Catalytic Electrophilic Amination Reactions

Ashley M. Berman

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry

Chapel Hill
2007

Approved by:

Professor Jeffrey S. Johnson
Professor Valerie S. Ashby
Professor Michael T. Crimmins
Professor Michel R. Gagné
Professor Cynthia K. Shauer

Abstract

ASHLEY M. BERMAN: Catalytic Electrophilic Amination Reactions
(Under the direction of Professor Jeffrey S. Johnson)

Chapter One: Copper-Catalyzed Electrophilic Amination of Organozinc Nucleophiles

The copper-catalyzed electrophilic amination of diorganozinc reagents using *O*-benzoyl hydroxylamines as electrophilic nitrogen sources has been developed. Simple and functionalized aryl-, heteroaryl-, benzyl, *n*-alkyl-, *s*-alkyl-, and *t*-alkyl nucleophiles couple with $R_2NOC(O)Ph$ and $RHNOC(O)Ph$ reagents in the presence of catalytic quantities of copper salts to provide tertiary and secondary amines, respectively, in generally good yields. In many cases the product may be isolated analytically pure after a simple extractive workup. The amination process is shown to tolerate a significant degree of steric demand. The amination of nominally unreactive C_{aryl}-H bonds via a sequential directed *ortho* metalation/transmetalation/catalytic amination reaction sequence is detailed. The direct Cu-catalyzed amination of Grignard reagents using cocatalysis by $ZnCl_2$ is described.
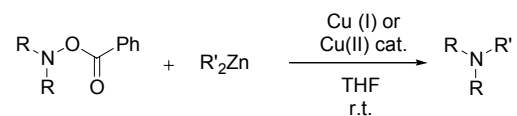
## Chapter Two: Nickel-Catalyzed Electrophilic Amination of Organozinc

Nucleophiles

The nickel-catalyzed electrophilic amination of organozinc halides using *O*-benzoyl hydroxylamines has been developed. Simple and functionalized aryl-, benzyl, and *n*-alkyl- nucleophiles couple with $R_2NOC(O)Ph$ reagents in the presence of catalytic quantities of $Ni(PPh_3)_2Cl_2$ to provide tertiary amines in generally good yields. The reaction is noteworthy for the mild reaction conditions employed and the ease of product purification (acid/base extractive work-up).
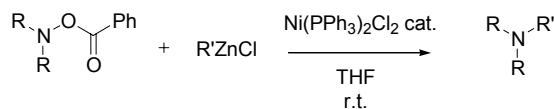
Chapter Three: Electrophilic Amination of *o*-Nitrobenzyl Silanes

The electrophilic amination of *o*-nitrobenzyl silanes using di-*tert*-butyl azodicarboxylate as electrophilic nitrogen source and catalytic tetrabutylammonium fluoride as activator has been developed. A wide variety of α-alkyl and 4'- substituted *o*-nitrobenzyl silanes couple with di-*tert*-butyl azodicarboxylate in the presence of catalytic quantities of tetrabutylammonium fluoride to provide *N*-benzyl hydrazides in good yields.
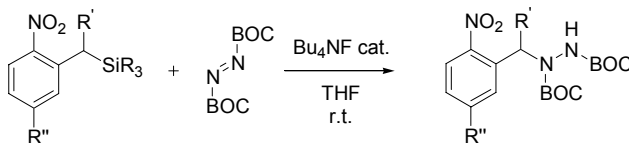
Acknowledgments

Acknowledgment is due to those individuals without whom completion of this body of work would not have been possible: Professor Jeffrey S. Johnson (advisor), Professors Valerie S. Ashby, Maurice S. Brookhart, Michael T. Crimmins, Michel R. Gagné, James P. Morken, Cynthia K. Schauer, and Joseph L. Templeton (defense committee and/or preliminary orals committee members), Dr. Xin Linghu, Dr. Mary Robert Nahm, Dr. David Nicewicz, Dr. Patrick Pohlhaus, Cory Bausch, Justin Potnick, Roy Bowman, Rebecca Duenes, Matthew Campbell, Andrew Satterfield, Shanina Sanders, Steve Greszler, Andrew Parsons, Chris Tarr, and others (Johnson Group colleagues past and present).

Lastly, very special thanks to Dr. Leonard Berman, Mrs. Marilena Berman, Scott, Wayne, Duangmala, LeeLee, Anne, Sue, Ahn, Lut, Sam, Bee, and Joe.

Dedicated to the memory of

cz pt vt

Table of Contents

Chapter One: **Copper-Catalyzed Electrophilic Amination of Organozinc Nucleophiles**

Chapter Two: **Nickel-Catalyzed Electrophilic Amination of Organozinc Nucleophiles**

Chapter Three: **Electrophilic Amination of *o*-Nitrobenzyl Silanes**

List of Tables

List of Schemes

List of Abbreviations and Symbols

Ac	acetate
acac	acetylacetonato
Ar	aryl
aq.	aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
BOC	butoxycarbonyl
br	broad
n-Bu	*n*-butyl
n-BuLi	*n*-butyl lithium
s-BuLi	*sec*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
cat.	catalytic amount or catalyst
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
conv.	conversion
cod	cyclooctadiene
*m*CPBA	*m*-chloroperbenzoic acid
Cy	cyclohexyl
d	doublet
D	*ortho* directing group
dba	dibenzylidene acetone
DDQ	2,3-dichloro-5,6-dicyanohydroquinone
DMAP	4-*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide

DMSO	dimethyl sulfoxide
eq	equation
equiv.	equivalents
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
EDG	electron donating group
FG	functional group
GLC	gas-liquid chromatography
h	hour
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HOAc	acetic acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared spectroscopy
Imes-HCl	1,2-bis(2,4,6-trimethylphenyl)imidazolium chloride
J	coupling constant
kPa	kilopascal
LRMS	low resolution mass spectroscopy
M	metal or molarity
m	multiplet
Me	methyl
MeCN	acetonitrile
2-MeTHF	2-methyltetrahydrofuran

mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
MOM	methoxymethyl
mp	melting point
N.R.	no reaction
Ns	4-nitrobenzenesulfonyl
PPh$_3$	triphenylphoshpine
PCy$_3$	tricylohexylphosphine
P(OPh)$_3$	triphenylphosphite
Ph	phenyl
Piv	pivolate
PMP	*p*-methoxyphenyl
ppm	parts per million
^{i}Pr	isopropyl
R	alkyl
r.t.	room temperature
s	singlet
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosilicate
T	temperature
t	triplet
TES	triethylsilyl
OTf	trifluoromethanesulfonate

TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMEDA	*N,N,N'N'*-tetramethylethylene diamine
Ts	toluenesulfonyl
X	anionic ligand
δ	chemical shift

Chapter One

Copper-Catalyzed Electrophilic Amination of Organozinc Nucleophiles

1.1 Introduction

The investigation of umpolung strategies in organic synthesis often produces reactions that are complementary to counterparts following normal polarity pathways.[1] In the context of amine synthesis, the effective application of the umpolung concept relies on the identification of useful electrophilic nitrogen synthons and reaction conditions that are sufficiently mild so as to tolerate functionality that might be required for subsequent manipulation. A large number of $R_2N(+)$ synthons have been developed for reactions with nucleophiles,[2] and recent advances from Erdik[3, 4] and Narasaka[5-8] have demonstrated that transition metal catalysts can potentiate the reactivity of Grignard reagents or zincates with oxime derivatives; however, in most instances electrophilic amination approaches are not currently competitive with catalytic nucleophilic amination strategies discovered and developed by Buchwald and Hartwig.[9, 10]

Because of the central role of amine synthesis in organic chemistry, the electrophilic amination problem continues to attract considerable interest.[11-14] Hydroxylamine derivatives occupy a prominent position in the development of umpolung C–N bond constructions, with key advances relying on the use of appropriate activating groups to facilitate the amination. The use of sulfonyl[15] and phosphinyl[16, 17] activation is

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

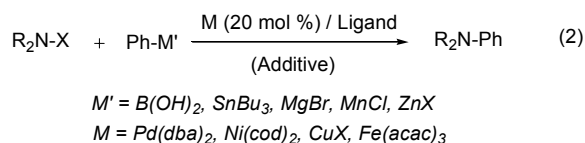In an effort to address the technology gap between nucleophilic and electrophilic catalytic amination, we initiated a search for a useful electrophilic amination protocol that would employ readily-accessible $R_2N(+)$ synthons and enjoy broad functional group compatibility. In this chapter we document the scope and limitations of a new copper-catalyzed C–N bond construction that couples *O*-benzoyl hydroxylamine derivatives and *in situ*-generated diorganozinc reagents (eq 1). Salient features of the protocol that will be detailed include: 1) remarkable tolerance of both steric hindrance at the reaction site and reactive functionality elsewhere in the molecules undergoing coupling; 2) mild reaction conditions (r.t., <1h) and ease of product isolation/purification (acid-base extractive workup); 3) broad scope with respect to the sp^3- and sp^2-hybridized nucleophiles; 4) capacity of the reaction to facilitate direct amination of C_{aryl}–H bonds using directed *ortho*-metalation; 5) direct amination of Grignard reagents using catalysis by Cu(II) and co-catalysis by Zn(II).This chapter has been previously published.[19-22]

$$R{\scriptstyle\diagdown}{\underset{R}{N}}{\scriptstyle\diagup}O{\scriptstyle\diagdown}{\underset{O}{}}{\scriptstyle\diagup}Ph \quad + \quad R'_2Zn \quad \xrightarrow[\substack{THF \\ r.t.}]{\substack{Cu\ (I)\ or \\ Cu(II)\ cat.}} \quad R{\scriptstyle\diagdown}{\underset{R}{N}}{\scriptstyle\diagup}R' \qquad (1)$$
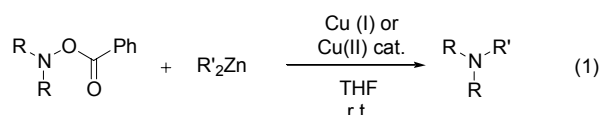
1.2 Results and Discussion
1.2.1 Initial Studies. We initiated our studies by evaluating conditions for the transition-metal catalyzed amination of organometallic reagents (eq 2).

$$R_2N\text{-}X \quad + \quad Ph\text{-}M' \quad \xrightarrow[\text{(Additive)}]{M\ (20\ mol\ \%)\ /\ Ligand} \quad R_2N\text{-}Ph \qquad (2)$$

$$M' = B(OH)_2,\ SnBu_3,\ MgBr,\ MnCl,\ ZnX$$
$$M = Pd(dba)_2,\ Ni(cod)_2,\ CuX,\ Fe(acac)_3$$
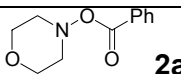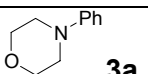
We intentionally limited our search in several key aspects: 1) Only those aminating reagents allowing for the direct delivery of sp^3-hybridized $R_2N(+)$ synthons would be considered; 2) only weak carbon donors would be evaluated. These criteria were imposed in the hopes of developing a more general protocol. *N,N*-Dialkyl-*N*-

chloroamines were initially investigated as aminating agent. Such compounds have been used sparingly in electrophilic amination,[2, 23] but their ease of synthesis renders them attractive starting materials. Results with $PhB(OH)_2$ and $PhSnBu_3$ proved disappointing under all conditions screened (transition-metal salt, supporting ligand, stoichiometric additive). Other organometallic reagents tested ($PhMgBr$, $PhMnCl$, Ph_2Mn, Ph_2Zn) likewise proved ineffective. The results with PhZnX proved promising, with yields of the desired tertiary amine reaching 10-20% for various transition metal/ligand combinations. In all cases, biphenyl formation was the major side reaction. All attempts to optimize conditions for the amination of PhZnX failed to provide substantial increases in yield, prompting us to explore the use of a different aminating agent.
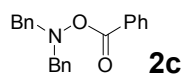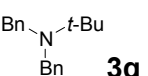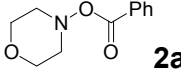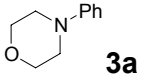
We next tested the hypothesis that *O*-acyl hydroxylamine derivatives might be effective reagents for the proposed C–N bond construction (Table 1-1). Despite their ease of synthesis and stability (vide infra), these compounds have not been employed extensively or effectively in the amination of organometallics. In combination with a ligand-free CuOTf catalyst, these reagents proved promising in the amination of RZnX (entries 1-4). A dramatic increase in yield was realized when R_2Zn was employed as organometallic reagent (entry 5). With such encouraging results, we next set out to prepare a series of *O*-benzoyl hydroxylamine derivatives and to evaluate their potential utility in the amination of R_2Zn reagents.

**Table 1-1.** Evaluation of Conditions for the Copper-Catalyzed Electrophilic Amination of Organozinc Reagents[a]
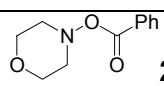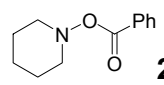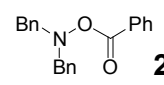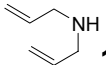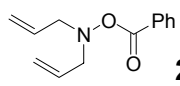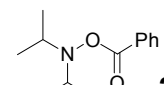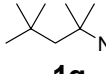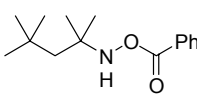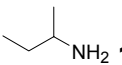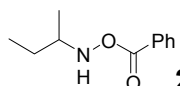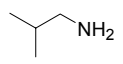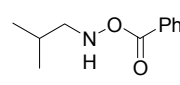
entry	R$_2$NOC(O)Ph	R'ZnX	product	% yield[b]
1	**2a**	PhZnCl	**3a**	29
2	**2a**	PhZnBr	**3a**	25
3	**2a**	PhZnI	**3a**	18
4	**2c**	*t*-BuZnCl	**3q**	18
5	**2a**	Ph$_2$Zn	**3a**	91

[a] 1.1 equiv of diorganozinc were employed. R$_2$Zn reagents were prepared via transmetalation of the corresponding RMgX or RLi reagent with 0.5 equiv of ZnCl$_2$. [b] Isolated yield of product of purity $\geq$ 95 % based on ^{1}H NMR spectroscopy and GLC analysis. Yield is based on the starting R$_2$N-OC(O)Ph.

1.2.2 Preparation of *O*-Benzoyl Hydroxylamines. The *O*-benzoyl hydroxylamines utilized in our studies were prepared via the oxidation of primary and secondary amines with benzoyl peroxide and an exogenous inorganic base, as originally reported by Ganem.[24] In the Ganem report extended reaction times (>12 h) and refluxing conditions are necessary. While this method results in acceptable yields of desired product, competitive *N*-acylation of the amine was noted as a problematic side reaction. We discovered that these same oxidations, when conducted in a polar aprotic solvent, proceed to completion at room temperature with competitive *N*-acylation greatly suppressed. Utilizing this modified procedure, we were able to prepare a variety of *O*-benzoyl hydroxylamines, both from primary and secondary amines, in uniformly high yields (Table 1-2).[25] The reactions are typically run on a 50 mmol scale of the limiting

reagent (benzoyl peroxide), and the products are easily purified by column chromatography. The majority of these compounds are crystalline solids and all show good stability (they can be stored indefinitely in the freezer without decomposition or loss of reactivity). Reaction times varied from 1 h for sterically unhindered primary and secondary amines (entries 1, 2, 8) to 24 h for the most sterically demanding primary and secondary amines tested (entries 3, 5, 6). In instances where the free hydroxylamine is readily available (e.g. Et_2NOH is commercially available), benzoylation represents a simple alternate route to these compounds. In the case of $Et_2N–OC(O)Ph$ (**2e**), acylation of the commercially available parent hydroxylamine resulted in clean formation of product (98 % isolated yield), representing an alternate route to these compounds. While the reaction works uniformly well for *N*-alkyl amines, heteroaromatic amines (e.g. imidazole) failed to undergo oxidation under the present reaction conditions. Attempted oxidation of methyl prolinate was likewise unsuccessful.

Table 1-2. Preparation of *O*-Benzoyl Hydroxylamines[a]

entry	R(R´)NH	R(R´)NOC(O)Ph	time (h)	% yield[c]
1	**1a**	**2a**	1	73
2	**1b**	**2b**	1	80
3[b]	**1c**	**2c**	24	68
4	**1d**	**2d**	4	92
5[b]	**1f**	**2f**	24	87
6[b]	**1g**	**2g**	24	91
7	**1h**	**2h**	6	89
8	**1i**	**2i**	1	61
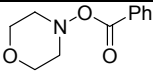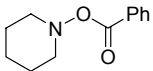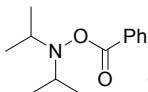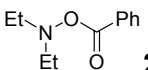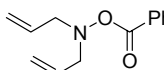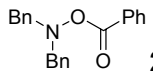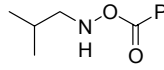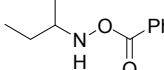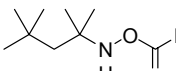
[a] 1.2 equiv of the amine was employed, 1.5 equiv of K_2HPO_4 was employed. [b] 2.5 equiv of the amine was employed, 1.5 equiv of K_2HPO_4 was employed. [c] Isolated yield of product of purity $\geq$ 95 % based on ^{1}H NMR spectroscopy (average of at least two experiments). Yield is based on the starting benzoyl peroxide.

1.2.3 Electrophilic Amination of Diorganozinc Reagents: Preparation of Secondary and Tertiary Amines. Our studies into the transition metal catalyzed electrophilic amination of weak carbon donors began with the discovery that copper salts catalyze the amination of R_2Zn reagents with *O*-benzoyl hydroxylamines under mild reaction conditions (r.t., <1h) (vida supra). With a convenient means of preparing our aminating

reagents (vida supra), we next set out to test the generality of this newly discovered amination protocol. The reaction is quite general, allowing for the facile preparation of a wide variety of both secondary and tertiary amines (Table 1-3). Aryl coupling proceeds in good to excellent yield for various *N*-monoalkyl- and *N,N*-dialkyl-*O*-benzoyl hydroxylamines (entries 1-3, 6-14, 18-20), allowing for the preparation of diverse aniline derivatives. Heteroaryl coupling is also realized in good yield (entry 4). These results offer a complement to existing transition-metal catalyzed methods for the arylation of amines. The preparation of tertiary benzyl amines is also possible using this methodology (entry 5). Likewise, alkyl coupling proceeds in good to excellent yield for primary, secondary, and tertiary dialkylzincs (entries 15-17, 21).

A high level of steric tolerance is apparent in these reactions, as evidenced by the facile coupling of sterically hindered ^{i}Pr$_2$N–OC(O)Ph (**2f**) with both di(*o*-tolyl)- and di(mesityl)zinc reagents (entries 9, 10). Sterically hindered secondary alkyl amines are also accessible using this methodology. The synthesis of *N,N-tert*-octyl-*tert*-butyl amine (**3u**), an immediate precursor to the useful lithio amide base LiN(^{t}Oct)^{t}Bu,[26] is exemplary; entry 21 reports the isolated yield (by distillation) for the preparation of **3u** on a 10 mmol scale. Although moderate compared to other entries in Table 1-3, the simplicity of the two step process represents an attractive route to this useful secondary amine.

Table 1-3. Scope of the Copper-Catalyzed Electrophilic Amination of Diorganozinc Reagents[a]

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

All reactions were complete within 15 – 60 min at room temperature, and simple acid-base extractive workup was sufficient to obtain analytically pure product in most instances. Both Cu(I) and Cu(II) salts catalyze the reaction with equal facility. Identical results are obtained when $CuCl_2$ is substituted for CuOTf under the standard reaction conditions (eq 3 and eq 4; cf Table 1-3, entries 1 and 17 respectively).

$$\text{(3)} \qquad 91\ \%\ \text{yield}$$

$$\text{(4)} \qquad 99\ \%\ \text{yield}$$
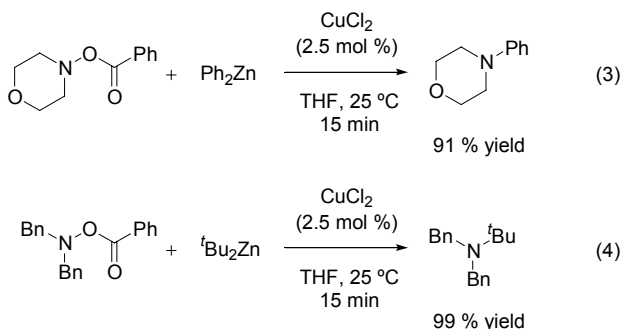
Additives and/or supporting ligands for the metal are unnecessary. The aminations were generally performed on a <1 mmol scale. Upon scale-up (25 mmol), we observed a slight decrease in yield (entry 1, 91%, 0.5 mmol scale; compared with 72%, 25 mmol scale). This may be attributed to a deleterious exotherm which becomes manifest on larger scale; the exotherm is easily managed by conducting the larger scale aminations at 0 °C.[22]

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

1.2.4 Preparation of Functionalized Aryl Amines. Knochel's recently-described I/Mg exchange reaction offers a useful route to functionalized aryl Grignard reagents.[27-29] Treatment of an electron deficient aryl iodide with RMgX (typically ^{i}PrMgBr) at low

9

temperatures results in rapid I/Mg exchange. Electron rich aryl iodides can also be accommodated when elevated reaction temperatures (room temperature) are employed. We envisioned utilizing such reagents in electrophilic amination processes, via an I/Mg exchange/transmetalation sequence, as a simple route to functionalized aryl amines (Scheme 1-1).
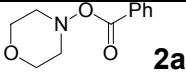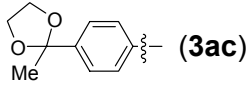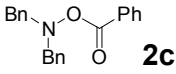
Scheme 1-1. Strategy for the Preparation of Functionalized Aryl Amines
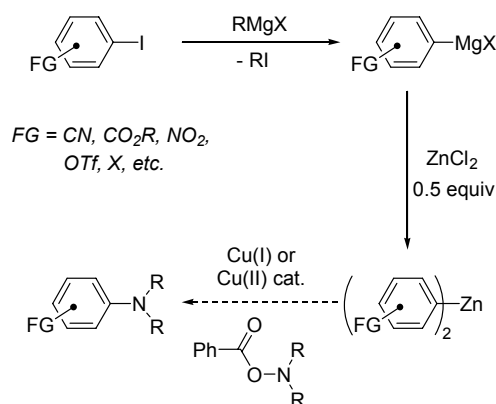
The Grignard reagents derived from I/Mg exchange readily undergo transmetalation with 0.5 equiv of $ZnCl_2$, giving access to functionalized diarylzinc reagents that can be used without prior isolation and/or purification. We were successful in employing such reagents in our copper catalyzed electrophilic amination protocol, giving access to a wide array of functionalized aryl amine products, which are readily purified by simple acid-base extractive workup (Table 1-4). The amination reaction shows broad functional group tolerance in the nucleophilic component. Diverse functional groups, including nitrile, ester, halide, triflate, and nitro are all tolerated under the reaction conditions. Those functional groups requiring prior protection were a phenol (as the derived acetate ester, entry 6) and ketone (as the derived ketal, entry 9). Interestingly, the reaction proceeds equally well for both electron deficient (entry 5) and electron rich (entry 8) Ar_2Zn reagents.

