

Zincative Functionalization of C–H Bonds Using Lithium Amide Zincate Bases

by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
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ABSTRACT

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Abstract

Carbon–hydrogen bond functionalization is a highly desirable transformation as C–H bonds are plentiful in feedstock chemicals and the direct introduction of valuable functional groups improves atom economy and efficiency. However, the field of direct C–H functionalization still has many challenges including regioselectivity, directing group limitations, and often harsh reaction conditions with toxic and rare transition metal catalysts. Deprotonative zincation has been demonstrated as a useful method to achieve C–H functionalization.

The direct C–H amination of a wide scope of arenes and heteroarenes has been achieved by copper-catalyzed electrophilic amination with *O*-benzoyl hydroxylamines. Key to the expanded scope of substrates is the use of a lithium zincate base, Li[ZnEt₂TMP] which can coordinate to a variety of common functionalities to direct zincation. The mild reaction conditions and compatibility with functional groups such as esters, nitriles and halides make this method orthogonal to many existing strategies.

Additionally, a novel lithium zincate base with inexpensive dicyclohexylamine has been developed and shown to be capable of efficient and regioselective zincation with an extensive scope of directing groups. Aryl and heteroaryl zincates can undergo direct electrophilic silylation and borylation without the need for any transition metal catalyst.

α -Functionalization of substituted amides and esters has been achieved by utilizing a tribasic lithium zincate for direct allylation and copper-catalyzed arylation and vinylation with aryl iodides and vinyl iodides. In summary, lithium zincate bases have been demonstrated to be broadly useful for diverse and regioselective C–H functionalization to introduce valuable complexity from simple starting materials.

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Abbreviations

Ac	acetate
acac	acetylacetonate
Ar	aryl
Bn	benzyl
Bpin	pinacolborane
bpy	2',2'-bipyridyl
Boc	<i>tert</i> -butyloxycarbonyl
Bu	butyl
Bz	benzoyl
Cy	cyclohexyl
dba	Dibenzylideneacetone
DCM	dichloromethane
DMP	2,2-dimethylpiperidinyl
DG	directing group
DMF	<i>N,N</i> -dimethylformamide
eh	2-ethylhexanoate
Et	ethyl
<i>i</i> -Pr	isopropyl

LDA	lithium diisopropylamide
MW	microwave irradiation
hetAr	heteroaryl
Me	methyl
<i>n</i> -BuLi	<i>n</i> -butyl lithium
ND	not detected
Ph	phenyl
Piv	pivalate
RBF	round bottom flask
rt	room temperature
TBS	<i>tert</i> -butyldimethylsilyl
<i>t</i> -Bu	<i>tert</i> -butyl
Tf	triflate
tfp	tri(2-furyl)phosphine
THF	tetrahydrofuran
TM	transition metal
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidinyl
TMSCl	chlorotrimethylsilane

SPhos

2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl

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1. Introduction

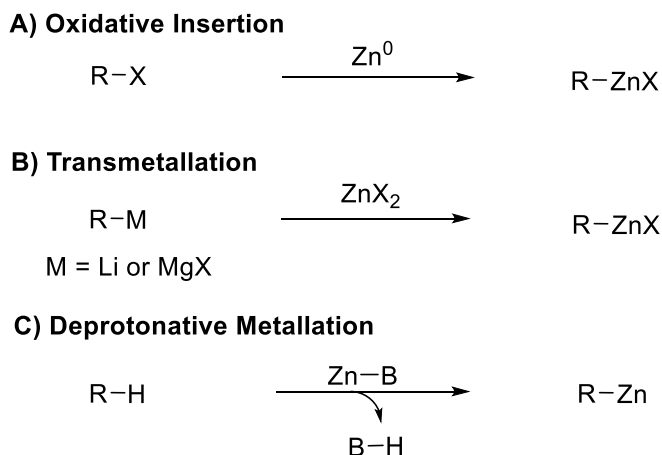
Deprotonative zincation has been demonstrated as a useful strategy for net C–H functionalization. Existing work utilizing zinc amide bases for deprotonative zincation as well as transformations with the generated organozinc reagents will be discussed.

