5.
- (20) Corey, E. J.; Gross, A. W. *Organic Synth.* **1987**, 65, 166-72.
- (21) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, 119, 6054-6058.
- (22) Urgaonkar, S.; Xu, J.-H.; Verkade, J. G. *J. Org. Chem.* **2003**, 68, 8416-8423.
- (23) Pearson, A. J.; Gelormini, A. M. *J. Org. Chem.* **1994**, 59, 4561-70.
- (24) Kotsuki, H.; Kobayashi, S.; Matsumoto, K.; Suenaga, H.; Nishizawa, H. *Synthesis* **1990**, 1147-8.
- (25) Watanabe, Y.; Tsuji, Y.; Ige, H.; Ohsugi, Y.; Ohta, T. *J. Org. Chem.* **1984**, 49, 3359-63.
- (26) Mackay, M. F.; Gale, D. J.; Wilshire, J. F. K. *Aust. J. Chem.* **2000**, 53, 715-722.
- (27) Guinot, S. G. R.; Hepworth, J. D.; Wainwright, M. *J. Chem. Soc. Perkin Trans. 2* **1998**, 297-304.