As was true for the unfunctionalized diorganozinc reagents, the use of 0.6 equiv of Ar_2Zn is feasible as demonstrated by the obtention of **3v** (74%), **3y** (74%), **3ab** (83%), and **3c** (71%) in yields comparable to those reported in Table 1-4.

Table 1-4. Scope of the Copper-Catalyzed Electrophilic Amination of Functionalized Diarylzinc Reagents[a]

$$R_2N-OC(O)Ph + Ar_2Zn \xrightarrow[\substack{THF, r. t. \\ 15 - 60\ min}]{\substack{[CuOTf]_2\cdot C_6H_6 \\ (1.25\ mol\ \%)}} R_2N-Ar$$

entry	R₂N-OC(O)Ph	Ar₂Zn (product)	% yield[d]
1	**2a**	*p*-NCPh (**3v**)	76
2	**2a**	*p*-EtO₂CPh (**3w**)	77
3	**2a**	*p*-ClPh (**3x**)	93
4	**2a**	*p*-FPh (**3y**)	71
5	**2a**	*m*-F₃CPh (**3z**)	74
6	**2a**	*p*-AcOPh (**3aa**)	76
7	**2a**	*p*-TfOPh (**3ab**)	95
8[b]	**2a**	*p*-MeOPh (**3c**)	81
9[b]	**2a**	(**3ac**)	79
10[c]	**2a**	*o*-O₂NPh (**3ad**)	83
11[c]	**2a**	2,4-(O₂N)₂Ph (**3ae**)	59
12[b]	**2a**	1-naphthyl (**3af**)	90
13	**2c**	*p*-CNPh (**3ag**)	95
14	**2c**	*p*-EtO₂CPh (**3ah**)	99
15	**2c**	*p*-ClPh (**3ai**)	88
16[b]	**2c**	*p*-MeOPh (**3aj**)	87
17[c]	**2c**	*o*-O₂NPh (**3ak**)	97

[a] 1.1 equiv of diarylzinc were employed. Ar₂Zn reagents were prepared from the corresponding ArI as follows: 1) ⁱPrMgBr, -35 °C, 1h 2) ZnCl₂, -35 °C, 10 min. [b] Ar₂Zn prepared from the corresponding ArI as follows: 1) ⁱPrMgBr, rt, 1h 2) ZnCl₂, rt, 10 min. [c] Ar₂Zn prepared from the corresponding ArI as follows: 1) PhMgBr, -35 °C, 10 min 2)

ZnCl$_2$, -35 °C, 10 min. [d] Isolated yield of product of ≥ 95 % purity as judged by ^{1}H NMR spectroscopy and GLC analysis (average of at least two experiments). Yield is based on the starting R$_2$N-OC(O)Ph.

1.2.5 Directed *Ortho* Lithiation/Amination Sequence. Directed *ortho* lithiation has been utilized extensively as a reliable tool for the functionalization of poorly reactive C$_{aryl}$–H bonds.[30] Most work in this area has focused on the utility of this methodology toward the construction of new C–C bonds.[31] Fewer studies have addressed the aspects of C–N bond construction. Seminal examples by Snieckus illustrate the potential utility of this methodology for the formation of new C–N bonds.[32, 33] We envisaged employing a directed *ortho* lithiation/transmetalation sequence to obtain Ar$_2$Zn reagents *in situ*. These reagents could then be used (without isolation and/or purification) in the title copper-catalyzed electrophilic amination protocol, allowing for the facile, selective oxidation of C$_{aryl}$–H bonds (Scheme 1-2).

Scheme 1-2. Strategy for the Directed *Ortho* Metalation/Amination Sequence
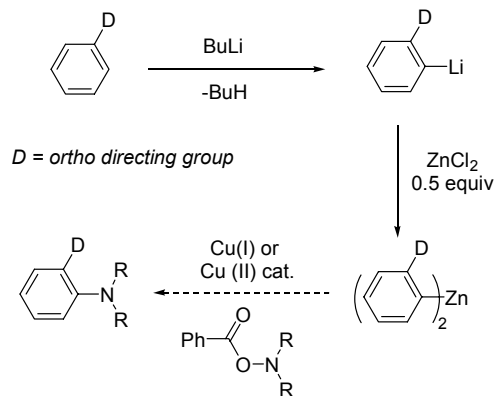
We tested this hypothesis for a number of arenes, employing the most commonly used directing groups in similar directed ortho lithiation protocols (Table 1-5). The reaction works equally well for both *N,N*-dialkylamide and methoxymethyl ether directing groups (entries 1,3). Somewhat less effective are the commonly employed *O*-aryl carbamate and oxazoline directing groups under the optimized reaction conditions (entries 2,4). A noticeable reduction in reaction rate is apparent for all substrates tested,

presumably a result of the enhanced coordination in the derived diorganozinc reagents. The symbiosis of directed *ortho* metalation/amination allows for the preparation of diverse amine products not readily accessible using previous methodology.

Table 1-5. Scope of the Directed *Ortho* Metalation/Amination Sequence[a]

entry	Ar$_2$Zn	product	% yield[c]
1		(3al)	88
2		(3am)	55
3[b]		(3an)	95
4		(3ao)	62

[a] 1.1 equiv of diarylzinc were employed. Ar$_2$Zn reagents were prepared from the corresponding arene as follows: 1) *sec*BuLi, TMEDA, -78 °C, 30 min; 2) ZnCl$_2$, -78 °C to rt, 30 min. [b] Ar$_2$Zn prepared from the corresponding arene as follows: 1) ^{t}BuLi, 0 °C, 1 h; 2) ZnCl$_2$, 0 °C to rt, 30 min. [c] Isolated yield of product of ≥ 95 % purity as judged by ^{1}H NMR spectroscopy and GLC analysis (average of at least two experiments). Yield is based on the starting R$_2$N-OC(O)Ph.

1.2.6 Double Metal Catalyzed Electrophilic Amination. The organozinc reagents employed in these studies were generally prepared from the corresponding RMgX or RLi reagent via transmetalation with 0.5 equiv of ZnCl$_2$. The resultant R$_2$Zn solution was

subsequently added to the remaining reaction components and amination allowed to proceed under normal reaction conditions. Recent reports in the literature suggest that *in situ* generation of organozinc reagents from RMgX is also possible using catalytic quantities of a Zn(II) salt.[34] This method obviates the use of large quantities of anhydrous zinc salts, which can present processing concerns on scale. We tested the feasibility of this protocol for our electrophilic amination reaction.

Studies early in this project illustrated the apparent incompatibility of $R_2NO–C(O)Ph$ reagents with RMgX nucleophiles: rapid acylation (ketone formation) of the Grignard reagent under standard reaction conditions was the predominant reaction pathway. Thus, for the proposed "catalytic-in-zinc" protocol to be successful, the projected transmetalation/amination must be faster than direct acylation. Gratifyingly, this is the case, and we observed good yields of the desired amination product when catalytic quantities of $ZnCl_2$ were employed (eq 5). An analogous experiment using morpholine-derived **2a**, 2.5 mol % of $CuCl_2$, and 10 mol % of $ZnCl_2$ gave *N*-phenylmorpholine (**3a**) in 69% isolated yield.

(5)

catalyst	cocatalyst	yield
none	none	4%
CuOTf (2.5%)	none	13%
CuOTf (2.5%)	$ZnCl_2$ (10%)	65%
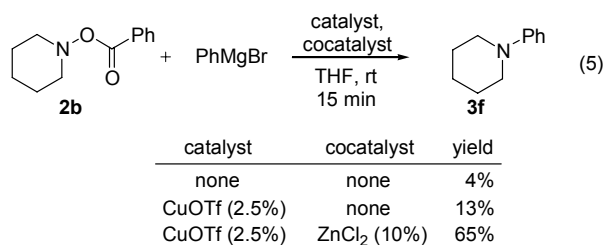
Our studies suggest that the rate of addition of the Grignard reagent is important, with both rapid (<1 min) and exceedingly slow (>60 min) additions resulting in lower product yield. Dropwise addition over the course of 5 min results in optimal yields. Reaction temperature is likewise crucial, with sub-ambient temperatures resulting in diminished yields and/or incomplete reaction.

Recent results from our labs illustrate that, under tightly controlled reaction conditions, the use of $ZnCl_2$ can be completely eliminated.[35] Employing catalytic $CuCl_2$

(2.5 – 15 mol %; substrate dependent) and a series of *N,N*-dialkyl-*O*-benzoyl hydroxylamines as limiting reagent, amination of RMgX proceeds smoothly at ambient temperature. In a further improvement, the use of catalytic copper can be eliminated, allowing for the uncatalyzed amination of RMgX.[35] In this instance, the use of *O*-2,4,6-trimethylbenzoyl hydroxylamine is requisite to minimize competitive acylation of RMgX, which is the predominant pathway when the standard *N,N*-dialkyl-*O*-benzoyl hydroxylamine is employed (vida supra).

1.3 Conclusion

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

1.4 References

(1)   Seebach, D. *Angew. Chem. Int. Ed.* **1979,** *18*, 239-258.

(2)   Erdik, E.; Ay, M. *Chem. Rev.* **1989,** *89*, 1947-80.

(3)   Erdik, E.; Ay, M. *Synth. React. Inorg. Met.-Org. Chem.* **1989,** *19*, 663-8.

(4)   Erdik, E.; Daskapan, T. *J. Chem. Soc. Perkin Trans. 1* **1999**, 3139-3142.

(5)   Tsutsui, H.; Hayakashi, Y.; Narasaka, K. *Chem. Lett.* **1997**, 317-318.

(6)   Tsutsui, H.; Ichikawa, T.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1999,** *72*, 1869-1878.

(7)   Narasaka, K. *Pure App. Chem.* **2002,** *74*, 143-149.

(8)   Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005**, 4505-4519.

(9)   Jiang, L.; Buchwald, S. L. *Metal-Catalyzed Cross-Coupling Reactions (2nd Edition)* **2004,** *2*, 699-760.

(10)   Hartwig, J. F. *Handbook of Organopalladium Chemistry for Organic Synthesis* **2002,** *1*, 1051-1096.

(11)   Erdik, E. *Tetrahedron* **2004,** *60*, 8747-8782.

(12)   Greck, C.; Drouillat, B.; Thomassigny, C. *Eur. J. Org. Chem.* **2004**, 1377-1385.

(13)   Dembech, P.; Seconi, G.; Ricci, A. *Eur. J. Chem.* **2000,** *6*, 1281-1286.

(14)   Greck, C.; Genet, J. P. *Synlett* **1997**, 741-748.

(15)   Boche, G.; Mayer, N.; Bernheim, M.; Wagner, K. *Angew. Chem.* **1978,** *90*, 733-4.

(16)   Colvin, E. W.; Kirby, G. W.; Wilson, A. C. *Tetrahedron Lett.* **1982,** *23*, 3835-6.

(17)   Boche, G.; Bernheim, M.; Schrott, W. *Tetrahedron Lett.* **1982,** *23*, 5399-402.

(18)   Oguri, T.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1975,** *23*, 167-72.

(19)   This chapter has been previously published: Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006,** *71*, 219-224.

(20)   Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004,** *126*, 5680-5681.

(21)   Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2005,** *70*, 364-366.

(22)   Berman, A. M.; Johnson, J. S.; Nora, G.; Miller, M. J. *Org. Synth.* **2006,** *83*, 31-37.

(23)   Sinha, P.; Knochel, P. *Synlett* **2006**, 3304-3308.

(24)   Biloski, A. J.; Ganem, B. *Synthesis* **1983**, 537-8.

(25)   White, E. H.; Reefer, J.; Erickson, R. H.; Dzadzic, P. M. *J. Org. Chem.* **1984,** *49*, 4872-6.

(26)   Corey, E. J.; Gross, A. W. *Org. Synth.* **1987,** *65*, 166-72.

(27)   Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003,** *42*, 4302-4320.

(28)   Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2004,** *43*, 897-900.

(29)   Sapountzis, I.; Knochel, P. *J. Am. Chem. Soc.* **2002,** *124*, 9390-9391.

(30)   Snieckus, V. *Chem. Rev.* **1990,** *90*, 879-933.

(31)   Anctil, E. J. G.; Snieckus, V. *J. Organomet. Chem.* **2002,** *653*, 150-160.

(32)   Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1983,** *24*, 3795-8.

(33)   Iwao, M.; Reed, J. N.; Snieckus, V. *J. Am. Chem. Soc.* **1982,** *104*, 5531-3.

(34)   Miller, J.; Farrell, R. P. *Tetrahedron Lett.* **1998,** *39*, 7275-7278.

(35)   Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007,** *9*, 1521-1524.

1.5 Supporting Information

I. Materials and Methods

General. Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model Avance 400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) spectrometer with tetramethylsilane or solvent resonance as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.24 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H 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] $ZnCl_2$ was dried under vacuum (0.1 mmHg) at 150 °C for 12 hours prior to use. 4-Iodobenzonitrile, 4-iodobenzoic acid ethyl ester, and 2-iodo-pyridine 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.

II. 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 is 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 is stirred and the amine (60 - 125 mmol) is added via syringe in one portion. The suspension is stirred at ambient temperature for the indicated reaction time. Deionized water (200 mL) is added and the contents are stirred vigorously for several minutes until all solid has dissolved. The reaction mixture is transferred to a 1-L separatory funnel and extracted with 150 mL of ethyl acetate. The organic phase is collected and washed with two 100-mL portions of saturated aq. NaHCO$_3$ solution. All of the aqueous fractions are combined and extracted with three 100-mL portions of ethyl acetate. All of the organic fractions are combined and washed with three 100-mL portions of deionized water, 100-mL of brine, dried over MgSO$_4$, and concentrated by rotary evaporation. The resulting crude product mixture is purified by flash column chromatography, eluting with the indicated solvent system, to afford desired product of $\geq$ 95 % purity as judged by ^{1}H NMR spectroscopy. The product was stored at sub-ambient temperature under anhydrous conditions.
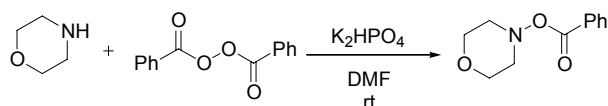
4-Benzoyloxymorpholine (2a). The title compound was prepared according to general procedure **A** using morpholine (5.20 mL, 60 mmol) with stirring for 1 h to yield 4-benzoyloxymorpholine (7.71 g, 37 mmol, 74 %) as a white solid following flash column chromatography with 50 % EtOAc:hexanes. Analytical data for the title compound: **IR** (Nujol, cm^{-1}) 2924, 2852, 1730, 1599, 1456, 1377, 1315, 1269, 1248, 1178, 1165, 1101, 1084, 1066, 1049, 1007, 922, 858, 712; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 8.00 - 7.98 (m, 2H), 7.58 – 7.53 (m, 1H), 7.45 – 7.41 (m, 2H), 3.96 (br d, *J* = 10.7 Hz, 2H), 3.85 (br t, *J* = 11.2 Hz, 2H), 3.43 (br d, 9.3 Hz, 2H), 3.03 (br t, 9.4 Hz, 2H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 164.6, 133.1, 129.4, 129.2, 128.4, 65.8, 57.0. **Anal.** Calcd for C$_{11}$H$_{13}$NO$_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.96; H, 6.40; N, 6.67.
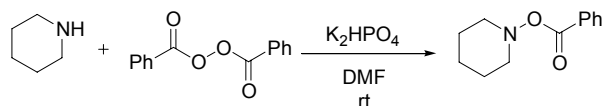
1-Benzoyloxypiperidine (2b). The title compound was prepared according to

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: **IR** (Nujol, cm^{-1}) 2924, 2856, 1731, 1452, 1377, 1369, 1253, 1183, 1091, 1070, 1018, 850, 716; **^{1}H 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 white solid following flash column chromatography with 15 % EtOAc:hexanes. Analytical data for the title compound: **IR** (thin film, cm^{-1}) 3067, 2979, 2937, 2875, 2615, 1707, 1601, 1451, 1383, 1321, 1210, 1177, 1072, 919, 874, 845, 761, 692, 663, 614; **^{1}H 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.
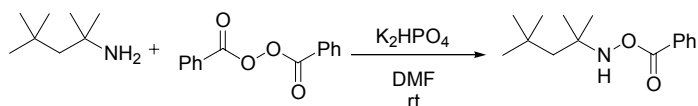
O-Benzoyl-N-tert-Octylhydroxylamine (2g). The title compound was prepared according to general procedure **A** using tert-octyl amine (20.1 mL, 125 mmol) with stirring for 24 h to yield O-benzoyl-N-tert-octylhydroxylamine (11.30 g, 45 mmol, 91 %) as a clear, colorless oil following flash column chromatography with 10 % EtOAc:hexanes. Analytical data for the title compound: **IR** (thin film, cm^{-1}) 3223, 3070, 2953, 2908, 2873, 1965, 1907, 1718, 1603, 1473, 1451, 1366, 1316, 1273, 1177, 1093, 1068, 1026, 796, 708; **^{1}H 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 is 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 is stirred and the amine (6.0 – 12.5 mmol) is added via syringe in one portion. The suspension is stirred at ambient temperature for the indicated reaction time. Deionized water (50 mL) is added and the contents are stirred vigorously for several minutes until all solid has dissolved. The reaction mixture is transferred to a 125-mL separatory funnel and extracted with 25 mL of ethyl acetate. The organic phase is collected and washed with two 25-mL portions of saturated aq. NaHCO$_3$ solution. All of the aqueous fractions are combined and extracted with three 25-mL portions of ethyl acetate. All of the organic fractions are 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 is purified by flash column chromatography, eluting with the indicated solvent system, to afford desired product of ≥ 95 % purity as judged by ^{1}H NMR spectroscopy. The product was stored at sub-ambient temperature under anhydrous conditions.
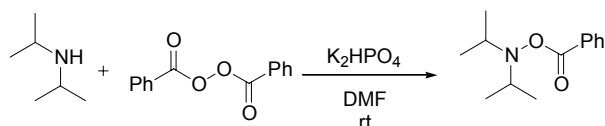

***O*-Benzoyl-*N,N*-Dibenzylhydroxylamine (2c).** The title compound was prepared according to general procedure **B** using dibenzylamine (2.7 mL, 12.5 mmol) with stirring for 24 h to yield *O*-benzoyl-*N,N*-dibenzylhydroxylamine (1.05 g, 3.3 mmol, 66%) as a white solid after flash chromatography with 1% EtOAc:hexanes. Analytical data for the title compound: **IR** (Nujol, cm^{-1}) 2952, 2926, 2854, 1726, 1456, 1377, 1254, 1095, 1068, 1026, 983, 751, 707; **^{1}H 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.
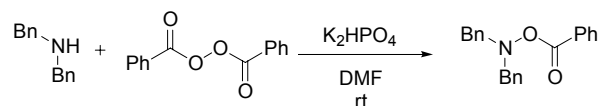

***O*-Benzoyl-*N,N*-Diallylhydroxylamine (2d).** The title compound was prepared according to general procedure **B** using *N,N*-diallyl amine (0.74 mL, 6.0 mmol) with stirring for 4 h to yield *O*-benzoyl-*N,N*-diallylhydroxylamine (1.00 g, 4.6 mmol, 92 %) as a

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, 1492, 1451, 1254, 1177, 1073, 1026, 989, 929, 819, 707; **^{1}H 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.
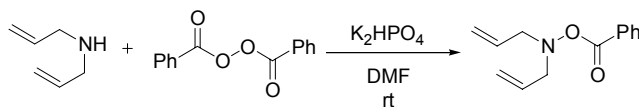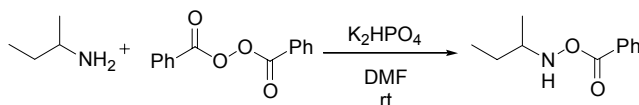

O-Benzoyl-N-sec-Butylhydroxylamine (2h). The title compound was prepared according to general procedure **B** using *N-sec*-butyl amine (0.61 mL, 6.0 mmol) with stirring for 6 h to yield *O*-benzoyl-*N-sec*-butylhydroxylamine (0.86 g, 4.5 mmol, 89 %) as a clear, colorless oil following flash column chromatography with 15 % EtOAc:hexanes. Analytical data for the title compound: **IR** (thin film, cm^{-1}) 3239, 3068, 2969, 2936, 2878, 1965, 1913, 1720, 1602, 1452, 1378, 1316, 1273, 1178, 1092, 1067, 1026, 830, 797, 708; **^{1}H 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.
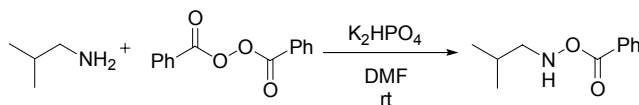
O-Benzoyl-N-iso-Butylhydroxylamine (2i). The title compound was prepared according to general procedure **B** using *N-iso*-butyl amine (0.60 mL, 6.0 mmol) with stirring for 1 h to yield *O*-benzoyl-*N-sec*-butylhydroxylamine (0.59 g, 3.1 mmol, 61 %) as a clear, colorless oil following flash column chromatography with 15 % EtOAc:hexanes. Analytical data for the title compound: **IR** (thin film, cm^{-1}) 3245, 3069, 2960, 2929, 2872, 1964, 1905, 1720, 1602, 1470, 1452, 1389, 1316, 1275, 1177, 1092, 1067, 1026, 791, 708; **^{1}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}C NMR** (100 MHz, CDCl$_3$) δ 166.9, 133.3, 129.3, 128.5, 60.1, 26.4, 20.5.