1.1 *The utility of organozinc reagents*

Organozinc reagents have long been known as highly useful intermediates in organic synthesis.¹ They have many advantages over other organometallic reagents, such as Grignard and organolithium reagents, due to their improved functional group compatibility (including esters, nitriles, halides, and sensitive heteroarenes) and ability to react under mild conditions. Many of these useful features are due to the covalent nature of the carbon–zinc bond (with an electronegativity difference of only 0.9); however, in turn, organozinc reagents are inherently less reactive. This challenge has largely been solved by transition metal catalysis, as organozinc reagents readily transmetalate to various transition metals, including palladium, nickel, copper and cobalt.²

Traditionally, organozinc reagents have been generated by either zinc insertion into a carbon–halide bond (Scheme 1A), or transmetalation of a more reactive intermediate onto zinc salts (Scheme 1B). In both cases, desirable direct C–H functionalization cannot be achieved as prefunctionalized intermediates are required. To make organozinc intermediates more useful in synthesis, deprotonative zincation has become increasingly popular in recent years (Scheme 1C). As C–H bonds are plentiful in

inexpensive and readily available starting materials, this method is ideal and maintains tolerance for halogens and other sensitive functional groups.



Scheme 1: Methods for generating organozinc reagents.

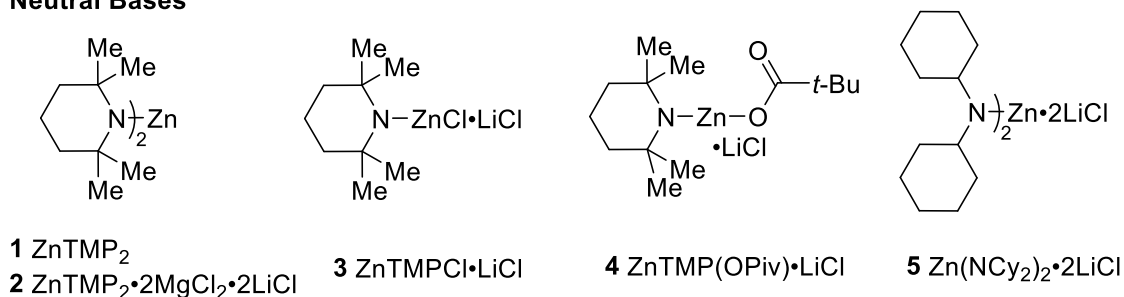
For deprotonative zincation to become a useful strategy in organic synthesis, efficient methods for regioselective C–H zincation are necessary as well as the exploration of reactions with the *in situ* formed organozinc intermediates. Key to the success of deprotonative zincation has been the development of various zinc bases. There have also been many examples of C–H functionalization utilizing different bases (often lithium amide bases) followed by *in situ* transmetallation onto zinc salts,³ however, only zincation with distinctly generated zinc bases will be discussed.

1.2 The development of zinc amide bases

To achieve C–H zincation, various zinc amide bases have been developed to enable deprotonation (Figure 1). The bases can be categorized as neutral or anionic based on the absence or presence of additional charge on zinc. Neutral zinc bases are only

effective on fairly acidic C–H bonds and generally cannot deprotonate unactivated substrates. Alternately, anionic zincate bases are known to be capable of deprotonating unactivated substrates through directing group-mediated coordination to the counterion, often lithium. By far, the most commonly used amide base has been 2,2,6,6-tetramethylpiperidine (TMP) which is sterically-hindered and non-nucleophilic. More recently, dicyclohexylamine (NCy₂) has emerged as a cost-effective alternative to TMP.^{3a}