23
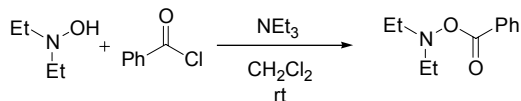
***O*-Benzoyl- *N,N*-Diethylhydroxylamine (2e).** An oven-dried round bottom flask equipped with magnetic stir bar and addition funnel was charged with *N,N*-diethylhydroxylamine (0.89 g, 1.0 mL, 10 mmol), freshly distilled triethylamine (1.0 g, 1.4 mL, 10 mmol), and anhydrous dichloromethane (10 mL). 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}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}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]

III. 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 is 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 is stirred at ambient temperature and an ethereal solution of the RMgX or RLi (1.1 mL, 1.1 mmol, 1.0 M) is added via cannula in one portion. The resulting solution is 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 is 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 is stirred and the previously generated diorganozinc solution (vida supra) is added via cannula in one portion. The resulting solution is stirred at ambient temperature for 1 h. Diethyl ether (10 mL) is added and the reaction mixture is transferred to a 125-mL   separatory funnel. The reaction mixture is

washed with three 10-mL portions of saturated aq. NaHCO$_3$ solution, and extracted with three 10-mL portions of 10 % aq. HCl solution. The aqueous extracts are basified with 10 % aq. NaOH solution, and extracted with three 10-mL portions of dichloromethane. The organic fraction is washed with 10-mL of brine, dried over Na$_2$SO$_4$, and concentrated by rotary evaporation, to afford the desired product of ≥ 95 % purity as judged by ^{1}H NMR spectroscopy.
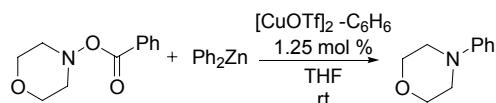
4-Phenylmorpholine (3a). The title compound was prepared according to general procedure **C** using 4-benzoyloxymorpholine (0.1031 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0028 g, 0.0056 mmol), and a tetrahydrofuran solution of diphenylzinc to yield 4-phenylmorpholine (0.0797 g, 0.49 mmol, 98%) as a white solid. The ^{1}H NMR spectrum was consistent with that reported in the literature.[4]
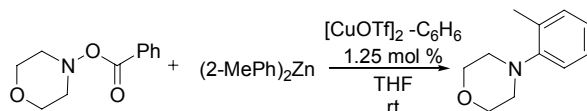
4-(2-Methylphenyl)morpholine (3b). The title compound was prepared according to general procedure **C** using 4-benzoyloxymorpholine (0.1035 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0031 g, 0.0062 mmol), and a tetrahydrofuran solution of di-*o*-tolylzinc to yield 4-(2-methylphenyl)morpholine (0.0858 g, 0.48 mmol, 97%) as a clear, pale yellow oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[5]
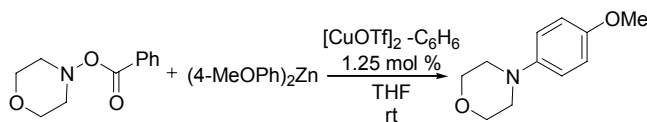
4-(4-Methoxyphenyl)morpholine (3c). The title compound was prepared according to general procedure **C** using 4-benzoyloxymorpholine (0.1035 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0032 g, 0.0064 mmol), and a tetrahydrofuran solution of bis-(4-methoxyphenyl)zinc to yield 4-(4-methoxyphenyl)morpholine (0.0911 g, 0.47 mmol, 94%) as a white solid. The ^{1}H 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 (0.1030 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0030 g, 0.0060 mmol), and a tetrahydrofuran solution of bis-(2-pyridinyl)zinc to yield 4-pyridin-2-yl-morpholine (0.0586 g, 0.36 mmol, 71%) as a yellow oil. The ^{1}H 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 (0.1037 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0031 g, 0.0062 mmol), and a diethyl ether solution of dibenzylzinc to yield 4-benzylmorpholine (0.0696 g, 0.39 mmol, 78%) as a clear, colorless oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[7]
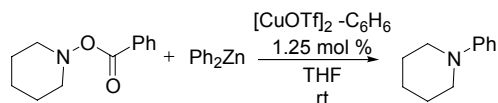
1-Phenylpiperidine (3f). The title compound was prepared according to general procedure **C** using 1-benzoyloxypiperidine (0.1025 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0033 g, 0.0066 mmol), and a tetrahydrofuran solution of diphenylzinc to yield 1-phenylpiperidine (0.0744 g, 0.46 mmol, 92%) as a clear, pale yellow oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[4]
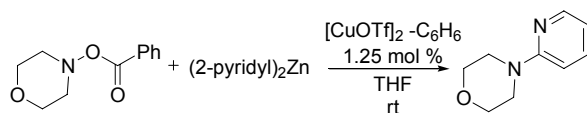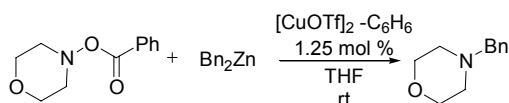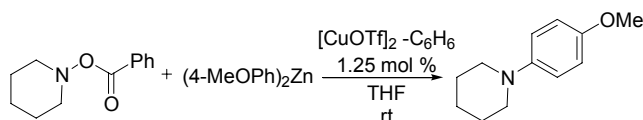

1-(4-Methoxyphenyl)piperidine (3g). The title compound was prepared according to general procedure **C** using 1-benzoyloxy-piperidine (0.1029 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0031 g, 0.0062 mmol), and a tetrahydrofuran solution of bis-(4-   methoxyphenyl)zinc to yield 1-(4-

methoxyphenyl)piperidine (0.0938 g, 0.49 mmol, 98%) as a clear, pale yellow oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[8]
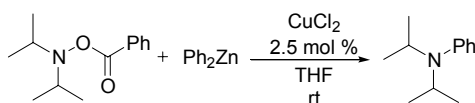

N,N-Diisopropylaniline (3h). The title compound was prepared according to general procedure **C** using *O*-benzoyl-*N,N*-diisopropylhydroxylamine (0.1105 g, 0.50 mmol), copper(II) chloride (0.0017 g, 0.0125 mmol), and a tetrahydrofuran solution of diphenylzinc to yield *N,N*-diisopropylaniline (0.0716 g, 0.40 mmol, 81 %) as a clear, colorless oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[9]
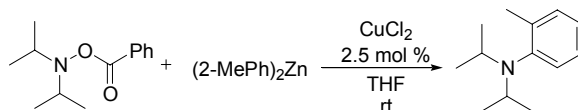
Diisopropyl-(2-Methylphenyl)amine (3i). The title compound was prepared according to general procedure **C** using *O*-benzoyl-*N,N*-diisopropylhydroxylamine (0.1105 g, 0.50 mmol), copper(II) chloride (0.0017 g, 0.0125 mmol), and a tetrahydrofuran solution of di-*o*-tolylzinc to yield diisopropyl-(2-methylphenyl)amine (0.0592 g, 0.31 mmol, 62 %) as a clear, colorless oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[10]
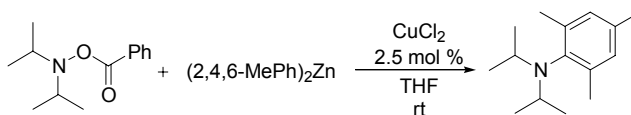
Diisopropyl-(2,4,6-Trimethylphenyl)amine (3j). The title compound was prepared according to general procedure **C** using *O*-benzoyl-*N,N*-diisopropylhydroxylamine (0.1105 g, 0.50 mmol), copper(II) chloride (0.0017 g, 0.0125 mmol), and a tetrahydrofuran solution of di-mesitylzinc to yield diisopropyl-(2,4,6-trimethylphenyl)amine (0.0842 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, 2624, 1720, 1608, 1479, 1381, 1371, 1339, 1301, 1250, 1192, 1110, 1012, 920, 856; **^{1}H 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.

$$\text{Et}_2\text{N-O-C(=O)Ph} + \text{Ph}_2\text{Zn} \xrightarrow[\substack{\text{THF} \\ \text{rt}}]{\substack{[\text{CuOTf}]_2\cdot\text{C}_6\text{H}_6 \\ 1.25 \text{ mol \%}}} \text{Et}_2\text{N-Ph}$$

N,N-Diethylaniline (3k). The title compound was prepared according to general procedure **C** using *N,N*-diethyl-*O*-benzoylhydroxylamine (0.0955 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0034 g, 0.0068 mmol), and a tetrahydrofuran solution of diphenylzinc to yield *N,N*-diethylaniline (0.0574 g, 0.39 mmol, 77%) as a clear, pale yellow oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[11]

$$\text{Et}_2\text{N-O-C(=O)Ph} + (2\text{-MePh})_2\text{Zn} \xrightarrow[\substack{\text{THF} \\ \text{rt}}]{\substack{[\text{CuOTf}]_2\cdot\text{C}_6\text{H}_6 \\ 1.25 \text{ mol \%}}} \text{Et}_2\text{N-(2-MePh)}$$

Diethyl-(2-methylphenyl)amine (3l). The title compound was prepared according to general procedure **C** using *N,N*-diethyl-*O*-benzoylhydroxylamine (0.0962 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0030 g, 0.0060 mmol), and a tetrahydrofuran solution of di-*o*-tolylzinc to yield diethyl-(2-methylphenyl)amine (0.0650 g, 0.40 mmol, 80 %) as a clear, pale yellow oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[12]

$$\text{(allyl)}_2\text{N-O-C(=O)Ph} + \text{Ph}_2\text{Zn} \xrightarrow[\substack{\text{THF} \\ \text{rt}}]{\substack{\text{CuCl}_2 \\ 2.5 \text{ mol \%}}} \text{(allyl)}_2\text{N-Ph}$$

N,N-Diallylaniline (3m). The title compound was prepared according to general procedure **C** using *O*-benzoyl-*N,N*-diallylhydroxylamine (0.1085 g, 0.50 mmol), copper(II) chloride (0.0017 g, 0.0125 mmol), and a tetrahydrofuran solution of diphenylzinc to yield *N,N*-diallylaniline (0.0827 g, 0.48 mmol, 96 %) as a clear, colorless oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[13]

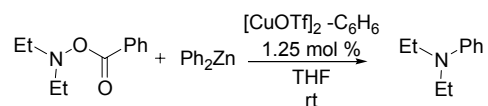$$\text{iso-Bu-NH-O-C(=O)Ph} + \text{Ph}_2\text{Zn} \xrightarrow[\substack{\text{THF} \\ \text{rt}}]{\substack{\text{CuCl}_2 \\ 2.5 \text{ mol \%}}} \text{iso-Bu-NH-Ph}$$

N-iso-Butylaniline (3r). The title compound was prepared according to general procedure **C** using *O*-benzoyl-*N-iso*-butylhydroxylamine (0.0965 g, 0.50 mmol), copper(II) chloride (0.0017 g, 0.0125 mmol), and a tetrahydrofuran solution of diphenylzinc to yield *N-sec*-butylaniline (0.0526 g, 0.35 mmol, 71 %) as a clear, colorless oil. The ^{1}H NMR spectrum was consistent   with that reported in the literature.[14]
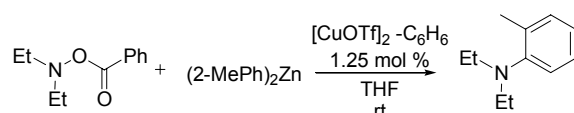
N-sec-Butylaniline (3s). The title compound was prepared according to general procedure **C** using O-benzoyl-N-sec-butylhydroxylamine (0.0965 g, 0.50 mmol), copper(II) chloride (0.0017 g, 0.0125 mmol), and a tetrahydrofuran solution of diphenylzinc to yield N-sec-butylaniline (0.0569 g, 0.38 mmol, 76 %) as a clear, pale brown colored oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[15]
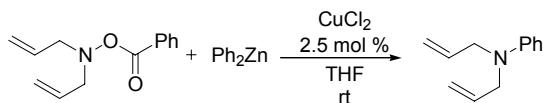
General Procedure (D) for the copper catalyzed amination of diorganozinc reagents. An oven-dried 10-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar is maintained under an inert atmosphere of argon and charged with zinc chloride (0.075 g, 0.55 mmol) and anhydrous tetrahydrofuran (2.0 mL). The solution is stirred at ambient temperature and an ethereal solution of the RMgX or RLi (1.1 mL, 1.1 mmol, 1.0 M) is added via cannula in one portion. The resulting solution is 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 is 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 is stirred and the previously generated diorganozinc solution (vida supra) is added via cannula in one portion. The resulting solution is stirred at ambient temperature for 1 h. Diethyl ether (10 mL) is added and the reaction mixture is transferred to a 125-mL separatory funnel. The reaction mixture is 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 is purified by flash column chromatography, eluting with the indicated solvent system, to afford desired product of $\geq$ 95 % purity as judged by ^{1}H NMR spectroscopy.
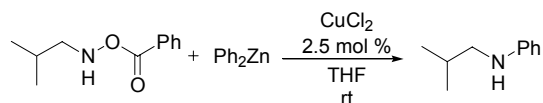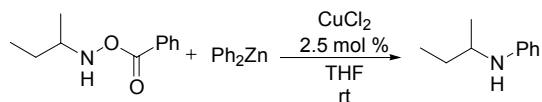

N,N-Dibenzylaniline (3n). The title compound was prepared according to general procedure **D** using O-benzoyl-N,N-dibenzylhydroxylamine (0.1585 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0033 g, 0.0066

29

mmol), and a tetrahydrofuran solution of diphenylzinc to yield *N,N*-dibenzylaniline (0.1286 g, 0.47mmol, 94 %) as a white solid following flash column chromatography with 1% EtOAc:hexanes. The ^{1}H 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 (0.1585 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0031 g, 0.0062 mmol), and a hexanes solution of diethylzinc to yield *N,N*-dibenzylethylamine (0.1022 g, 0.46 mmol, 91%) as a clear, pale yellow oil following flash column chromatography with 10% EtOAc:hexanes. The ^{1}H NMR spectrum was consistent with that reported in the literature.[17]

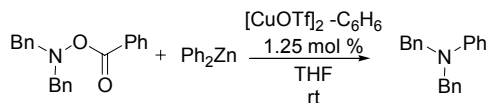**N,N-Dibenzylisopropylamine (3p).** The title compound was prepared according to general procedure **D** using *O*-benzoyl-*N,N*-dibenzylhydroxylamine (0.1591 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0029 g, 0.0058 mmol), and a tetrahydrofuran solution of diisopropylzinc to yield *N,N*-dibenzylisopropylamine (0.0976 g, 0.41 mmol, 82%) as a clear, colorless oil following flash column chromatography with 2.5% EtOAc:hexanes. The ^{1}H NMR spectrum was consistent with that reported in the literature.[18]

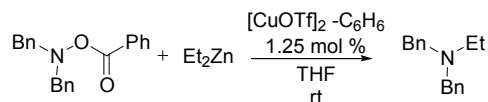**N,N-Dibenzyl-*tert*-butylamine (3q).** The title compound was prepared according to general procedure **D** using *O*-benzoyl-*N,N*-dibenzylhydroxylamine (0.1589 g, 0.50 mmol), copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0031 g, 0.0062 mmol), and a tetrahydrofuran solution of di-*tert*-butylzinc to yield *N,N*-dibenzyl-*tert*-butylamine (0.1250 g, 0.495 mmol, 99 %) as a white solid with no purification necessary. The ^{1}H NMR spectrum was consistent with that reported in the literature.[19]
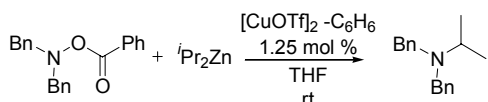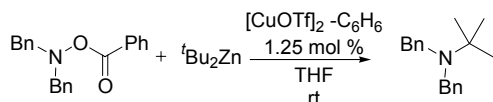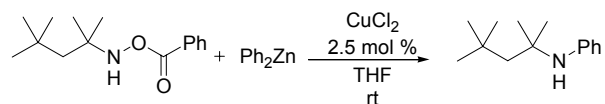
N-tert-Octylaniline (3t). The title compound was prepared according to general procedure **D** using *O*-benzoyl-*N-tert*-octylhydroxylamine (0.1245 g, 0.50 mmol), copper(II) chloride (0.0017 g, 0.0125 mmol), and a tetrahydrofuran solution of diphenylzinc to yield *N-tert*-octylaniline (0.0658 g, 0.32 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) 3422, 3091, 3056, 2954, 2907, 2871, 1601, 1497, 1480, 1385, 1365, 1325, 1312, 1262, 1246, 1224, 1181, 1153, 1081, 1032, 995, 867, 746, 693; **¹H NMR** (400 MHz, CDCl₃) 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); **¹³C NMR** (100 MHz, CDCl₃) δ 146.9, 128.9, 117.3, 116.5, 55.2, 53.1, 31.8, 31.7, 30.5.
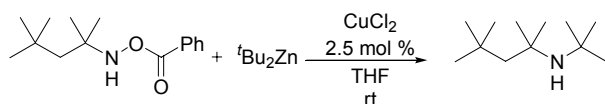
N-tert-Octyl-N-tert-Butylamine (3u). An oven-dried 100-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar is maintained under an inert atmosphere of argon and charged with zinc chloride (1.50 g, 11 mmol) and anhydrous tetrahydrofuran (22 mL). The solution is stirred and cooled in an ice bath and a tetrahydrofuran solution of *t*BuMgCl (22 mL, 22 mmol, 1.0 M) is added via cannula in one portion. The resulting solution is stirred for 20 min at ambient temperature prior to use (vida infra). An oven-dried 100-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar is 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 is stirred and the previously generated di-*tert*-butylzinc solution (vida supra) is added via cannula in one portion. The resulting solution is stirred at ambient temperature for 1 h. Diethyl ether (100 mL) is added and the reaction mixture is transferred to a 500-mL separatory funnel. The reaction mixture is 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 is purified by distillation under reduced pressure (50 mbar, 70 °C bp) to yield *N-tert*-octylaniline (0.7905 g, 4.3 mmol, 43 %) as a clear, colorless oil. The ¹H NMR spectrum was consistent with that reported in the literature.[20]

IV. 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]$_2$·C$_6$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), 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 ^{1}H 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 (0.1258 g, 0.55 mmol), 4-(benzoyloxy)morpholine (0.0520 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0016 g, 0.0031 mmol) to yield 4-(morpholin-4-yl)-benzonitrile (0.0370 g, 0.20 mmol, 79%) as a white solid. The ^{1}H NMR spectrum was

consistent with that reported in the literature.[21]
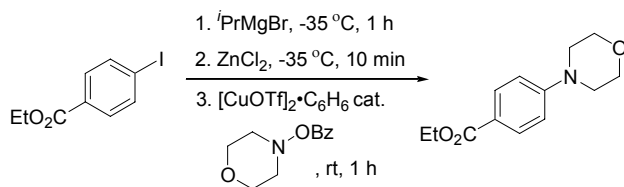
4-(Morpholin-4-yl)-benzoic acid ethyl ester (3w). The title compound was prepared according to General Procedure **E** using 4-iodobenzoic acid ethyl ester (0.1520 g, 0.55 mmol), 4-(benzoyloxy)morpholine (0.0518 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0017 g, 0.0031 mmol) to yield 4-(morpholin-4-yl)-benzoic acid ethyl ester (0.0443 g, 0.19 mmol, 75%) as a white solid. The ^{1}H NMR spectrum was consistent with that reported in the literature.[22]
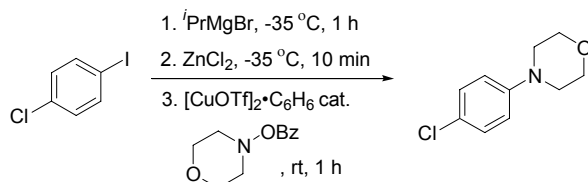
4-(4-Chlorophenyl)-morpholine (3x). The title compound was prepared according to General Procedure **E** using 1-chloro-4-iodo-benzene (0.1312 g, 0.55 mmol), 4-(benzoyloxy)morpholine (0.0520 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0016 g, 0.0031 mmol) to yield 4-(4-chlorophenyl)-morpholine (0.0477 g, 0.24 mmol, 97%) as a white solid. The ^{1}H NMR spectrum was consistent with that reported in the literature.[23]
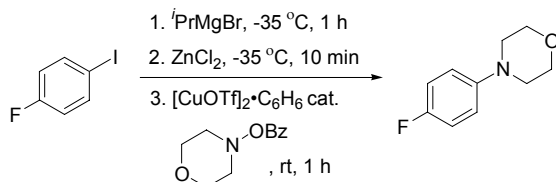
4-(4-Fluorophenyl)-morpholine (3y). The title compound was prepared according to General Procedure **E** using 1-fluoro-4-iodo-benzene (0.1224 g, 0.55 mmol), 4-(benzoyloxy)morpholine (0.0518 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0016 g, 0.0031 mmol) to yield 4-(4-fluorophenyl)-morpholine (0.0327 g, 0.18 mmol, 72%) as a pale yellow oil. Analytical data for the title compound: **^{1}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}C NMR (100 MHz, CDCl$_3$) δ 117.6, 117.5, 115.7, 115.5, 66.9, 50.4.
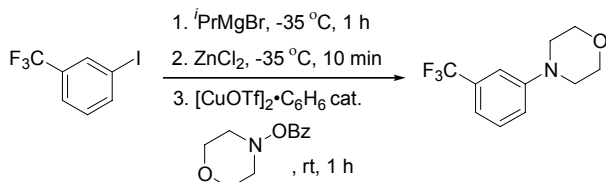
4-(3-Trifluoromethyl-phenyl)-morpholine (3z). The title compound was prepared according to General Procedure **E** using 1-iodo-3-trifluoromethyl-benzene (0.1496 g, 0.55 mmol), 4-(benzoyloxy)morpholine (0.0519 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0017 g, 0.0031 mmol) to yield 4-(3-trifluoromethyl-phenyl)-morpholine (0.0416 g, 0.18 mmol, 72%) as a pale yellow oil. Analytical data for the title compound: ^{1}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}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 °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]$_2$·C$_6$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 ≥95 % purity as judged by

34

^{1}H 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 (0.0518 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0016 g, 0.0031 mmol) to yield 4-(4-acetoxyphenyl)-morpholine (0.0408 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; ^{1}**H 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 C$_{12}$H$_{15}$NO$_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.12; H, 6.91; N, 6.15.
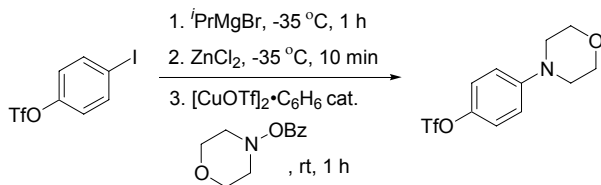
Trifluoromethanesulfonic acid 4-(morpholin-4-yl)-phenyl ester (3ab). The title compound was prepared according to General Procedure **F** using trifluoromethanesulfonic acid 4-iodo-phenyl ester (0.1936 g, 0.55 mmol) 4-(benzoyloxy)morpholine (0.0518 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0016 g, 0.0031 mmol) to yield trifluoromethanesulfonic acid 4-(morpholin-4-yl)-phenyl ester (0.0737 g, 0.24 mmol, 95%) as a clear oil after flash chromatography with 30% ethyl acetate:hexanes. The ^{1}H NMR spectrum was consistent with that reported in the literature.[24]
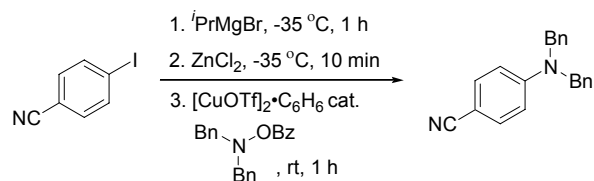
4-Dibenzylamino-benzonitrile (3ag). The title compound was prepared according to General Procedure **F** using 4-iodobenzonitrile (0.1259 g, 0.55 mmol), *O*-benzoyl-*N,N*-dibenzylhydroxylamine (0.0793 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0016 g, 0.0031 mmol) to yield 4-dibenzylamino-benzonitrile (0.0712 g, 0.24 mmol, 96%) as a white solid after flash chromatography with 15% ethyl acetate:hexanes. Analytical data for the title compound: **^{1}H 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.
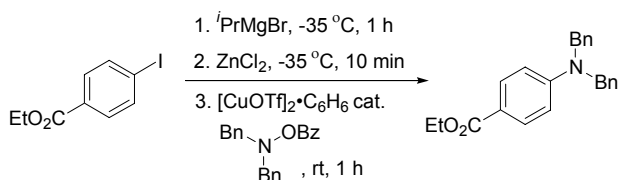
4-Dibenzylamino-benzoic acid ethyl ester (3ah). The title compound was prepared according to General Procedure **F** using 4-iodobenzoic acid ethyl ester (0.1518 g, 0.55 mmol), *O*-benzoyl-*N,N*-dibenzylhydroxylamine (0.0793 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0016 g, 0.0031 mmol) to yield 4-dibenzylamino-benzoic acid ethyl ester (0.0855 g, 0.25 mmol, 100%) as a white solid after flash chromatography with 5% ethyl acetate:hexanes. Analytical data for the title compound: **^{1}H 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.
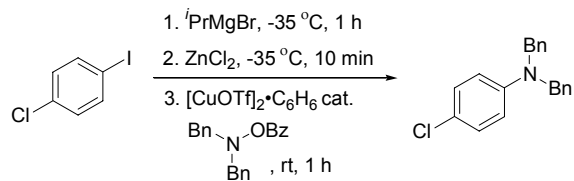
N-(4-Chloro-phenyl)-dibenzylamine (3ai).** The title compound was prepared according to General Procedure **F** using 1-chloro-4-iodo-benzene (0.1312 g, 0.55 mmol), *O*-benzoyl-*N,N*-dibenzylhydroxylamine (0.0792 g, 0.25 mmol), and copper(I)

trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0016 g, 0.0031 mmol) to yield *N*-(4-chloro-phenyl)-dibenzylamine (0.0709 g, 0.23 mmol, 92%) as a white solid after flash chromatography with 1% ethyl acetate:hexanes. The ^{1}H 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 °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 °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 °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]$_2$·C$_6$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 ≥95 % purity as judged by ^{1}H 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 (0.1369 g, 0.55 mmol), 4-(benzoyloxy)morpholine (0.0518 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0016 g, 0.0031 mmol) to yield 4-(2-nitro-phenyl)-morpholine (0.0515 g, 0.25 mmol, 100%)   as a yellow, viscous oil after flash

chromatography with 15% ethyl acetate:hexanes. The ^{1}H 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 (0.1617 g, 0.55 mmol), 4-(benzoyloxy)morpholine (0.0518 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0016 g, 0.0031 mmol) to yield 4-(2,4-dinitro-phenyl)-morpholine (0.0372 g, 0.15 mmol, 59%) as a yellow solid after flash chromatography with 30% ethyl acetate:hexanes. The ^{1}H NMR spectrum was consistent with that reported in the literature.[26]
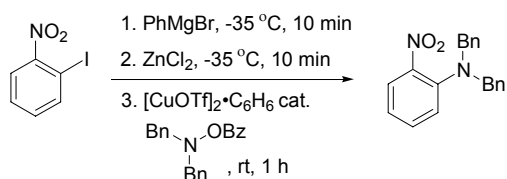
N-(2-nitrophenyl)-dibenzylamine (3ak). The title compound was prepared according to General Procedure **G** using 1-iodo-2-nitrobenzene (0.1369 g, 0.55 mmol), *O*-benzoyl-*N,N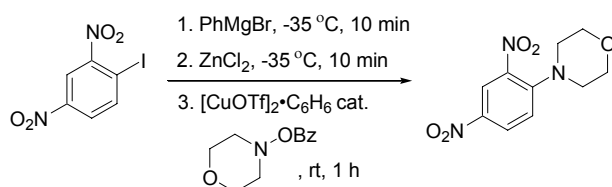*-dibenzylhydroxylamine (0.0792 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0016 g, 0.0031 mmol) to yield *N*-(2-nitro-phenyl)-dibenzylamine (0.0764 g, 0.24 mmol, 96%) as a yellow, viscous oil after flash chromatography with 15% ethyl acetate:hexanes. Analytical data for the title compound: **^{1}H NMR** (400 MHz, CDCl$_3$) 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); **^{13}C NMR** (100 MHz, CDCl$_3$) 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]$_2$·C$_6$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 ≥95 % purity as judged by ^{1}H 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 (0.1594 g, 0.55 mmol), 4-(benzoyloxy)morpholine (0.0518 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0016 g, 0.0031 mmol) to yield 2-(4-morpholin-4-yl-phenyl)-2-methyl-1,3-dioxolane (0.0512 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; **^{1}H NMR** (400 MHz, CDCl$_3$) 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); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 150.8, 134.6, 126.2, 115.1, 108.8, 66.9, 64.4, 49.2, 27.5. **Anal.** Calcd for C$_{14}$H$_{19}$NO$_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.33; H, 7.77; N, 5.61.
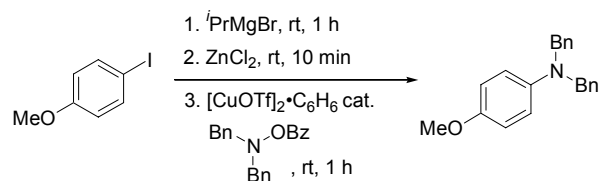
N-(4-Methoxyphenyl)-dibenzylamine (3aj). The title compound was prepared according to General Procedure **H** using 4-iodoanisole (0.1287 g, 0.55 mmol), *O*-benzoyl-*N,N*-dibenzylhydroxylamine (0.0792 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0016 g, 0.0031 mmol) to yield *N*-(4-methoxyphenyl)-dibenzylamine (0.0681 g, 0.22 mmol, 90%) as a white solid after flash chromatography with 5% ethyl acetate:hexanes. The ^{1}H 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]$_2$·C$_6$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), 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 ^{1}H 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 (0.1398 g, 0.55 mmol), 4-(benzoyloxy)morpholine (0.0518 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0016 g, 0.0031 mmol) to yield 4-(naphthalen-1-yl)-morpholine (0.0481 g, 0.23 mmol, 90%) as a white solid. The ^{1}H NMR spectrum was consistent with that reported in the literature.[27]

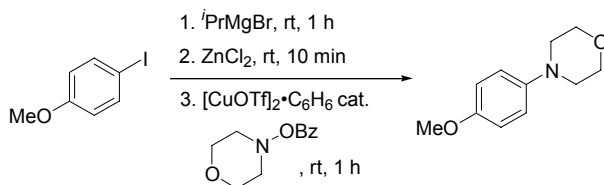**4-(4-Methoxyphenyl)-morpholine (3c).** The title compound was prepared according to General Procedure **I** using 4-iodoanisole (0.1287 g, 0.55 mmol), 4-(benzoyloxy)morpholine (0.0518 g, 0.25 mmol), and copper(I) trifluoromethanesulfonate benzene complex ([CuOTf]$_2$·C$_6$H$_6$, 0.0016 g, 0.0031 mmol) to yield 4-(4-methoxyphenyl)-morpholine (0.0403 g, 0.21 mmol, 83%) as a white solid. The ^{1}H NMR spectrum was consistent with that reported in the literature.[22]

V. 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 is maintained under an inert atmosphere of argon and charged with tetramethylethylene diamine (0.0703 g, 0.61 mmol) and anhydrous tetrahydrofuran (2.5 mL). The solution is 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) is added via syringe along edges of flask. The resulting solution is stirred for 10 min at -78 °C and a tetrahydrofuran solution of the functionalized arene (1.5 mL, 0.55 mmol, 0.4M) is added via syringe

gradually along edges of flask. The solution is stirred at -78 °C for 30 min. A tetrahydrofuran solution of $ZnCl_2$ (1.0 mL, 0.0375 g, 0.28 mmol, 0.3M) is added via syringe along edges of flask and the solution is stirred at -78 °C for 15 min. The cold bath is removed and the solution is allowed to gradually warm to ambient temperature over the course of 15 min prior to use (vida infra). An oven-dried 25-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar is maintained under an inert atmosphere of argon and charged with 4-benzoyloxymorpholine (0.0518 g, 0.25 mmol), copper(II) chloride (0.0008 g, 0.0063 mmol), and anhydrous tetrahydrofuran (2.5 mL). The solution is stirred and the previously generated diarylzinc solution (vida supra) is added via cannula in one portion. The resulting solution is stirred at ambient temperature for the indicated reaction time. Diethyl ether (10 mL) is added and the reaction mixture is transferred to a 125-mL separatory funnel. The reaction mixture is 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 is purified by flash column chromatography, eluting with the indicated solvent system, to afford desired product of $\geq$ 95 % purity as judged by ^{1}H NMR spectroscopy.
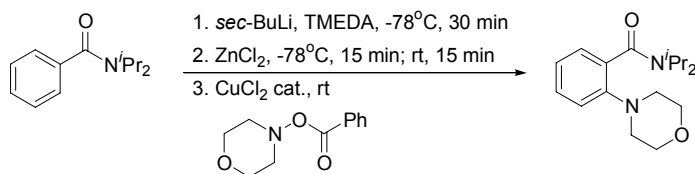
2-Morpholino-*N,N*-Diisopropylbenzamide (3al). The title compound was prepared according to general procedure **J** using *N,N*-diisopropylbenzamide (0.1128 g, 0.55 mmol) with stirring for 1 h to yield 2-morpholino-*N,N*-diisopropylbenzamide (0.0639 g, 0.22 mmol, 88 %) as a clear, pale yellow oil following 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, 1226, 1119, 1035, 936, 850, 766; **^{1}H 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, 4 H), 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.
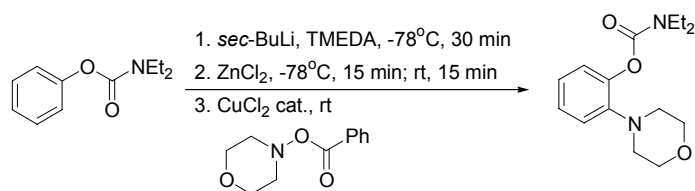
N,N-Diethylcarbamic acid 2-Morpholinophenyl ester (3ao). The title compound was prepared according to general procedure **J** using *N,N*-diethylcarbamic acid phenyl ester (0.1067 g, 0.55 mmol) with stirring for 12 h to yield *N,N*-diethylcarbamic acid 2-morpholinophenyl ester (0.0435 g, 0.16 mmol, 62 %) 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, 1379, 1272, 1236, 1193, 1153, 1118, 940, 754; **^{1}H 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, 4 H), 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.
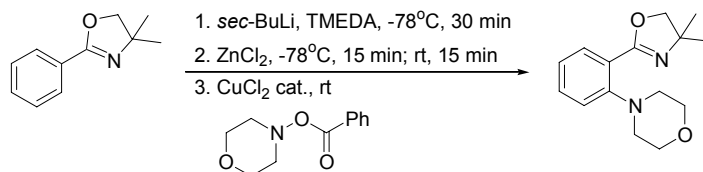
2-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-1-Morpholinobenzene (3am). The title compound was prepared according to general procedure **J** using 4,4-dimethyl-2-phenyl-4,5-dihydro-oxazole (0.0963 g, 0.55 mmol) with stirring for 4 h to yield 2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-1-morpholinobenzene (0.0358 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: Analytical data for the title compound: **IR** (thin film, cm^{-1}) 2964, 2927, 2893, 2858, 2818, 2361, 1723, 1646, 1598, 1492, 1448, 1374, 1309, 1228, 1116, 1068, 1037, 935, 765, 698; **^{1}H 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$_3$) δ163.0, 151.4, 131.7, 131.6, 121.8, 121.7, 118.1, 78.9, 67.4, 67.1, 52.3, 28.3.
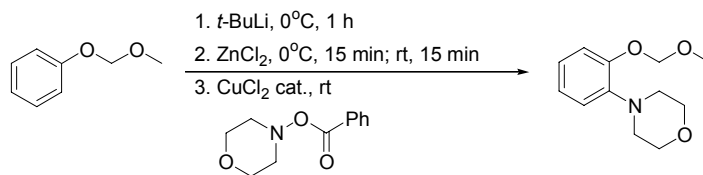
1-Methoxymethyloxy-2-Morpholinobenzene (3an). An oven-dried 25-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar is maintained under an inert atmosphere of argon and charged with methoxymethyl phenyl ether (0.0759 g, 0.55 mmol) and anhydrous diethyl ether (2.0 mL). The solution is stirred and cooled in an ice bath and a pentane solution of *t*-BuLi (0.40 mL, 0.61 mmol, 1.5 M) is added via syringe along edges of flask. The resulting solution is stirred for 1 h at 0 °C and a tetrahydrofuran solution of $ZnCl_2$ (1.0 mL, 0.0375 g, 0.28 mmol, 0.3M) is added via syringe along edges of flask and the solution is stirred at 0 °C for 15 min. The cold bath is removed and the solution is allowed to gradually warm to ambient temperature over the course of 15 min prior to use (vida infra). An oven-dried 25-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar is maintained under an inert atmosphere of argon and charged with 4-benzoyloxymorpholine (0.0518 g, 0.25 mmol), copper(II) chloride (0.0008 g, 0.0063 mmol), and anhydrous tetrahydrofuran (2.5 mL). The solution is stirred and the previously generated diarylzinc solution (vida supra) is added via cannula in one portion. The resulting solution is stirred at ambient temperature for 6 h. Diethyl ether (10 mL) is added and the reaction mixture is transferred to a 125-mL separatory funnel. The reaction mixture is 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 is 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, 1154, 1119, 1078, 995, 926, 856, 752; **^{1}H NMR** (400 MHz, CDCl$_3$) 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); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 150.0, 142.2, 123.1, 122.8, 118.4, 116.6, 95.2, 67.3, 56.3, 51.2.

VI. 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. 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. *Org. 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.

Chapter Two

Nickel-Catalyzed Electrophilic Amination of Organozinc Nucleophiles

2.1 Introduction

The dichotomous behavior of diorganozinc and organozinc halide reagents is common in the application of these compounds in organic synthesis.[1] The divergence is manifested, sometimes dramatically, in different activity of nominally similar compounds. We recently had occasion to note significant disparities in reaction efficiency of RZnX and R_2Zn reagents in the context of copper-catalyzed electrophilic aminations, with the latter providing results far superior to the former (refer to Chapter 1). In this chapter we document our efforts to bridge this gap through the discovery that nickel complexes successfully catalyze the electrophilic amination of organozinc halides (eq 1).

$$R'_2Zn$$
$$CuCl_2 \ (2.5 \ mol \ \%)$$

THF, r.t.

$$R'ZnCl$$
$$Ni(PPh_3)_2Cl \ (2.5 \ mol \ \%)$$

THF, r.t.

(1)
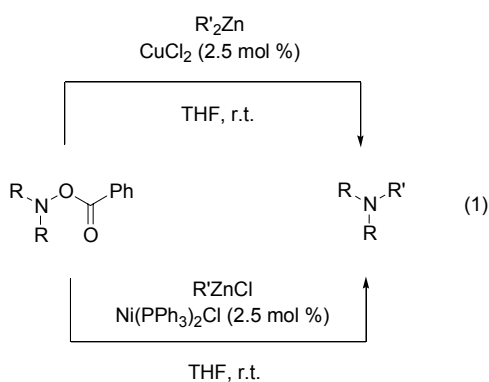
This study was initiated as part of a broader effort to develop new methods for C–N bond formation.[2] As previously discussed, of the modern methods currently available, the Buchwald–Hartwig cross coupling reaction has gained prominence as a general protocol for the preparation of aryl amines, representing the state of the art in metal-catalyzed nucleophilic amination.[3, 4] While typically performed under palladium

catalysis, other transition metals have proven to be competent catalysts as well. Of particular interest are reports by Buchwald and others on nickel-catalyzed nucleophilic amination.[5-7]

Electrophilic amination of nonstabilized carbanions represents an alternative approach to amine synthesis, and is noteworthy for its use of the umpolung strategy for C–N bond construction.[8-10] Early examples have focused on the amination of highly reactive carbon donors (RLi and RMgX), and have generally been hampered by modest yields and/or harsh reaction conditions. Reports by Erdik and Narasaka on the metal-catalyzed amination of nonstabilized carbanions employing O-sulfonyl oximes as $H_2N(+)$ synthons represent an improvement on previous methodology, but have as yet been limited to the preparation of non-functionalized aniline derivatives.[11, 12] Rieke's observation that organozinc halide reagents undergo amination with azodicarboxylates is also germane to the present investigation.[13, 14]

2.2 Results and Discussion

2.2.1 Initial Studies. In the course of our initial screen of potential catalysts and reagents for the union of weak organic nucleophiles with $R_2N(+)$ synthons, nickel arose as a candidate metal for the reaction of RZnX with O-benzoyl hydroxylamines. Efforts to build upon this preliminary finding focused on the identity of the nickel complex. Ni(COD)$_2$ was chosen as a readily available source of Ni(0) and was evaluated for catalytic competence in the presence of a number of neutral ligands (Table 2-1).

Table 2-1. Effect of Ligation on the Nickel-Catalyzed Electrophilic Amination of

Phenylzinc Bromide[a]
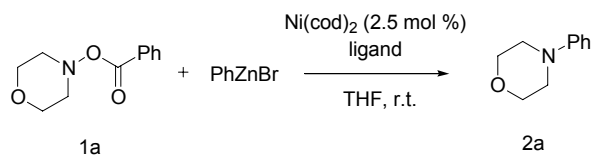
entry	ligand	time (h)	% yield[d]
1	none	24	56
2	1,10-phenanthroline[b]	15	24
3	BINAP[b]	24	56
4	Imes-HCl[c]	0.25	53
5	PCy$_3$[c]	0.25	40
6	P(OPh)$_3$[c]	0.25	65
7	PPh$_3$[c]	0.25	71
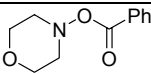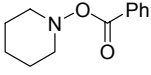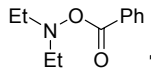
[a] 1.1 equiv of PhZnBr was employed. PhZnBr was prepared from PhMgBr via transmetallation with 1.0 equiv ZnBr$_2$. [b] 2.5 mol % ligand employed. [c] 5.0 mol % ligand employed. [d] Isolated yield of product of purity $\geq$ 95 % based on ^{1}H NMR spectroscopy analysis. Yield is based on the starting R$_2$N-OC(O)Ph.

In the absence of ligand, amination proceeds slowly and only in modest yields

(entry 1). When a chelating diamine (entry 2) or (bis)phosphine (entry 3) is employed,

the reaction rate is once again severely hampered and modest yields obtained. We

observed a dramatic acceleration in rate when monodentate ligands were employed (15

min vs. 15 h), along with a more subtle electronic and/or steric effect on yield (entries 4–

7). When an electron-rich and sterically hindered *N*-heterocyclic carbene or

trialkylphosphine is employed, modest yields of product are obtained (entries 4 and 5).

With the electron-poor and sterically neutral triphenylphosphite, an improvement in yield

is observed (entry 6). Our best results were obtained with the electronically and sterically

neutral triphenylphosphine ligand (entry 7), affording 71% yield of desired product under

unoptimized conditions. The air stable and commercially available Ni(PPh$_3$)$_2$Cl$_2$ complex

was also found to be a competent catalyst for this reaction, and was employed in all

subsequent studies.

2.2.2 Electrophilic Amination of Organozinc Halide Reagents: Preparation of

Tertiary Amines. With a convenient nickel catalyst in hand, we next set out to study the

scope of the reaction. The RZnX reagents employed in this study were generated *in situ*

from the corresponding RMgX via transmetalation with 5.0 equivalents of $ZnCl_2$, and

were used without isolation and/or purification. The *O*-benzoyl hydroxylamines were

prepared as previously described (refer to Chapter 1). As illustrated in Table 2-2, a

variety of aryl fragments undergo amination in good yields (entries 1-3, 6-8, 10, 11).

Alkyl (primary) and benzyl fragments likewise undergo transfer to the $R_2N(+)$ electrophile

in acceptable yields (entries 4, 5, 9). Attempted amination of secondary and tertiary alkyl

RZnCl failed to yield the desired product, instead giving complex reaction mixtures in all

cases. This is in contrast to the aforementioned copper system, in which the amination

of secondary and tertiary alkyl fragments occurs readily (refer to Chapter 1).

Unfortunately, use of RZnX reagents prepared from direct insertion of Zn(0) into the

corresponding R–X electrophile resulted in significantly depressed yields.

Table 2-2. Scope of the Nickel-Catalyzed Electrophilic Amination of Organozinc Halides[a]
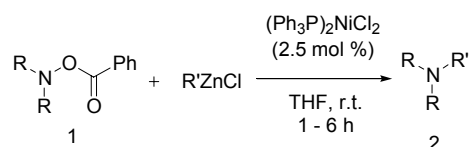
entry	$R_2N-OC(O)Ph$	R'ZnCl (product)	% yield[b]
1	**1a**	Ph (**2a**)	89
2	**1a**	2-MePh (**2b**)	73
3	**1a**	4-MeOPh (**2c**)	89
4	**1a**	Bn (**2d**)	85
5	**1a**	^{n}octyl (**2e**)	58
6	**1b**	Ph (**2f**)	77
7	**1b**	2-MePh(**2g**)	72
8	**1b**	4-MeOPh (**2h**)	92
9	**1b**	Bn (**2i**)	68
10	**1c**	Ph (**2j**)	71
11	**1c**	4-MeOPh (**2k**)	92
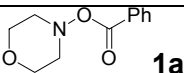
[a] 1.1 equiv of R'ZnCl was employed. R'ZnCl was prepared from the corresponding R'MgX via transmetallation with 5.0 equiv $ZnCl_2$. [b] Isolated yield of product of purity $\geq$ 95 % based on ^1H NMR spectroscopy and GLC analysis (average of at least two experiments). Yield is based on the starting $R_2N-OC(O)Ph$.

2.2.3 Preparation of Functionalized Aryl Amines. The preparation of functionalized tertiary aryl amines was also explored.[15, 16] The requisite functionalized ArZnCl reagents were generated *in situ* from the corresponding aryl iodide (ArI) via I–Mg exchange, transmetalation sequence (5.0 equiv $ZnCl_2$) as previously described (refer to Chapter 1).[17] As illustrated in Table 2-3, nitrile, ester, and halide functionalities are all accommodated employing the nickel catalyst system. In general, amination with functionalized ArZnCl nucleophiles proved to be markedly sluggish, with extended

reaction times and/or incomplete consumption of starting material observed in several

instances.

Table 2-3. Scope of the Nickel-Catalyzed Electrophilic Amination of Functionalized

Arylzinc Halides[a]
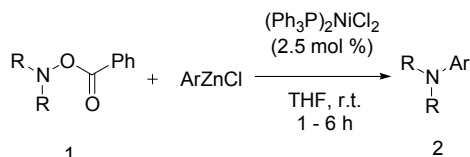
entry	R_2N-OC(O)Ph	ArZnCl (product)	% yield[b]
1	*(structure)* **1a**	*p*-NCPh (**2l**)	56
2	**1a**	*p*-EtO$_2$CPh (**2m**)	59
3	**1a**	*p*-ClPh (**2n**)	84
4	**1a**	*m*-F$_3$CPh (**2o**)	82

[a] 1.1 equiv of ArZnCl were employed. ArZnCl reagents were prepared from the corresponding ArI as follows: 1) ^{i}PrMgBr, -35 °C, 1h 2) ZnCl$_2$ (5.0 equiv), -35 °C, 20 min. [b] Isolated yield of product of $\geq$ 95 % purity as judged by ^{1}H NMR spectroscopy and GLC analysis (average of at least two experiments). Yield is based on the starting R_2N-OC(O)Ph.

2.3 Conclusion

In conclusion, we have developed a nickel-catalyzed electrophilic amination of

organozinc halides that complements our previously reported copper-catalyzed system

for the amination of R_2Zn reagents. As in the copper system, the present protocol is

noteworthy for the mild reaction conditions employed (r.t.) and the ease of product

purification (acid/base extractive work up) to obtain analytically pure material. The RZnCl

reagents employed were prepared via transmetalation from the corresponding RMgX

and used without prior isolation and/or purification. While the nickel system lacks the

generality of the copper system, the present report nonetheless expands upon the

repertoire of experimental conditions that may be employed in such processes and

documents a new metal center that is competent for the catalysis of electrophilic

amination.

2.4 References

(1)   Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React.* **2001,** *58*, 417-731.

(2)   Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003,** *42*, 5400-5449.

(3)   Hartwig, J. F. *Handbook of Organopalladium Chemistry for Organic Synthesis* **2002,** *1*, 1051-1096.

(4)   Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002,** *219*, 131-209.

(5)   Wolfe, J. P.; Buchwald, S. L. *Journal of the American Chemical Society* **1997,** *119*, 6054-6058.

(6)   Tasler, S.; Lipshutz Bruce, H. *J. Org. Chem.* **2003,** *68*, 1190-9.

(7)   Desmarets, C.; Schneider, R.; Fort, Y. *J. Org. Chem.* **2002,** *67*, 3029-3036.

(8)   Erdik, E.; Ay, M. *Chem. Rev.* **1989,** *89*, 1947-80.

(9)   Greck, C.; Genet, J. P. *Synlett* **1997**, 741-748.

(10)   Dembech, P.; Seconi, G.; Ricci, A. *Eur. J. Chem.* **2000,** *6*, 1281-1286.

(11)   Erdik, E.; Daskapan, T. *J. Chem. Soc. Perkin Trans. 1* **1999**, 3139-3142.

(12)   Narasaka, K. *Pure App. Chem.* **2002,** *74*, 143-149.

(13)   Velarde-Ortiz, R.; Guijarro, A.; Rieke, R. D. *Tetrahedron Lett.* **1998,** *39*, 9157-9160.

(14)   This chapter has been previously published: Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799-1801.

(15)   Sapountzis, I.; Knochel, P. *J. Am. Chem. Soc.* **2002,** *124*, 9390-9391.

(16)   Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2004,** *43*, 897-900.

(17)   Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003,** *42*, 4302-4320.
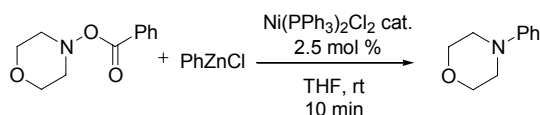
2.5 Supporting Information

I. Materials and Methods

General. Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model Avance 400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) spectrometer with tetramethylsilane or solvent resonance as the internal standard (^{1}H NMR: TMS at 0.00 ppm, CDCl$_3$ at 7.24 ppm; ^{13}C NMR: CDCl$_3$ at 77.0 ppm). ^{1}H 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, 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 atmosphere of 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] Zinc chloride was dried under vacuum (0.1 mmHg) at 150 °C for 12 hours prior to use. 4-Benzoyloxy-morpholine, 1-benzoyloxy-piperidine, and *O*-benzoyl-*N,N*-diethylhydroxylamine were prepared as described previously.[2] 4-Iodobenzonitrile and 4-iodobenzoic acid ethyl ester were prepared from the corresponding aryl bromides according to the method of Buchwald.[3] All other reagents were obtained from commercial sources and used without further purification.

II. Electrophilic Amination of Organozinc Halide Reagents: Preparation of Tertiary Amines

General Procedure (A) for the nickel catalyzed amination of organozinc reagents.
An oven-dried 25-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar is maintained under an inert atmosphere of argon and charged with zinc chloride (0.3748 g, 2.75 mmol), and anhydrous tetrahydrofuran (5.0 mL). The solution is stirred at room temperature and a 1.0 M ethereal solution of the Grignard reagent (0.55 mL, 0.55 mmol) is added via syringe in one portion. The resulting suspension is stirred at room temperature for 15 minutes prior to use (vida infra). An oven-dried 25-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar is maintained under an inert atmosphere of argon and charged with the *O*-acyl hydroxylamine (0.50 mmol), bis(triphenylphosphine)nickel(II) chloride (0.0082 g, 0.0125 mmol), and anhydrous tetrahydrofuran (5.0 mL). The suspension is stirred at room temperature and the previously generated organozinc halide suspension (vida supra) is added via cannula in one portion. The resulting suspension is stirred at room temperature until all *O*-acyl hydroxylamine has been consumed as judged by TLC analysis. Diethyl ether (15 mL) is added and the reaction mixture is transferred to a 125-mL separatory funnel. The reaction mixture is washed with three 10-mL portions of saturated aq. NaHCO$_3$ solution, the aqueous layer is extracted with three 10-mL portions of dichloromethane, and the organic fractions are combined and concentrated by rotary evaporation. The resulting residue is dissolved in diethyl ether (10 mL) and extracted with three 10-mL portions of 10 % aq. HCl solution The aqueous extracts are basified with 40-mL of 10 % aq. NaOH solution, and extracted with three 10-mL portions of dichloromethane. The organic fraction is washed with 15-mL of brine, dried over Na$_2$SO$_4$, and concentrated by rotary evaporation, to afford the desired product of ≥95 % purity as judged by ^{1}H NMR spectroscopy and GLC analysis.

4-Phenylmorpholine (2a). The title compound was prepared according to General Procedure **A** using 4-benzoyloxy-morpholine (0.1035 g, 0.50 mmol) and a 1.0 M tetrahydrofuran solution of phenylmagnesium bromide to yield 0.0708 g (87 %) of 4-phenylmorpholine as a white solid. The ^{1}H NMR spectrum was consistent with that reported in the literature.[4]
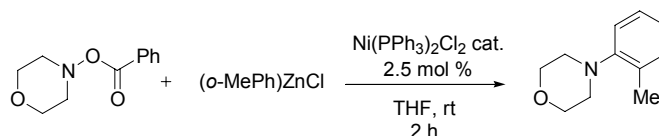
4-(2-Methylphenyl)morpholine (2b). The title compound was prepared according to General Procedure **A** using 4-benzoyloxy-morpholine (0.1035 g, 0.50 mmol) and a 1.0 M tetrahydrofuran solution of 2-methylphenylmagnesium bromide to yield 0.0586 g (66 %) of 4-(2-methylphenyl)morpholine as a clear oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[5]
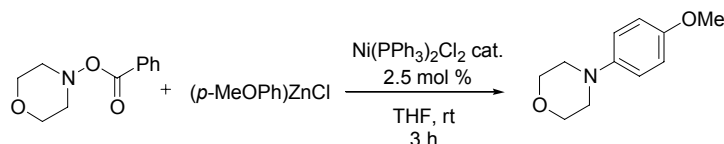
4-(4-Methoxyphenyl)morpholine (2c). The title compound was prepared according to General Procedure **A** using 4-benzoyloxy-morpholine (0.1035 g, 0.50 mmol) and a 1.0 M tetrahydrofuran solution of 4-methoxyphenylmagnesium bromide to yield 0.0847 g (88 %) of 4-(4-methoxyphenyl)morpholine as a white solid. The ^{1}H NMR spectrum was consistent with that reported in the literature.[4]
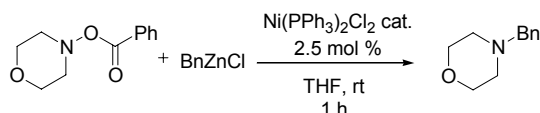

4-Benzylmorpholine (2d). The title compound was prepared according to General Procedure **A** using 4-benzoyloxy-morpholine (0.1035 g, 0.50 mmol) and a 1.0 M diethyl ether solution of benzylmagnesium bromide to yield 0.0799 g (90 %) of 4-benzylmorpholine as a clear oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[6]

1-Phenylpiperidine (2f). The title compound was prepared according to General Procedure **A** using 1-benzoyloxy-piperidine (0.1025 g, 0.50 mmol) and a 1.0 M tetrahydrofuran solution of phenylmagnesium bromide to yield 0.0623 g (77 %) of 1-phenylpiperidine as a pale yellow oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[4]

1-(2-Methylphenyl)piperidine (2g). The title compound was prepared according to

56

General Procedure **A** using 1-benzoyloxy-piperidine (0.1025 g, 0.50 mmol) and a 1.0 M tetrahydrofuran solution of 2-methylphenylmagnesium bromide to yield 0.0630 g (72 %) of 1-(2-methylphenyl)piperidine as a clear oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[7]

Ni(PPh$_3$)$_2$Cl$_2$ cat.
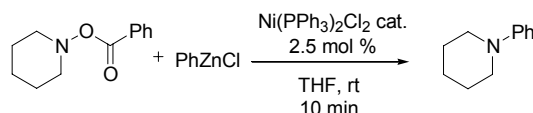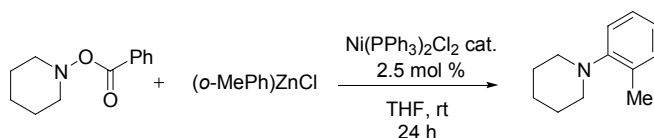2.5 mol %
THF, rt
30 min

+ (*p*-MeOPh)ZnCl

1-(4-Methoxyphenyl)piperidine (2h). The title compound was prepared according to General Procedure **A** using 1-benzoyloxy-piperidine (0.1025 g, 0.50 mmol) and a 1.0 M tetrahydrofuran solution of 4-methoxyphenylmagnesium bromide to yield 0.0875 g (92 %) of 1-(4-methoxyphenyl)piperidine as a pale yellow oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[8]

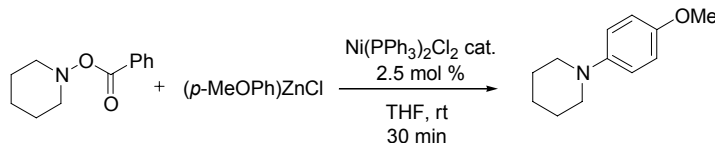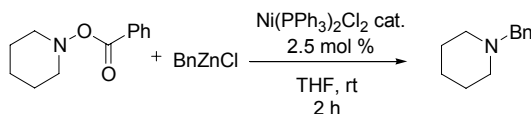Ni(PPh$_3$)$_2$Cl$_2$ cat.
2.5 mol %
THF, rt
2 h

+ BnZnCl

4-Benzylpiperidine (2i). The title compound was prepared according to General Procedure **A** using 1-benzoyloxy-piperidine (0.1025 g, 0.50 mmol) and a 1.0 M diethyl ether solution of benzylmagnesium bromide to yield 0.0642 g (73 %) of 4-benzylpiperidine as a clear oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[9]

Ni(PPh$_3$)$_2$Cl$_2$ cat.
2.5 mol %
THF, rt
10 min

+ PhZnCl
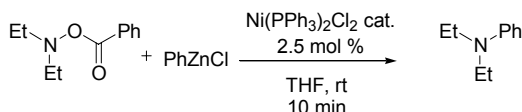
***N,N*-Diethylaniline (2j).** The title compound was prepared according to General Procedure **A** using *N,N*-diethyl-*O*-benzoylhydroxylamine (0.0955 g, 0.50 mmol) and a 1.0 M tetrahydrofuran solution of phenylmagnesium bromide to yield 0.0577 g (77 %) of *N,N*-diethylaniline as a clear oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[10]

Ni(PPh$_3$)$_2$Cl$_2$ cat.
2.5 mol %
THF, rt
1 h

+ (*p*-MeOPh)ZnCl
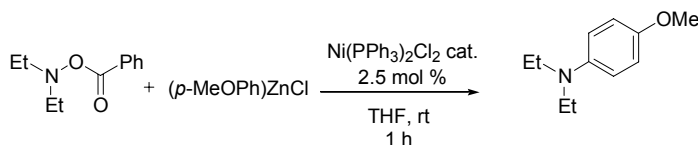
Diethyl-(4-methoxyphenyl)amine (2k). The title compound was prepared according to General Procedure **A** using *N,N*-diethyl-*O*-benzoylhydroxylamine (0.0962 g, 0.50 mmol) and a 1.0 M tetrahydrofuran solution of 4-methoxyphenylmagnesium bromide to yield 0.0784 g (88 %) of diethyl-(4-methoxyphenyl)amine as a pale yellow oil. The ^{1}H NMR spectrum was consistent with that reported in the literature..
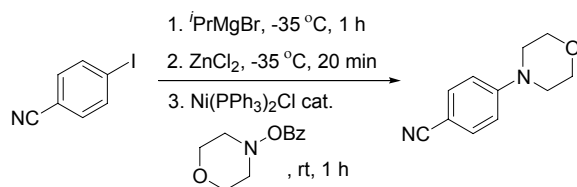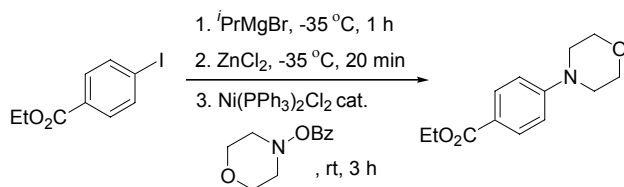
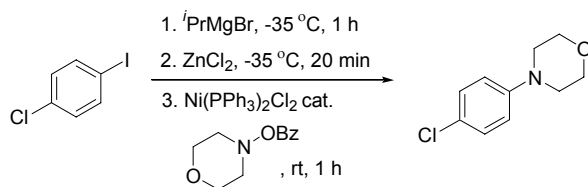## III. Preparation of Functionalized Aryl Amines

General Procedure (B) for the nickel catalyzed amination of functionalized arylzinc halide 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 (5.0 mL, 0.55 M) was slowly added along the edges of the flask and the reaction mixture was stirred at -35 °C for 20 minutes. A second oven-dried round bottom flask equipped with magnetic stir bar was charged with the *O*-acyl hydroxylamine (0.50 mmol), bis(triphenylphosphine)nickel(II) chloride (0.0082 g, 0.0125 mmol), and anhydrous tetrahydrofuran (5.0 mL). The suspension is stirred at room temperature and the previously generated organozinc halide suspension (vida supra) is added via cannula in one portion. The resulting suspension is stirred at room temperature until all *O*-acyl hydroxylamine has been consumed as judged by TLC analysis. Diethyl ether (15 mL) is added and the reaction mixture is transferred to a 125-mL separatory funnel. The reaction mixture is washed with three 10-mL portions of saturated aq. $NaHCO_3$ solution, the aqueous layer is extracted with three 10-mL portions of dichloromethane, and the organic fractions are combined and concentrated by rotary evaporation. The resulting residue is dissolved in diethyl ether (10 mL) and extracted with three 10-mL portions of 10 % aq. HCl solution The aqueous extracts are basified with 40-mL of 10 % aq. NaOH solution, and extracted with three 10-mL portions of dichloromethane. The organic fraction is washed with 15-mL of brine, dried over Na_2SO_4, and concentrated by rotary evaporation, to afford the desired product of ≥95 % purity as judged by ^{1}H NMR spectroscopy and GLC analysis.
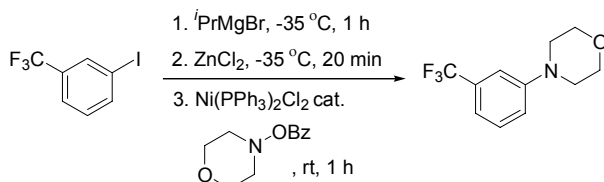

4-(Morpholin-4-yl)-benzonitrile (2l). The title compound was prepared according to General Procedure **B** using 4-iodobenzonitrile (0.1258 g, 0.55 mmol) and 4-benzoyloxy-morpholine (0.1035 g, 0.50 mmol) to yield 4-(morpholin-4-yl)-benzonitrile (0.0527 g, 0.28 mmol, 56%) as a white solid. The ^{1}H NMR spectrum was consistent with that reported in the literature.[11]

1. ^{i}PrMgBr, -35 °C, 1 h
2. ZnCl$_2$, -35 °C, 20 min
3. Ni(PPh$_3$)$_2$Cl$_2$ cat.

EtO$_2$C (4-iodobenzoic acid ethyl ester) + 4-benzoyloxy-morpholine (N-OBz), rt, 3 h → EtO$_2$C-phenyl-morpholine

4-(Morpholin-4-yl)-benzoic acid ethyl ester (2m). The title compound was prepared according to General Procedure **B** using 4-iodobenzoic acid ethyl ester (0.1520 g, 0.55 mmol) and 4-benzoyloxy-morpholine (0.1035 g, 0.50 mmol) to yield 4-(morpholin-4-yl)-benzoic acid ethyl ester (0.0682 g, 0.29 mmol, 59%) as a white solid. The ^{1}H NMR spectrum was consistent with that reported in the literature.[12]

1. ^{i}PrMgBr, -35 °C, 1 h
2. ZnCl$_2$, -35 °C, 20 min
3. Ni(PPh$_3$)$_2$Cl$_2$ cat.

Cl (1-chloro-4-iodo-benzene) + 4-benzoyloxy-morpholine (N-OBz), rt, 1 h → Cl-phenyl-morpholine

4-(4-Chlorophenyl)-morpholine (2n). The title compound was prepared according to General Procedure **B** using 1-chloro-4-iodo-benzene (0.1312 g, 0.55 mmol) and 4-benzoyloxy-morpholine (0.1035 g, 0.50 mmol) to yield 4-(4-chlorophenyl)-morpholine (0.0830 g, 0.42 mmol, 84%) as a white solid. The ^{1}H NMR spectrum was consistent with that reported in the literature.[13]

1. ^{i}PrMgBr, -35 °C, 1 h
2. ZnCl$_2$, -35 °C, 20 min
3. Ni(PPh$_3$)$_2$Cl$_2$ cat.

F$_3$C (1-iodo-3-trifluoromethyl-benzene) + 4-benzoyloxy-morpholine (N-OBz), rt, 1 h → F$_3$C-phenyl-morpholine

4-(3-Trifluoromethyl-phenyl)-morpholine (2o). The title compound was prepared according to General Procedure **B** using 1-iodo-3-trifluoromethyl-benzene (0.1496 g, 0.55 mmol) and 4-benzoyloxy-morpholine (0.1035 g, 0.50 mmol) to yield 4-(3-trifluoromethyl-phenyl)-morpholine (0.0925 g, 0.40 mmol, 82%) as a pale yellow oil. Analytical data for the title compound: **^{1}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}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

IV. References

(1)   Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001,** *78*, 64.

(2)   Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006,** *71*, 219-224.

(3)   Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002,** *124*, 14844-14845.

(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)   Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* **2001,** *2002*, 523-528.

(7)   Walkup, R. E.; Searles, S., Jr. *Tetrahedron* **1985,** *41*, 101-6.

(8)   Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999,** *55*, 12829-12842.

(9)   Katritzky, A. R.; Fan, W. *J. Org. Chem.* **1990,** *55*, 3205-9.

(10)   Djakovitch, L.; Wagner, M.; Kohler, K. *J. Organomet. Chem.* **1999,** *592*, 225-234.

(11)   Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997,** *119*, 6054-6058.

(12)   Urgaonkar, S.; Xu, J.-H.; Verkade, J. G. *J. Org. Chem.* **2003,** *68*, 8416-8423.

(13)   Pearson, A. J.; Gelormini, A. M. *J. Org. Chem.* **1994,** *59*, 4561-70.

Chapter Three

Electrophilic Amination of *o*-Nitrobenzyl Silanes

3.1 Introduction

Nitrogen-rich compounds are ubiquitous in Nature. Consequently, the development of methodology for their concise preparation continues to be an active area of research.[1, 2] *N*-Alkyl hydrazides represent a particularly important class of nitrogen containing compounds.[3] *N*-Alkyl hydrazides and derivatives thereof are readily converted to many important classes of heterocycles, including pyrazoles, pyrazolones, and 1,2,4-triazoles.[4] They have likewise found utility as precursors to azatides, an important class of peptidomimetic compounds used as surrogate peptides.[5]

Classic approaches to *N*-substituted hydrazines have exploited the innate nucleophilicity of the parent hydrazine.[3] Seminal contributions by Ragnarsson and others on the *N*-alkylation of orthogonally protected hydrazines[6, 7] and hydrazones[8] are particularly noteworthy. Catalytic nucleophilic amination protocols developed by Buchwald[9-11] and others[12, 13] have expanded the scope of this manifold to include *N*-aryl and *N*-vinyl substituted hydrazine derivatives. Electrophilic amination protocols represent an alternative strategy, and have been explored extensively. Hydrazination of nonstabilized carbanions (ArLi,[14, 15] ArMgX,[14] ArZnX[16]) and electron-rich arenes[17-19] with azodicarboxylates is established methodology for the preparation of *N*-aryl hydrazides.[20, 21] Catalytic enantioselective electrophilic hydrazination of enolates[22, 23] and enamines[24, 25] with azodicarboxylates provides rapid access to enantioenriched *N*-alkyl hydrazides. These adducts can be further elaborated in few steps, providing access to a variety of

optically acitve α-amino carbonyl and α-amino alcohol derivatives.[26] Very recently, Carreira has described a metal catalyzed hydrohydrazination of olefins with azodicarboxylates and phenylsilane as hydride source, providing a general method for the preparation of highly substituted *N*-alkyl hydrazides.[27, 28]

Activated benzyl silanes have found broad utility as latent benzyl anions, with application in C−C bond forming reactions.[29-32] The use of benzyl silanes in analogous C−N bond forming reactions has been far less successful.[33, 34] An early study on the nitration of 1-(trimethylsilylmethyl)-4-naphthalene is telling: nitration of the benzyl C−Si bond proceeds in modest yields with competitive nitration of the arene ring predominating.[35] Despite its current state of underdevelopment, such methodology would provide access to valuable aminated benzyl fragments.

Much more successful have been studies focused on the electrophilic amination of allyl silanes with aryl diazonium salts and nitrenes (generated *in situ* from the Lewis acid catalyzed decomposition of PhI=NTs or the base promoted decomposition of NsONHCO$_2$Et).[36-38] Examples from Panek on the electrophilic amination of allyl silanes with nitronium and nitrosium salts represent the state of the art in C−Si bond amination.[39-42] The reaction proceeds with chirality transfer via an *anti*-S$_E$' addition process, providing access to enantioenriched allyl amine precursors in high yields starting from the enantiopure allysilanes. While these examples of the electrophilic amination of allyl silanes are encouraging, little work to date has focused on the conceptually similar electrophilic amination of benzyl silanes (vida supra). It was our intention to bridge this technology gap in the development of new methodology for the concise electrophilic amination of benzyl silanes (eq 1).
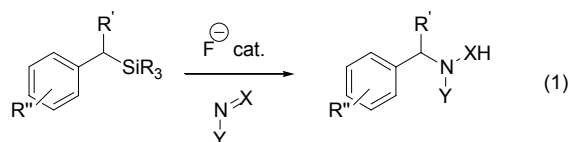
3.2 Results and Discussion

3.2.1 Initial Studies. We initially focused on identifying a suitable benzylsilane framework and electrophilic nitrogen source to promote the desired benzylic amination. Initial results with unsubstituted benzyl silanes proved discouraging. Activation with either catalytic tetrabutylammonium fluoride (TBAF) or tetrabutylammonium triphenyldifluorosilicate (TBAT) under forcing conditions (refluxing THF, 24 h) resulted in the isolation of only modest quantities of the expected *N*-benzylhydrazides when azodicarboxylates were employed as electrophilic nitrogen source. Similar results were obtained with iminomalonate, an electrophilic aminating reagent that has recently found utility in the amination of non-stabilized carbanions (eq 2).[43]
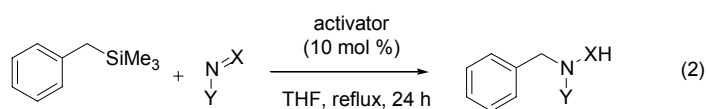
YN=X	activator	yield
i-PrO$_2$C–N=N–CO$_2$$i$-Pr	TBAF	6
	TBAT	11
PMP–N=C(CO$_2$Et)(CO$_2$Et)	TBAF	trace
	TBAT	trace

We next turned our attention to 2-(trimethylsilylmethyl)benzamides, substrates that have proven effective benzyl anion equivalents in analogous C–C bond forming reactions. Employing azodicarboxylates as electrophilic nitrogen source, activation with stoichiometric TBAF resulted in the isolation of desired product in 63% yield. Switching to TBAT as stoichiometric activator, only trace quantities of the expected adduct were observed. The opposite trend was noted with iminomalonate. In this case 51% yield of desired product was obtained with stoichiometric TBAT as activator (9% yield with stoichiometric TBAF) (eq 3).

i-Pr$_2$N–C(=O) ... SiMe$_3$ + YN=X → (activator, 1.0 equiv.; THF, r.t., 24 h) → i-Pr$_2$N–C(=O) ... N(Y)–XH   (3)
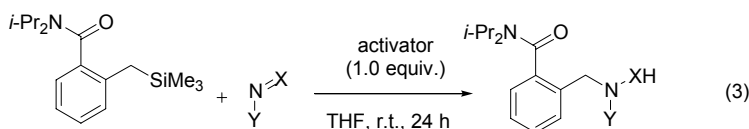
YN=X	activator	yield
BOC–N=N–BOC	TBAF	63
	TBAT	trace
PMP–N=C(CO$_2$Et)(CO$_2$Et)	TBAF	9
	TBAT	51

Apart from such divergent results, the reactions with 2-(trimethylsilymethyl)-benzamide proved difficult to reproduce. In general, the reactions were quite sluggish, in many instances resulting in incomplete consumption and/or decomposition of starting material after 24 h. Use of catalytic activator (TBAF or TBAT) provided inferior results in all cases studied. A solvent screen failed to provide the anticipated boost in yield, and the reactions with 2-(trimethylsilylmethyl)benzamide were abandoned.[44] While these initial results proved encouraging, it became clear that the presence of a suitable electron-withdrawing substituent in the *ortho* position of the requisite benzyl silane would be crucial to the success of this approach.

3.2.2 Preparation of *o*-Nitrobenzyl Silanes. Bartoli has illustrated the utility of *o*-nitrobenzyl silanes as latent benzyl anion equivalents in C–C bond forming reactions.[45] Recently, researchers at Merck have extended this methodology toward the preparation of KDR kinase inhibitors.[46-50] We envisioned such *o*-nitrobenzyl silanes would provide the optimal framework for our proposed benzyl amination protocol. A series of *o*-nitrobenzyl silanes were prepared in acceptable yields starting from the nitroarene according to the method of Bartoli. Sensitive functionalities (e.g. ethyl ester, acetate, iodide) can be accommodated when the reaction is run at low temperatures. The *o*-

nitrobenzyl silanes show good stability properties; they can be stored indefinitely at sub-ambient temperatures without noticeable loss of reactivity (Table 3-1).

***Table 3-1.*** Preparation of *o*-Nitrobenzyl Silanes[a]
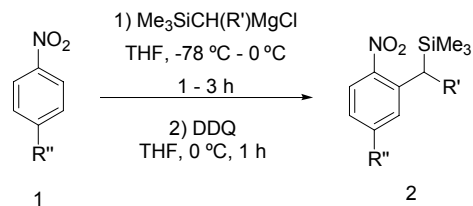
entry	nitroarene	Me$_3$SiCH(R')MgCl (product)	% yield[b]
1	(NO$_2$, OMe) **1a**	Me$_3$SiCH$_2$MgCl (**2a**)	49
2	**1a**	Me$_3$SiCH(CH$_3$)MgCl (**2b**)	52
3	**1a**	Me$_3$SiCH(Cy)MgCl (**2c**)	28
4	(NO$_2$, Cl) **1b**	Me$_3$SiCH$_2$MgCl (**2d**)	62
5	**1b**	Me$_3$SiCH(CH$_3$)MgCl (**2e**)	40
6	(NO$_2$, I) **1c**	(**2f**)	58
7	(NO$_2$, OAc) **1d**	(**2g**)	40
8	(NO$_2$, OTMS) **1e**	(**2h**)	39
9	(NO$_2$, CO$_2$Et) **1f**	(**2i**)	40

[a] 1.1 equiv of Me$_3$SiCH(R')MgCl were employed. 1.2 equiv of DDQ were employed. [b] Isolated yield of product of purity $\geq$ 95 % based on ^{1}H NMR spectroscopy and HRMS analysis (average of at least two experiments). Yield is based on the starting nitroarene.

While Bartoli's method provides rapid access to a wide variety of *o*-nitrobenzyl silanes from cheap nitroarene starting materials, this methodology is limited in several key aspects: 1) The presence of a "blocking" group in the *para*-position of the starting nitroarene is mandatory to provide regiocontrol in the Grignard addition; 2) the requisite starting materials for the Grignard reagent (i.e. α-trimethylsilylalkylhalides) are not commercially available in all but a few cases, and are difficult to access from known methodology.[51-53]

We envisioned an alternate route to *o*-nitrobenzyl silanes that would avoid the limitations inherent in Bartoli's approach. Hydrogenation of vinyl silanes would provide easy access to the desired *o*-nitrobenzyl silanes under exceptionally mild conditions.[54] The requisite vinyl silanes are in turn accessible via the highly regioselective hydrosilylation of *ortho*-substituted internal aryl alkynes as developed by Alami (Scheme 3-1).[55]

***Scheme 3-1.*** Strategy for the Preparation of *o*-Nitrobenzyl Silanes
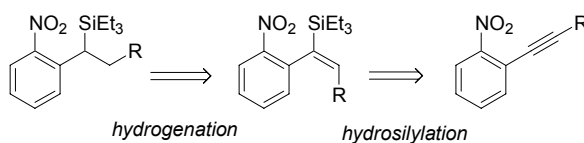
Starting from the aryl alkynes **4a** and **4b** (Scheme 3-2), readily accessible via the Sonogashira cross-coupling reaction, hydrosilylation proceeded in high yields to afford the desired vinyl silanes **5a** and **5b** as single regioisomers (not shown). Attempts at hydrogenation of **5a** and **5b** directly under various conditions failed to afford the expected products; in all cases only recovered starting material was obtained.[56] After additional experimentation it was discovered that reduction of the nitro functionality to the free amine was necessary to facilitate clean hydrogenation to the saturated benzyl silanes. Hydrogenative reduction of the nitro function with catalytic Pt/C afforded the expected anilines **6a** and **6b** in high yields. Using Crabtree's catalyst, hydrogenation of the vinyl silane now proceeded under mild conditions to afford high yields of the

saturated benzyl silanes **7a** and **7b** (not shown). Finally, oxidation with *m*-

chloroperbenzoic acid[57] afforded the desired *o*-nitrobenzyl silanes **2j** and **2k** in four

overall steps from readily available starting materials. This method represents a

complementary strategy for the preparation of *o*-nitrobenzyl silanes, providing access to

substrates otherwise inaccessible using Bartoli's method.

Scheme 3-2. Conditions for the Preparation of *o*-Nitrobenzyl Silanes **2j** and **2k**
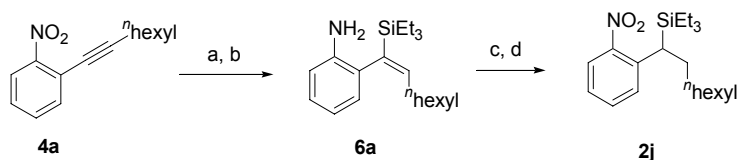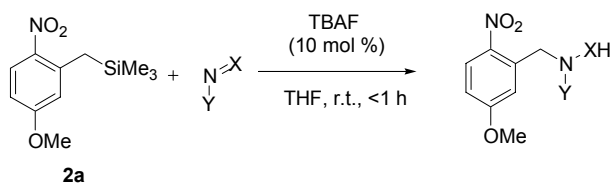

Conditions: a) Et_3SiH, PtO_2, 60 ºC, 5 h (87%); b) H_2 (25 bar), Pt/C, MeOH, r.t., 24 h
(77%); c) H_2 (25 bar), $[Ir(PCy_3)(py)(cod)]PF_6$, CH_2Cl_2, r.t., 24 h (72%); d) *m*CPBA,
$ClCH_2CH_2Cl$, 83 ºC, 2 h (74%).
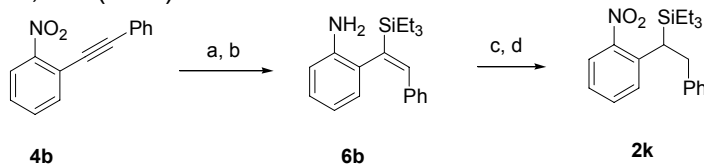
Conditions: a) Et_3SiH, PtO_2, 60 ºC, 2 h (92%); b) H_2 (25 bar), Pt/C, MeOH, r.t., 24 h
(71%); c) H_2 (25 bar), $[Ir(PCy_3)(py)(cod)]PF_6$, CH_2Cl_2, r.t., 24 h (98%); d) *m*CPBA,
$ClCH_2CH_2Cl$, 83 ºC, 2 h (53%).

3.2.3 Electrophilic Amination of *o*-Nitrobenzyl Silanes: Preparation of *N*-Benzyl

Hydrazides. With access to the requisite *o*-nitrobenzyl silanes, we next evaluated their

potential utility as latent benzyl anion equivalents in the proposed electrophilic amination

protocol. A series of electrophilic aminating reagents were evaluated with *o*-nitrobenzyl

silane **2a** and catalytic TBAF as activator (Table 3-2). Amination proceeded rapidly

under exceptionally mild conditions (r.t., <1 h) for a series of azo (entries 1, 3, 4) and

imino (entry 2) derived electrophilic aminating reagents. The reaction did not work for

representative sulfonyl azides, nitrosoarenes, nitronium salts, or *O*-acyl hydroxylamines,

resulting only in decomposition in all cases (entries 5-8).

Table 3-2. Conditions Evaluated for the Electrophilic Amination of *o*-Nitrobenzyl Silanes[a]
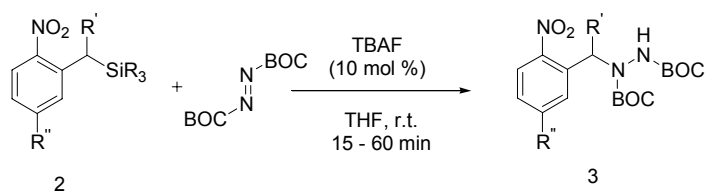
NO$_2$ / SiMe$_3$ / OMe **2a** + Y–N=X → TBAF (10 mol %) / THF, r.t., <1 h → NO$_2$ / N–XH / Y / OMe

entry	YN=X	% yield[b]
1	Ph–N=N–Ts	55
2	PMP–N=C(CO$_2$Et)(CO$_2$Et)	67
3	BOC–N=N–BOC	68
4	*i*-PrO$_2$C–N=N–CO$_2$*i*-Pr	95
5	2,4,6-tri-*i*-Pr-C$_6$H$_2$–SO$_2$N$_3$	0
6	Ph–NO	0
7	NO$_2$BF$_4$	0
8	morpholine-N–O–C(=O)–Ph	0
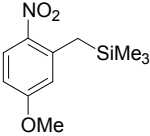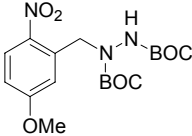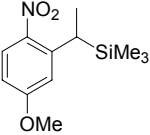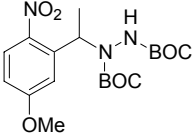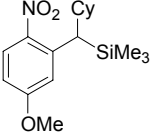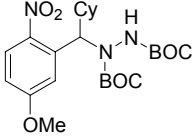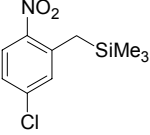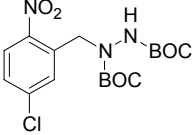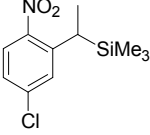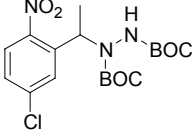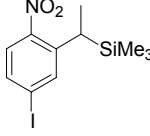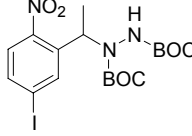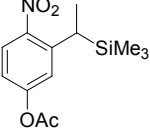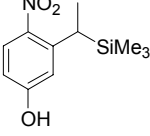
[a] 1.1 equiv of the YN=X were employed. [b] Isolated yield of product of purity ≥ 95 % based on ^{1}H NMR spectroscopy analysis (average of at least two experiments). Yield is based on the starting *o*-nitrobenzylsilane.
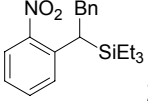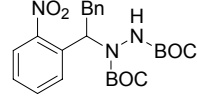
With azodicarboxylates proving the most effective electrophilic nitrogen reagents evaluated (entries 3, 4), and being immediate precursors to important *N*-benzyl hydrazide adducts (vida supra), we next set out to evaluate the scope of this novel benzyl amination with a series of diverse *o*-nitrobenzyl silanes. All reactions were performed on a 1.0 mmol scale of the limiting reagent (*o*-nitrobenzyl silane) using catalytic TBAF (10 mol %) as activator and di-*tert*-butyl azodicarboxylate (1.1 equiv.) as the electrophilic nitrogen source. The reactions proceed under mild conditions (r.t., <1 h) to afford the desired *N*-benzyl hydrazide products in good to excellent yields after

purification by column chromatography (Table 3-3). The reaction scope is quite broad, with a wide variety of functionality tolerated (methyl ether, chloride, iodide, ethyl ester) on the arene ring. The reaction did not work when acetate or hydroxy functionalities were present, presumably due to competitive acylation or protonation respectively of the putative hydrazido intermediate in these cases (entries 7, 8). The identity of the α-alkyl side-chain can be varied without deleterious effect. Methyl, cyclohexyl, *n*-heptyl, and benzyl side-chains are all readily accommodated in the reaction, illustrating the steric tolerance of the current protocol (entries 2, 3, 10, 11).

Table 3-3. Scope of the Hydrazination of o-Nitrobenzyl Silanes[a]

Reaction scheme:

NO$_2$, R' substituted aryl with SiR$_3$ (**2**) + BOC–N=N–BOC (di-BOC azodicarboxylate) →[TBAF (10 mol %), THF, r.t., 15 - 60 min] product **3** (NO$_2$, R', N(BOC)–NH–BOC, R")

entry	o-nitrobenzyl silane	product	% yield[b]
1	**2a** (NO$_2$, CH$_2$SiMe$_3$, OMe)	**3a** (NO$_2$, CH$_2$–N(BOC)–NH–BOC, OMe)	78
2	**2b** (NO$_2$, CH(CH$_3$)SiMe$_3$, OMe)	**3b** (NO$_2$, CH(CH$_3$)–N(BOC)–NH–BOC, OMe)	95
3	**2c** (NO$_2$, CH(Cy)SiMe$_3$, OMe)	**3c** (NO$_2$, CH(Cy)–N(BOC)–NH–BOC, OMe)	99
4	**2d** (NO$_2$, CH$_2$SiMe$_3$, Cl)	**3d** (NO$_2$, CH$_2$–N(BOC)–NH–BOC, Cl)	83
5	**2e** (NO$_2$, CH(CH$_3$)SiMe$_3$, Cl)	**3e** (NO$_2$, CH(CH$_3$)–N(BOC)–NH–BOC, Cl)	95
6	**2f** (NO$_2$, CH(CH$_3$)SiMe$_3$, I)	**3f** (NO$_2$, CH(CH$_3$)–N(BOC)–NH–BOC, I)	77
7	**2g** (NO$_2$, CH(CH$_3$)SiMe$_3$, OAc)		0
8	**2h** (NO$_2$, CH(CH$_3$)SiMe$_3$, OH)		0

entry	o-nitrobenzyl silane	product	% yield[b]
9	**2i**	**3g**	100
10	**2j**	**3h**	84
11	**2k**	**3i**	88

[a] 1.1 equiv of di-*tert*-butyl azodicarboxylate were employed. [b] Isolated yield of product of purity ≥ 95 % based on ^{1}H NMR spectroscopy and HRMS analysis (average of at least two experiments). Yield is based on the starting *o*-nitrobenzylsilane.
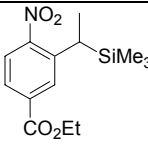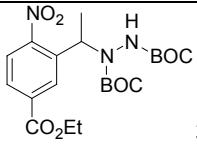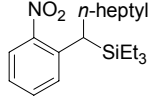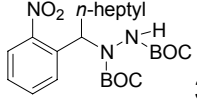
3.3 Conclusion

In conclusion, we have developed a novel method for the hydrazination of *o*-nitrobenzyl silanes with di-*tert*-butyl azodicarboxylate and catalytic TBAF as activator. The reaction provides rapid access to *N*-benzylhydrazides under exceptionally mild conditions (r.t., <1 h). Many of the requisite *o*-nitrobenzyl silanes are prepared from the corresponding nitroarene in one-step using established methodology. A novel route to previously inaccessible *o*-nitrobenzyl silanes has also been developed, which takes advantage of the regioselective hydrosilylation of aryl alkynes, further enhancing the scope of this methodology.

3.4 References

(1)   Erdik, E. *Tetrahedron* **2004,** *60*, 8747-8782.

(2)   Greck, C.; Drouillat, B.; Thomassigny, C. *Eur. J. Org. Chem.* **2004**, 1377-1385.

(3)   Ragnarsson, U. *Chem. Soc. Rev.* **2001,** *30*, 205-213.

(4)   Coispeau, G.; Elguero, J. *Bull. Soc. Chim. Fr.* **1970**, 2717-36.

(5)   Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996,** *118*, 2539-44.

(6)   Maeorg, U.; Grehn, L.; Ragnarsson, U. *Angew. Chem. Int. Ed.* **1996,** *35*, 2626-2627.

(7)   Rasmussen, L. K. *J. Org. Chem.* **2006,** *71*, 3627-3629.

(8)   Meyer, K. G. *Synlett* **2004**, 2355-2356.

(9)   Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001,** *3*, 3803-3805.

(10)   Martin, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006,** *45*, 7079-7082.

(11)   Rivero, M. R.; Buchwald, S. L. *Org. Lett.* **2007,** *9*, 973-976.

(12)   Barluenga, J.; Moriel, P.; Aznar, F.; Valdes, C. *Org. Lett.* **2007,** *9*, 275-278.

(13)   Lim, Y.-K.; Lee, K.-S.; Cho, C.-G. *Org. Lett.* **2003,** *5*, 979-982.

(14)   Demers, J. P.; Klaubert, D. H. *Tetrahedron Lett.* **1987,** *28*, 4933-4.

(15)   Katritzky, A. R.; Wu, J.; Verin, S. V. *Synthesis* **1995**, 651-3.

(16)   Velarde-Ortiz, R.; Guijarro, A.; Rieke, R. D. *Tetrahedron Lett.* **1998,** *39*, 9157-9160.

(17)   Leblanc, Y.; Boudreault, N. *J. Org. Chem.* **1995,** *60*, 4268-71.

(18)   Boudreault, N.; Leblanc, Y. *Org. Synth.* **1997,** *74*, 241-247.

(19)   Yadav, J. S.; Reddy, B. V. S.; Veerendhar, G.; Rao, R. S.; Nagaiah, K. *Chem. Lett.* **2002**, 318-319.

(20)   Tsubrik, O.; Kisseljova, K.; Maeorg, U. *Synlett* **2006**, 2391-2394.

(21)   Uemura, T.; Chatani, N. *J. Org. Chem.* **2005,** *70*, 8631-8634.

(22)   Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997,** *119*, 6452-6453.

(23)   Liu, X.; Li, H.; Deng, L. *Org. Lett.* **2005,** *7*, 167-169.

(24)   Juhl, K.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002,** *124*, 2420-2421.

(25)   List, B. *J. Am. Chem. Soc.* **2002,** *124*, 5656-5657.

(26)   Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2002,** *41*, 1790-1793.

(27)   Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006,** *128*, 11693-11712.

(28)   Waser, J.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2004,** *43*, 4099-4102.

(29)   Bennetau, B. *Science of Synthesis* **2002,** *4*, 825-836.

(30)   Thayumanavan, S.; Park, Y. S.; Farid, P.; Beak, P. *Tetrahedron Lett.* **1997,** *38*, 5429-5432.

(31)   Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996,** *61*, 6901-6905.

(32)   Bartoli, G.; Bosco, M.; Caretti, D.; Dalpozzo, R.; Todesco, P. E. *J. Org. Chem.* **1987,** *52*, 4381-4.

(33)   Koizumi, T.; Fuchigami, T.; Nonaka, T. *Bull. Chem. Soc. Jpn.* **1989,** *62*, 219-25.

(34)   Suzuki, H.; Murashima, T.; Kozai, I.; Mori, T. *J. Chem. Soc. Pekin Trans. 1* **1993**, 1591-7.

(35)   Lokos, M.; Hegyes, P.; Foldeak, S. *J. Organomet. Chem.* **1984,** *275*, 27-31.

(36)   Mayr, H.; Grimm, K. *J. Org. Chem.* **1992,** *57*, 1057-9.

(37)   Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173-3199.

(38)   Loreto, M. A.; Tardella, P. A.; Tofani, D. *Tetrahedron Lett.* **1995,** *36*, 8295-8.

(39)   Panek, J. S.; Beresis, R. T. *J. Am. Chem. Soc.* **1993,** *115*, 7898-9.

(40)   Beresis, R. T.; Masse, C. E.; Panek, J. S. *J. Org. Chem.* **1995,** *60*, 7714-15.

(41)   Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995,** *95*, 1293-316.

(42)   Masse, C. E.; Knight, B. S.; Stavropoulos, P.; Panek, J. S. *J. Am. Chem. Soc.* **1997,** *119*, 6040-6047.

(43)   Niwa, Y.; Takayama, K.; Shimizu, M. *Tetrahedron Lett.* **2001,** *42*, 5473-5476.

(44)   See supporting information for conditions evaluated.

(45)   Bartoli, G.; Bosco, M.; Dalpozzo, R.; Todesco, P. E. *J. Org. Chem.* **1986,** *51*, 3694-6.

(46)   Kuethe, J. T.; Wong, A.; Qu, C.; Smitrovich, J.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2005,** *70*, 2555-2567.

(47)   Kuethe, J. T.; Wong, A.; Journet, M.; Davies, I. W. *J. Org. Chem.* **2005,** *70*, 3727-3729.

(48)   Wong, A.; Kuethe, J. T.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2004,** *69*, 7761-7764.

(49)   Kuethe, J. T.; Wong, A.; Davies, I. W. *Org. Lett.* **2003,** *5*, 3721-3723.

(50)   Kuethe, J. T.; Wong, A.; Davies, I. W. *Org. Lett.* **2003,** *5*, 3975-3978.

(51)   Barrett, A. G. M.; Hill, J. M.; Wallace, E. M.; Flygare, J. A. *Synlett* **1991**, 764-70.

(52)   Linderman, R. J.; Ghannam, A. *J. Am. Chem. Soc.* **1990,** *112*, 2392-8.

(53)   Linderman, R. J.; Ghannam, A. *J. Org. Chem.* **1988,** *53*, 2878-80.

(54)   Kaellstroem, K.; Munslow, I. J.; Hedberg, C.; Andersson, P. G. *Adv. Synth. Catal.* **2006,** *348*, 2575-2578.

(55)   Hamze, A.; Provot, O.; Alami, M.; Brion, J.-D. *Org. Lett.* **2005,** *7*, 5625-5628.

(56)   See supporting information for conditions evaluated.

(57)   Gilbert, K. E.; Borden, W. T. *J. Org. Chem.* **1979,** *44*, 659-61.

3.5 Supporting Information

I. Materials and Methods

General. Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model Avance 400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) spectrometer with tetramethylsilane or solvent resonance as the internal standard (^{1}H NMR: TMS at 0.00 ppm, CDCl$_3$ at 7.24 ppm; ^{13}C NMR: CDCl$_3$ at 77.0 ppm). ^{1}H 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. Combustion analyses were performed by Atlantic Microlab Inc., Norcross, GA. Mass spectrum analyses were performed by the University of North Carolina Mass Spectrum facility, Chapel Hill, NC. 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 by 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 and dichloromethane were dried by passage through a column of neutral alumina under nitrogen prior to use.[1] Tetrabutylammonium fluoride was purchased from Aldrich as a 1.0 M solution in THF (containing ca. 5 % water) and used without further purification. (E)-Triethyl-(1-(2-nitrophenyl)-1-octenyl)-silane (**5a**) and (E)-Triethyl-(1-(2-nitrophenyl)-2-phenylethenyl)-silane (**5b**) were prepared as previously described.[2] All other reagents were obtained from commercial sources and used without further purification.

II. Preparation of *o*-Nitrobenzyl Silanes

General Procedure (A) for the preparation of *O*-nitrobenzyl silanes. The same general procedure described by Bartoli et. al. was followed.[3] An oven-dried 100-mL, three-necked, round-bottomed flask equipped with a reflux condenser, additional funnel, and Teflon-coated magnetic stirbar is charged with magnesium turnings (0.40 g, 16.5 mmol), iodine (25.0 mg, 0.10 mmol), and tetrahydrofuran (3.0 mL). The addition funnel is charged with the chloroalkyl-trialkyl-silane (5.5 mmol) and tetrahydrofuran (2.0 mL). The contents of the addition funnel are added dropwise to a stirred suspension of the magnesium turnings with concurrent heating to initiate reaction (indicated by a loss of the deep red color of the solution). Dropwise addition is continued at such a rate as to maintain a gentle reflux (total addition time of 20 min). The reaction mixture is heated at reflux for an additional 30 min, cooled to room temperature, and used as is in the next reaction (vida infra). An oven-dried 250-mL, one-necked round-bottomed flask equipped with a Teflon-coated magnetic stirbar is charged with the nitrobenzene (5.0 mmol), tetrahydrofuran (20 mL), and the solution cooled to the specified temperature. The previously generated Grignard solution is added dropwise via cannula (total addition time of 5 min) and the solution is stirred for the indicated time. The reaction mixture is brought to 0 °C and an ethereal solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 1.36 g, 6.0 mmol) in tetrahydrofuran (20 mL) is added dropwise via cannula (total addition time of 20 min). The reaction mixture is stirred at 0 °C for 1 hour. 5 % aq. Acetic acid solution (50 mL) is added and the contents are stirred vigorously for several minutes. The reaction mixture is transferred to a 500-mL separatory funnel and extracted with three 100 mL portions of ethyl acetate. The organic phase is collected and washed with two 100-mL portions of saturated aq. $NaHCO_3$ solution, one 100 mL portion of saturated aq. NaCl, dried over $MgSO_4$, and concentrated by rotary evaporation. The resulting crude product mixture is purified by flash column chromatography, eluting with the indicated solvent system, to afford desired product of $\geq$ 95 % purity as judged by ^{1}H NMR spectroscopy. The product was stored under anhydrous conditions.
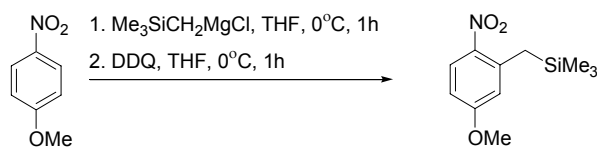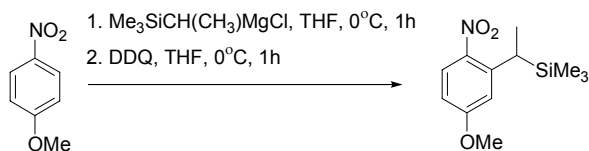

3-(Trimethylsilyl-methyl)-4-nitroanisole (2a). The title compound was prepared according to general procedure **A** using chloromethyl-trimethyl-silane (0.77 mL, 5.5
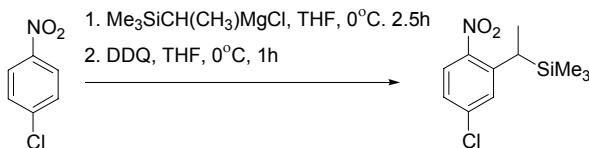
mmol) and 4-nitroanisole (0.77 g, 5.0 mmol) with stirring for 1 h at 0 ºC to yield 3-(trimethylsilylmethyl)-4-nitroanisole (0.58 g, 2.5 mmol, 49 %) as a yellow oil following flash column chromatography with 10 % EtOAc:hexanes. The ^{1}H NMR spectrum was consistent with that reported in the literature.[3]

NO$_2$ / Cl

1. Me$_3$SiCH$_2$MgCl, THF, 0ºC, 2.5h
2. DDQ, THF, 0ºC, 1h

→ NO$_2$ / SiMe$_3$ / Cl
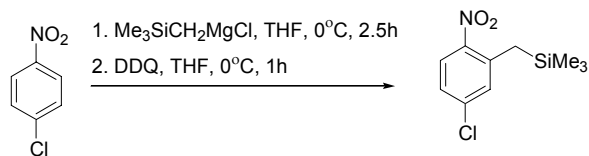
2-(Trimethylsilyl-methyl)-4-chloro-nitrobenzene (2d). The title compound was prepared according to general procedure **A** using chloromethyl-trimethyl-silane (0.77 mL, 5.5 mmol) and 4-chloro-nitrobenzene (0.79 g, 5.0 mmol) with stirring for 2.5 h at 0 ºC to yield 2-(trimethylsilylmethyl)-4-chloro-nitrobenzene (0.76 g, 3.1 mmol, 62 %) as a yellow oil following flash column chromatography with 5 % EtOAc:hexanes. The ^{1}H NMR spectrum was consistent with that reported in the literature.[3]

NO$_2$ / OMe

1. Me$_3$SiCH(CH$_3$)MgCl, THF, 0ºC, 1h
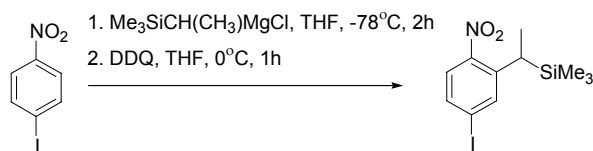2. DDQ, THF, 0ºC, 1h

→ NO$_2$ / SiMe$_3$ / OMe

3-(Trimethylsilyl-1-ethyl)-4-nitroanisole (2b). The title compound was prepared according to general procedure **A** using (1-chloroethyl)-trimethyl-silane (0.76 g, 5.5 mmol) and 4-nitroanisole (0.77 g, 5.0 mmol) with stirring for 1 h at 0 ºC to yield 3-(trimethylsilyl-1-ethyl)-4-nitroanisole (0.66 g, 2.6 mmol, 52 %) as a yellow oil following flash column chromatography with 10 % EtOAc:hexanes. Analytical data for the title compound: **^{1}H NMR** (400 MHz, CDCl$_3$) 7.95 – 7.92 (m, 1H), 6.69 – 6.65 (m, 2H), 3.85 (s, 3H), 3.36 (q, 1H), 1.35 (d, 3H), -0.05 (s, 9H); **Anal.** Calcd for C$_{12}$H$_{19}$NO$_3$Si: C, 56.88; H, 7.56; N, 5.53. Found: C, 56.99; H, 7.54; N, 5.58; **HRMS** (ESI+) Calcd for C$_{12}$H$_{19}$NO$_3$Si+Na: 276.103; Found: 276.103.

NO$_2$ / Cl

1. Me$_3$SiCH(CH$_3$)MgCl, THF, 0ºC. 2.5h
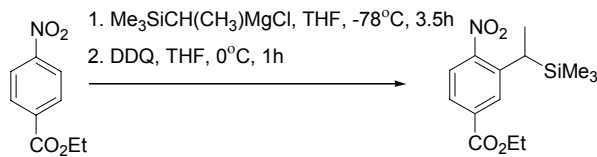2. DDQ, THF, 0ºC, 1h

→ NO$_2$ / SiMe$_3$ / Cl

2-(Trimethylsilyl-1-ethyl)-4-chloro-nitrobenzene (2e). The title compound was prepared according to general procedure **A** using (1-chloroethyl)-trimethyl-silane (0.76 g, 5.5 mmol) and 4-chloro-nitrobenzene (0.79 g, 5.0 mmol) with stirring for 2.5 h at 0 ºC to
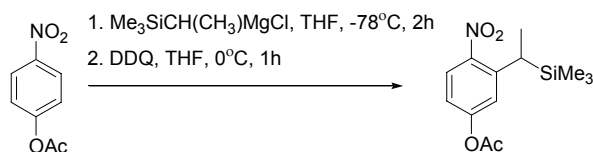
yield 2-(trimethylsilyl-1-ethyl)-4-chloro-nitrobenzene (0.52 g, 2.0 mmol, 40 %) as a yellow oil following flash column chromatography with 5 % EtOAc:hexanes. Analytical data for the title compound: ^{1}**H NMR** (400 MHz, CDCl$_3$) 7.80 – 7.77 (m, 1H), 7.27 – 7.16 (m, 2H), 3.17 (q, 1H), 1.38 (d, 3H), -0.01 (s, 9H); **Anal.** Calcd for C$_{11}$H$_{16}$ClNO$_2$Si: C, 51.25; H, 6.26; N, 5.43. Found: C, 51.29; H, 6.35; N, 5.49; **MS** (ESI+) Calcd for C$_{11}$H$_{16}$ClNO$_2$SiNa: 280.054; Found: 280.1.
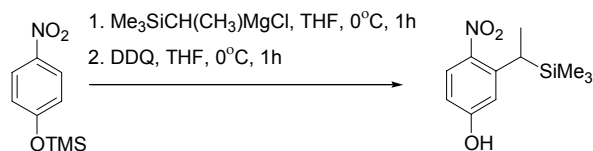

2-(Trimethylsilyl-1-ethyl)-4-iodo-nitrobenzene (2f). The title compound was prepared according to general procedure **A** using (1-chloroethyl)-trimethyl-silane (0.76 g, 5.5 mmol) and 4-iodo-nitrobenzene (1.25 g, 5.0 mmol) with stirring for 2 h at -78 °C to yield 2-(trimethylsilyl-1-ethyl)-4-iodo-nitrobenzene (1.01 g, 2.9 mmol, 58 %) as a yellow oil following flash column chromatography with 10 % EtOAc:hexanes. Analytical data for the title compound: ^{1}**H NMR** (400 MHz, CDCl$_3$) 7.59 – 7.59 (m, 1H), 7.51 – 7.50 (m, 2H), 3.03 (q, 1H), 1.35 (d, 3H), -0.05 (s, 9H); **Anal.** Calcd for C$_{11}$H$_{16}$INO$_2$Si: C, 37.83; H, 4.62; N, 4.01. Found: C, 37.66; H, 4.66; N, 4.15; **MS** (ESI+) Calcd for C$_{11}$H$_{16}$INO$_2$Si+Na: 371.989; Found: 372.0.

Ethyl 3-(trimethylsilyl-1-ethyl)-4-nitrobenzoate (2i). The title compound was prepared according to general procedure **A** using (1-chloroethyl)-trimethyl-silane (0.76 g, 5.5 mmol) and ethyl 4-nitrobenzoate (0.98 g, 5.0 mmol) with stirring for 3.5 h at -78 °C to yield ethyl 3-(trimethylsilyl-1-ethyl)-4-nitrobenzoate (0.59 g, 2.0 mmol, 40 %) as a yellow oil following flash column chromatography with 10 % EtOAc:hexanes. Analytical data for the title compound: ^{1}**H NMR** (400 MHz, CDCl$_3$) 7.95 – 7.94 (m, 1H), 7.84 – 7.81 (m, 1H), 7.75 – 7.73 (m, 1H), 4.39 (q, 2H), 2.94 (q, 1H), 1.40 (m, 6H), -0.04 (s, 9H); **Anal.** Calcd for C$_{14}$H$_{21}$NO$_4$Si: C, 56.92; H, 7.17; N, 4.74. Found: C, 57.02; H, 7.22; N, 4.82; **HRMS** (ESI+) Calcd for C$_{14}$H$_{21}$NO$_4$Si+Na: 318.114; Found: 318.112.

3-(Trimethylsilyl-1-ethyl)-1-acetoxy-4-nitrobenzene (2g). The title compound was prepared according to general procedure **A** using (1-chloroethyl)-trimethyl-silane (0.76 g, 5.5 mmol) and 1-acetoxy-4-nitrobenzene (0.91 g, 5.0 mmol) with stirring for 2 h at -78 °C to yield 3-(trimethylsilyl-1-ethyl)-1-acetoxy-4-nitrobenzene (0.57 g, 2.0 mmol, 40 %) as a yellow oil following flash column chromatography with 10 % EtOAc:hexanes. Analytical data for the title compound: **^{1}H NMR** (400 MHz, CDCl$_3$) 7.87 – 7.84 (m, 1H), 6.97 – 6.92 (m, 2H), 3.19 (q, 1H), 2.31 (s, 3H), 1.36 (d, 3H), -0.05 (s, 9H); **Anal.** Calcd for C$_{14}$H$_{19}$NO$_4$Si: C, 55.49; H, 6.81; N, 4.98. Found: C, 55.35; H, 6.84; N, 5.06; **HRMS** (ESI+) Calcd for C$_{13}$H$_{19}$NO$_4$Si+Na: 304.098; Found: 304.097.


3-(Trimethylsilyl-1-ethyl)-4-nitrophenol (2h). The title compound was prepared according to general procedure **A** using (1-chloroethyl)-trimethyl-silane (0.76 g, 5.5 mmol) and 4-nitrophenoxytrimethylsilane (1.06 g, 5.0 mmol) with stirring for 2 h at -78 °C to yield 3-(trimethylsilyl-1-ethyl)-4-nitrophenol (0.47 g, 2.0 mmol, 40 %) as a yellow oil following flash column chromatography with 20 % EtOAc:hexanes. Analytical data for the title compound: **^{1}H NMR** (400 MHz, CDCl$_3$) 7.90 – 7.88 (m, 1H), 6.67 – 6.59 (m, 2H), 6.0 (br s, 1H), 3.36 (q, 1H), 1.34 (d, 3H), -0.05 (s, 9H); **Anal.** Calcd for C$_{11}$H$_{17}$NO$_3$Si: C, 55.20; H, 7.16; N, 5.85. Found: C, 54.82; H, 7.22; N, 5.75; **HRMS** (ESI+) Calcd for C$_{11}$H$_{17}$NO$_3$Si+Na: 262.088; Found: 262.088.

General Procedure (B) for the preparation of vinyl silanes 6a and 6b. A 100-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar is charged with the vinyl silane (15 mmol), 5% activated platinum on carbon (1.0 g), and methanol (50 mL). The suspension is vigorously stirred at ambient temperature under a hydrogen gas atmosphere (25 bar) in a Paar bomb for 24 hours. Alternatively, the reaction can be performed under ambient hydrogen gas pressure (1 atm). The reaction mixture is filtered through a pad of Celite with concomitant washing of the filter cake with three 25-mL portions of diethyl ether. The filtrate is collected and concentrated by rotary

evaporation. The resulting crude product mixture is purified by flash column chromatography, eluting with the indicated solvent system, to afford desired product of $\geq$ 95 % purity as judged by ^{1}H NMR spectroscopy.
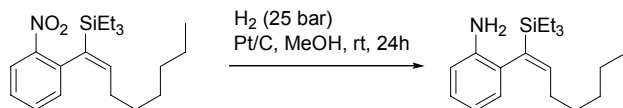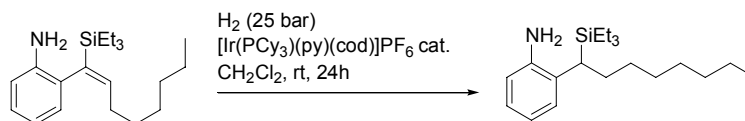

(E)-Triethyl-(1-(2-aminophenyl)-oct-1-enyl)-silane (6a). The title compound was prepared according to general procedure **B** using (E)-triethyl-(1-(2-nitrophenyl)-oct-1-enyl)-silane (5.6 g, 16.3 mmol) with stirring for 24 h to yield (E)-triethyl-(1-(2-aminophenyl)-oct-1-enyl)-silane (4.01 g, 12.6 mmol, 77%) as a clear, colorless oil after flash chromatography with 5% Et$_2$O:hexanes. Analytical data for the title compound: ^{1}**H NMR** (400 MHz, CDCl$_3$) 6.99 – 6.97 (m, 1H), 6.69 – 6.68 (m, 3H), 6.06 (t, 7.0 J, 1H), 3.72 (br s, 2H), 1.91 (q, 7.0 J, 2H), 1.32 – 1.16 (m, 8H), 0.91 – 0.81 (m, 12H), 0.59 – 0.53 (m, 6H).
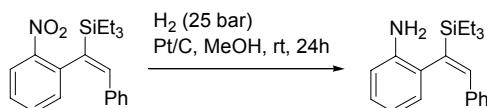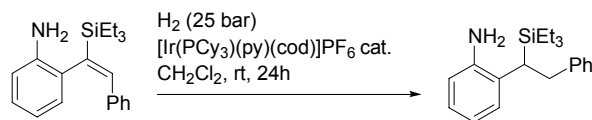

(E)-Triethyl-(1-(2-aminophenyl)-2-phenylvinyl)-silane (6b). The title compound was prepared according to general procedure **B** using (E)-triethyl-(1-(2-nitrophenyl)-2-phenylvinyl)-silane (5.3 g, 15.4 mmol) with stirring for 24 h to yield (E)-triethyl-(1-(2-aminophenyl)-2-phenylvinyl)-silane (3.38 g, 10.9 mmol, 71%) as a yellow oil after flash chromatography with 5% Et$_2$O:hexanes. Analytical data for the title compound: ^{1}**H NMR** (400 MHz, CDCl$_3$) 7.14 – 7.01 (m, 6H), 6.87 – 6.65 (m, 4H), 3.45 (br s, 2H), 0.97 – 0.92 (m, 9H), 0.71 – 0.62 (m, 6H); **Anal.** Calcd for C$_{20}$H$_{27}$NSi: C, 77.61; H, 8.79; N, 4.53. Found: C, 77.56; H, 8.95; N, 4.57; **HRMS** (ESI+) Calcd for C$_{20}$H$_{27}$NSi+H: 310.199; Found: 310.196.

General Procedure (C) for the preparation of *o*-aminobenzyl silanes 7a and 7b. An oven-dried 100-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar is charged with the vinyl silane (15 mmol), Crabtree's catalyst ([Ir(PCy$_3$)(py)(cod)]PF$_6$, 51 mg, 6.3 x 10^{-4} mmol), and dichloromethane (25 mL). The reaction mixture is stirred at ambient temperature under a hydrogen gas atmosphere (25 bar) in a Paar bomb for 24 hours. Alternatively, the reaction can be performed under ambient hydrogen gas pressure (1 atm). The reaction mixture is concentrated by rotary

evaporation. The resulting crude product mixture is purified by flash column chromatography, eluting with the indicated solvent system, to afford desired product of $\geq$ 95 % purity as judged by ^{1}H NMR spectroscopy.
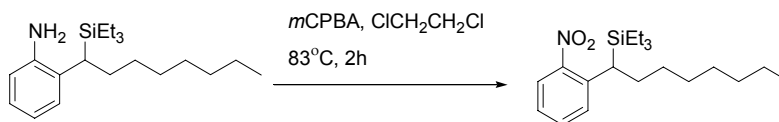

Triethyl-(1-(2-aminophenyl)-1-octyl)-silane (7a). The title compound was prepared according to general procedure **C** using (E)-triethyl-(1-(2-aminophenyl)-oct-1-enyl)-silane (4.01 g, 12.6 mmol) with stirring for 24 h to yield triethyl-(1-(2-aminophenyl)-1-octyl)-silane (2.88 g, 9.0 mmol, 72%) as a golden brown oil after flash chromatography with 10% Et$_2$O:hexanes. Analytical data for the title compound: [1]**H NMR** (400 MHz, CDCl$_3$) δ 6.99 – 6.88 (m, 2H), 6.75 – 6.64 (m, 2H), 2.10 – 2.06 (m, 1H), 3.48 (br s, 2H), 1.74 – 1.72 (m, 2H), 1.25 – 1.17 (m, 12H), 0.94 – 0.81 (m, 12H), 0.58 – 0.50 (m, 6H).
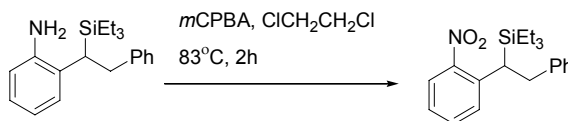

Triethyl-(1-(2-aminophenyl)-2-phenethyl)-silane (7b). The title compound was prepared according to general procedure **C** using (E)-triethyl-(1-(2-aminophenyl)-2-phenylvinyl)-silane (4.77 g, 15.4 mmol) with stirring for 24 h to yield triethyl-(1-(2-aminophenyl)-2-phenethyl)-silane (1.26 g, 4.0 mmol, 26%) as a golden brown oil after flash chromatography with 10% Et$_2$O:hexanes. Analytical data for the title compound: [1]**H NMR** (400 MHz, CDCl$_3$) δ 7.14 – 7.06 (m, 4H), 6.99 – 6.97 (m, 2H), 6.89 – 6.85 (m, 1H), 6.75 – 6.70 (m, 1H), 6.55 – 6.50 (m ,1H), 3.13 – 2.94 (m, 2H), 2.48 – 2.46 (m, 1H), 0.94 – 0.90 (m, 9H), 0.65 – 0.59 (m, 6H); **Anal.** Calcd for C$_{20}$H$_{29}$NSi: C, 77.11; H, 9.38; N, 4.50. Found: C, 76.81; H, 9.33; N, 4.50; **HRMS** (ESI+) Calcd for C$_{20}$H$_{29}$NSi+H: 312.215; Found: 312.211.

General Procedure (D) for the preparation of *o*-nitrobenzyl silanes 2j and 2k. An oven-dried 50-mL, one-necked, round-bottomed flask equipped with a reflux condenser and a Teflon-coated magnetic stirbar is charged with the benzyl silane (1.0 mmol), *m*-chloroperbenzoic acid (*m*CPBA, 0.90 g, 5.2 mmol), and 1,2-dichloroethane (10 mL). The reaction mixture is stirred at 83 ºC for the specified time. The reaction mixture is cooled to ambient temperature, filtered through a pad of Celite with concomitant washing of the

filter cake with three 10-mL portions of 1,2-dichloroethane. The filtrate is transferred to a 125-mL separatory funnel and washed with two 25 mL portions of saturated aq. NaHCO$_3$ solution, one 25 mL portion of saturated aq. NaCl solution, dried over Na$_2$SO$_4$, and concentrated by rotary evaporation. The resulting crude product mixture is purified by flash column chromatography, eluting with the indicated solvent system, to afford desired product of $\geq$ 95 % purity as judged by ^{1}H NMR spectroscopy.


Triethyl-(1-(2-nitrophenyl)-1-octyl)-silane (2j). The title compound was prepared according to general procedure **D** using triethyl-(1-(2-aminophenyl)-1-octyl)-silane (0.32 g, 1.0 mmol) with stirring for 2 h to yield triethyl-(1-(2-nitrophenyl)-1-octyl)-silane (0.26 g, 0.74 mmol, 74%) as a yellow oil after flash chromatography with 5% Et$_2$O:hexanes. Analytical data for the title compound: ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 7.70 – 7.67 (m, 1H), 7.47 – 7.41 (m, 1H), 7.31 – 7.28 (m, 1H), 7.19 – 7.13 (m, 1H), 2.99 – 2.94 (m, 1H), 1.75 – 1.73 (m, 2H), 1.23 – 1.17 (m, 8H), 0.86 – 0.80 (m, 12H), 0.59 – 0.47 (m, 6H); **Anal.** Calcd for C$_{20}$H$_{35}$NO$_2$Si: C, 68.71; H, 10.09; N, 4.01. Found: C, 68.53; H, 10.18; N, 4.10; **HRMS** (ESI+) Calcd for C$_{20}$H$_{35}$NO$_2$Si+Na: 372.233; Found: 372.234.


Triethyl-(1-(2-nitrophenyl)-2-phenethyl)-silane (2k). The title compound was prepared according to general procedure **D** using triethyl-(1-(2-aminophenyl)-2-phenethyl)-silane (0.31 g, 1.0 mmol) with stirring for 2 h to yield triethyl-(1-(2-nitrophenyl)-2-phenethyl)-silane (0.18 g, 0.53 mmol, 53%) as a yellow powder after flash chromatography with 5% Et$_2$O:hexanes. Analytical data for the title compound: ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 7.61 – 7.59 (m, 1H), 7.42 – 7.41 (m, 2H), 7.12 – 6.95 (m, 6H), 3.56 – 3.52 (m, 1H), 3.19 – 2.98 (m, 2H), 0.91 – 0.87 (m, 9H), 0.67 – 0.55 (m, 6H); **Anal.** Calcd for C$_{20}$H$_{27}$NO$_2$Si: C, 70.34; H, 7.97; N, 4.10. Found: C, 70.06; H, 7.97; N, 4.07; **HRMS** (ESI+) Calcd for C$_{20}$H$_{27}$NO$_2$Si+Na: 364.171; Found: 364.172.

III. Electrophilic Amination of *o*-Nitrobenzyl Silanes: Preparation of *o*-Nitrobenzylhydrazides.

General Procedure (E) for the hydrazination of *o*-nitrobenzyl silanes. An oven-dried 10-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar is charged with the benzylsilane (0.50 mmol), di-*tert*-butyl azodicarboxylate (0.1266 g, 0.55 mmol), and tetrahydrofuran (2.0 mL). The solution is stirred at ambient temperature and an ethereal solution of tetrabutylammonium fluoride (TBAF, 50 µL, 0.050 mmol, 1.0 M in tetrahydrofuran) is added via syringe in one portion. The resulting solution is stirred for the indicated time at ambient temperature. The reaction mixture is concentrated by rotary evaporation. The resulting crude product mixture is purified by flash column chromatography, eluting with the indicated solvent system, to afford desired product of $\geq$ 95 % purity as judged by ^{1}H NMR spectroscopy.
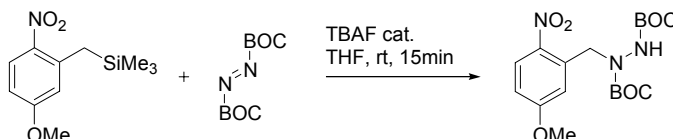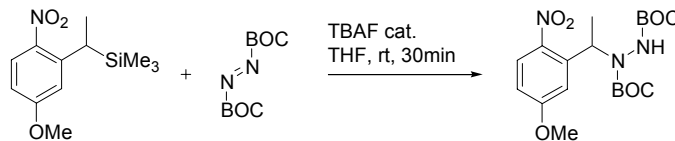

N-[(2-nitro-5-methoxyphenyl)methyl]-*N,N'*-di(*tert*-butoxycarbonyl)hydrazinecarboxylic acid *tert*-butyl ester (3a). The title compound was prepared according to general procedure **E** using 3-(trimethylsilylmethyl)-4-nitroanisole (0.1185 g, 0.50 mmol) with stirring for 15 min to yield *N*-[(2-nitro-5-methoxyphenyl)methyl]-*N,N'*-di(*tert*-butoxycarbonyl)hydrazinecarboxylic acid *tert*-butyl ester (0.1544 g, 0.39 mmol, 78%) as a white powder after flash chromatography with 20% EtOAc:hexanes. Analytical data for the title compound: ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 8.11 – 8.09 (m, 1H), 6.85 – 6.83 (m, 1H), 6.45 – 6.39 (m, 1H), 5.04 (br s, 2H), 3.88 (s, 3H), 1.43 (br s, 18H); **Anal.** Calcd for C$_{18}$H$_{27}$N$_3$O$_7$: C, 54.40; H, 6.85; N, 10.57; Found: C, 54.70; H, 7.02; N, 10.41. **HRMS** (ESI+) Calcd for C$_{18}$H$_{27}$N$_3$O$_7$+Na: 420.175; Found: 420.176.
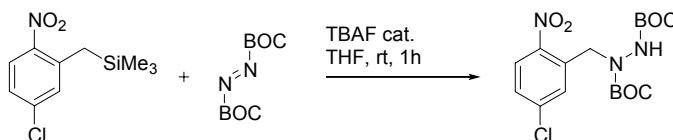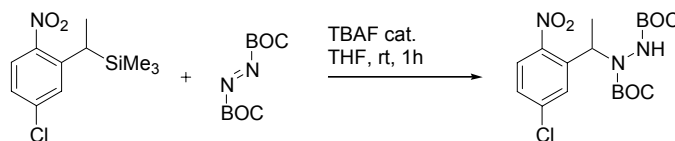

N-[(2-nitro-5-chlorophenyl)methyl]-*N,N'*-di(*tert*-butoxycarbonyl)hydrazinecarboxylic acid *tert*-butyl ester (3d). The title compound was prepared according to general procedure **E** using 2-(trimethylsilylmethyl)-4-chloro-nitrobenzene (0.1219 g, 0.50 mmol) with stirring for 1 h to yield *N*-[(2-nitro-5-chlorophenyl)methyl]-*N,N'*-di(*tert*-butoxycarbonyl)hydrazinecarboxylic acid *tert*-butyl ester (0.1671 g, 0.42 mmol, 84%) as a white powder after flash chromatography with

20% EtOAc:hexanes. Analytical data for the title compound: ^{1}**H NMR** (400 MHz, CDCl$_3$)
δ 7.97 – 7.95 (m, 1H), 7.59 – 7.37 (m, 2H), 6.39 (bs, 1H), 4.99 (br s, 2H), 1.44 (br s,
18H); **Anal.** Calcd for C$_{17}$H$_{24}$ClN$_3$O$_6$: C, 50.81; H, 6.02; N, 10.46. Found: C, 51.26; H,
6.15; N, 10.31. **HRMS** (ESI+) Calcd for C$_{17}$H$_{24}$ClN$_3$O$_6$Na: 424.125; Found: 424.124.

N-[(2-nitro-5-methoxyphenyl)-1-ethyl]-N,N'-di(tert-
butoxycarbonyl)hydrazinecarboxylic acid tert-butyl ester (3b). The title compound
was prepared according to general procedure **E** using 3-(trimethylsilyl-1-ethyl)-4-
nitroanisole (0.1267 g, 0.50 mmol) with stirring for 30 min to yield N-[(2-nitro-5-
methoxyphenyl)-1-ethyl]-N,N'-di(tert-butoxycarbonyl)hydrazinecarboxylic acid tert-butyl
ester (0.1963 g, 0.48 mmol, 96%) as a white powder after flash chromatography with
30% EtOAc:hexanes. Analytical data for the title compound: ^{1}**H NMR** (400 MHz, CDCl$_3$)
δ 7.92 – 7.90 (m, 1H), 6.83 – 6.80 (m, 1H), 6.21 (br s, 1H), 5.79 (br s, 1H), 3.88 (s, 3H),
1.54 – 1.19 (br s, 22H); **Anal.** Calcd for C$_{19}$H$_{29}$N$_3$O$_7$: C, 55.46; H, 7.10; N, 10.21. Found:
C, 55.65; H, 7.03; N, 10.04. **HRMS** (ESI+) Calcd for C$_{19}$H$_{29}$N$_3$O$_7$+Na: 434.190; Found:
434.188.

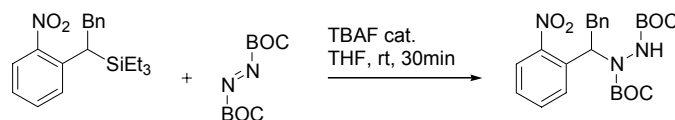**N-[(2-nitro-5-chlorophenyl)-1-ethyl]-N,N'-di(tert-**
butoxycarbonyl)hydrazinecarboxylic acid tert-butyl ester (3e). The title compound
was prepared according to general procedure **E** using 2-(trimethylsilyl-1-ethyl)-4-chloro-
nitrobenzene (0.1289 g, 0.50 mmol) with stirring for 1 h to yield N-[(2-nitro-5-
chloroyphenyl)-1-ethyl]-N,N'-di(tert-butoxycarbonyl)hydrazinecarboxylic acid tert-butyl
ester (0.1976 g, 0.48 mmol, 96%) as a white powder after flash chromatography with
20% EtOAc:hexanes. Analytical data for the title compound: ^{1}**H NMR** (400 MHz, CDCl$_3$)
δ 7.74 – 7.72 (m, 1H), 7.26 – 7.24 (m, 1H), 6.22 (br s, 1H), 5.69 (br s, 1H), 1.60 – 1.32
(m, 21H); **Anal.** Calcd for C$_{18}$H$_{26}$ClN$_3$O$_6$: C, 51.99; H, 6.30; N, 10.10. Found: C, 52.27; H,
6.37; N, 10.00; **HRMS** (ESI+) Calcd for C$_{18}$H$_{26}$ClN$_3$O$_6$Na: 438.141; Found: 438.144.
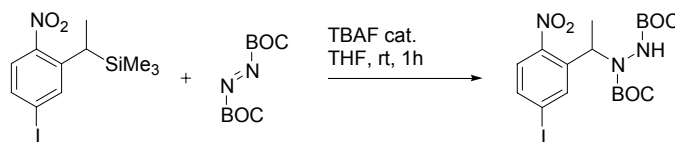
N-[(2-nitro-5-iodophenyl)-1-ethyl]-N,N'-di(*tert*-butoxycarbonyl)hydrazinecarboxylic acid *tert*-butyl ester (3f). The title compound was prepared according to general procedure **E** using 2-(trimethylsilyl-1-ethyl)-4-iodo-nitrobenzene (0.1746 g, 0.50 mmol) with stirring for 1 h to yield N-[(2-nitro-5-iodophenyl)-1-ethyl]-N,N'-di(*tert*-butoxycarbonyl)hydrazinecarboxylic acid *tert*-butyl ester (0.1959 g, 0.39 mmol, 78%) as a white powder after flash chromatography with 10% EtOAc:hexanes. Analytical data for the title compound: **Anal.** Calcd for $C_{18}H_{26}IN_3O_6$: C, 42.61; H, 5.17; N, 8.28. Found: C, 43.12; H, 5.30; N, 8.27; **HRMS** (ESI+) Calcd for $C_{18}H_{26}IN_3O_6$+Na: 530.076; Found: 530.079.
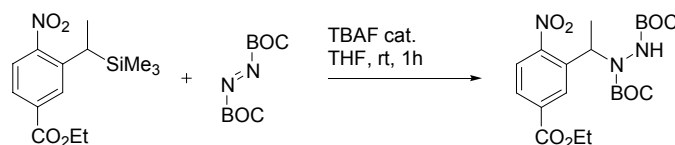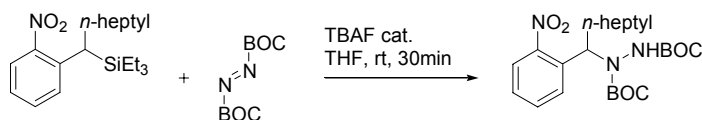
N-[(2-nitro-5-ethoxycarbonylphenyl-carboxylic acid ethyl ester)-1-ethyl]-N,N'-di(*tert*-butoxycarbonyl)hydrazinecarboxylic acid *tert*-butyl ester (3g). The title compound was prepared according to general procedure **E** using ethyl 3-(trimethylsilyl-1-ethyl)-4-nitrobenzoate (0.1477 g, 0.50 mmol) with stirring for 1 h to yield title compound (0.2297 g, 0.50 mmol, 100%) as a white powder after flash chromatography with 20% EtOAc:hexanes. Analytical data for the title compound: **^{1}H NMR** (400 MHz, CDCl₃) δ 8.30 (bs, 1H), 8.03 – 8.00 (m, 1H), 7.76 – 7.31 (m, 1H), 6.20 (bs, 1H), 5.68 (bs, 1H), 4.40 (q, 2H), 1.60 – 0.83 (m, 24H); **Anal.** Calcd for $C_{21}H_{31}N_3O_8$: C, 55.62; H, 6.89; N, 9.27. Found: C, 55.85; H, 7.02; N, 9.19; **HRMS** (ESI+) Calcd for $C_{21}H_{31}N_3O_8$+Na: 476.201; Found: 476.203.

N-[(2-nitrophenyl)-1-benzyl]-N,N'-di(*tert*-butoxycarbonyl)hydrazinecarboxylic acid *tert*-butyl ester (3i). The title compound was prepared according to general procedure **E** using triethyl-(1-(2-nitrophenyl)-2-phenethyl)-silane (0.0854 g, 0.25 mmol), di-*tert*-butyl azodicarboxylate (0.0633 g, 0.28 mmol), tetrahydrofuran (1.0 mL), and tetrabutylammonium fluoride (TBAF, 25 µL, 0.025 mmol, 1.0 M in tetrahydrofuran) with stirring for 30 min to yield title compound (0.1001 g, 0.22 mmol, 88%) as a white powder

after flash chromatography with 20% EtOAc:hexanes. Analytical data for the title compound: **Anal.** Calcd for $C_{24}H_{31}N_3O_6$: C, 63.00; H, 6.83; N, 9.18. Found: C, 63.01; H, 6.93; N, 8.90. **HRMS** (ESI+) Calcd for $C_{24}H_{31}N_3O_6$+Na: 480.211; Found: 480.212.

N-[(2-nitrophenyl)-1-heptyl]-N,N'-di(tert-butoxycarbonyl)hydrazinecarboxylic acid tert-butyl ester (3h). The title compound was prepared according to general procedure **E** using triethyl-(1-(2-nitrophenyl)-1-octyl)-silane (0.0874 g, 0.25 mmol), di-*tert*-butyl azodicarboxylate (0.0633 g, 0.28 mmol), tetrahydrofuran (1.0 mL), and tetrabutylammonium fluoride (TBAF, 25 µL, 0.025 mmol, 1.0 M in tetrahydrofuran) with stirring for 30 min to yield title compound (0.0966 g, 0.21 mmol, 84%) as a clear, colorless oil after flash chromatography with 20% EtOAc:hexanes. Analytical data for the title compound: ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 7.70 – 7.38 (m, 4H), 5.89 – 5.67 (m, 2H), 2.03 – 0.81 (m, 32H); **Anal.** Calcd for $C_{24}H_{39}N_3O_6$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.03; H, 8.50; N, 8.81; **HRMS** (ESI+) Calcd for $C_{24}H_{39}N_3O_6$+Na: 488.274; Found: 488.273.

IV. Additional Experimental Data

Table 3-4. Conditions Screened for the Electrophilic Amination of 2-(Trimethylsilyl-alkyl)benzamides[a]
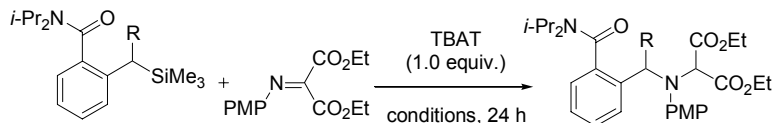
entry	R	conditions	% yield[b]
1	H	DMSO, r.t.	21
2		DMF, r.t.	trace
3		2-MeTHF, r.t.	0
4		Et$_2$O, r.t	0
5		MeCN, r.t.	39
6		CH$_2$Cl$_2$, r.t.	28
7		THF, r.t.	51
8		THF, reflux	44
9	Me	THF, r.t.	0
10		THF, reflux	0

[a] 1.1 equiv of iminomalonate were employed. [b] Isolated yield of product of purity ≥ 95 % based on ^{1}H NMR spectroscopy. Yield is based on the starting (trimethylsilyl-alkyl)benzamide.

Table 3-5. Conditions Screened for the Hydrogenation of Vinyl Silane **5a**
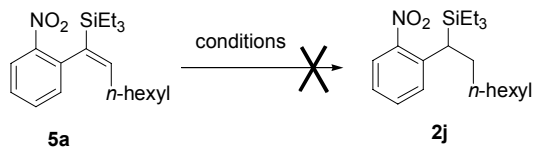
entry	conditions	results
1	 *o*-xylene, reflux, 40 min	recovered starting material
2	 MeOH, r.t., 24 h	
3	 NaOAc, THF/H$_2$O, reflux, 4 h	
4	 NaOAc, THF/H$_2$O, reflux, 4 h	

entry	conditions	results
5	KO_2C N=N CO_2K AcOH, MeOH, r.t. 5 h	recovered starting material
6	KO_2C N=N CO_2K AcOH, MeOH, reflux, 24 h	
7	H_2 (50 bar) $Rh(PPh_3)_3Cl$, THF/t-BuOH, r.t. 24 h	
8	H_2 (50 bar) $[Ir(PCy_3)(py)(cod)]PF_6$, CH_2Cl_2 r.t., 24 h	

V. References

(1)   Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001,** *78*, 64.

(2)   Hamze, A.; Provot, O.; Alami, M.; Brion, J.-D. *Org. Lett.* **2005,** *7*, 5625-5628.

(3)   Bartoli, G.; Bosco, M.; Dalpozzo, R.; Todesco, P. E. *J. Org. Chem.* **1986,** *51*, 3694-6.