Neutral Bases



Anionic Bases

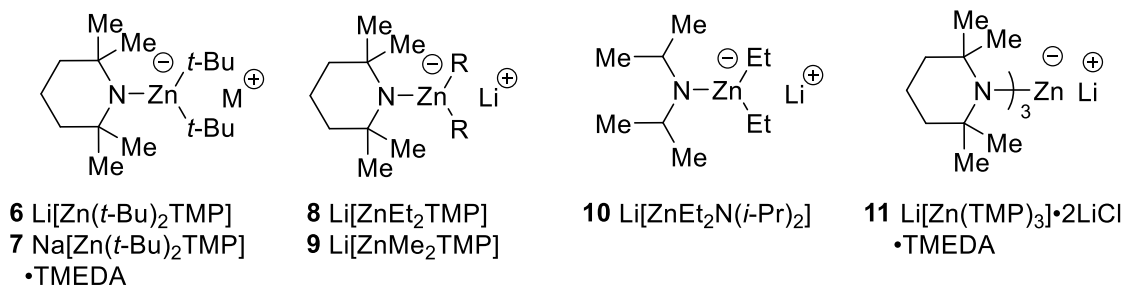


Figure 1: Existing zinc amide bases used for deprotonative zincation

Neutral dibasic ZnTMP₂ (**1**) was first synthesized and characterized in 1998,⁴ however, it was not demonstrated to be capable of deprotonative zincation until 2007 by Hagadorn.⁵ Concurrently, Knochel developed ZnTMP₂·2MgCl₂·2LiCl (**2**) containing magnesium and lithium salts as an effective base for the zincation of arenes and

heteroarenes.⁶ One equivalent of these bases can deprotonate two equivalents of substrate, generating diorganozinc intermediates. Two years later, Knochel developed a mono-basic version ZnTMPCl·LiCl (**3**) with lithium chloride but no magnesium chloride, which generates organozinc chloride reagents.⁷ One advantage of this base is that it can zincate sensitive substrates at room temperature. Typically, organozinc reagents are air and moisture sensitive, but it was found that organozinc pivalates can have improved air-stability. In 2013, Knochel developed a pivalate version of the base ZnTMP(OPiv)·LiCl (**4**) which can directly generate easily-handled, air-stable organozinc pivalates.⁸ While TMP has been very useful as an amide base, it is rather expensive as a stoichiometric reagent. Dicyclohexylamine is much less expensive and is still relatively sterically hindered and non-nucleophilic. Recently, a dicyclohexylamine base Zn(NCy₂)₂·2LiCl (**5**) was found able to undergo metalation at high temperature under continuous flow conditions.⁹

Anionic zincate bases have been developed since 1999 when Kondo and Uchiyama reported the synthesis and reactivity of Li[Zn(*t*-Bu)₂TMP] (**6**).¹⁰ This anionic base has lithium as the counterion, TMP as the amide base and *tert*-butyl as the dialkyl groups. The reactivity of this base has been extensively studied, however its synthesis requires the isolation of pyrophoric di-*tert*-butylzinc which is not commercially available. An analogous sodium zincate base, Na[Zn(*t*-Bu)₂TMP](TMEDA) (**7**), has been developed and studied mostly mechanistically.¹¹ Similar bases Li[ZnEt₂TMP] (**8**)¹² and Li[ZnMe₂TMP] (**9**)¹³ have been made with the corresponding dialkylzinc reagents. As diethylzinc is

commercially available, the synthesis of **8** is more facile than other bases, however, its reactivity had not been extensively explored. Interestingly, the less sterically-hindered **9** promotes aryl bromide elimination and the formation of benzyne, which does not occur with **6**.¹³ In one example, a diethyl zincate base has been made with diisopropylamine instead of TMP as $\text{Li}[\text{ZnEt}_2\text{N}(i\text{-Pr})_2]$ (**10**).¹⁴ Finally, lithium amide zinc complexes have been studied in the form of $\text{Li}[\text{Zn}(\text{TMP})_3] \cdot 2\text{LiCl} \cdot \text{TMEDA}$ (**11**) which is synthesized from a 3:1 ratio of LiTMP to $\text{ZnCl}_2 \cdot \text{TMEDA}$, can also facilitate metalation.^{3f, 15} The various applications of these zinc bases will be detailed below.

1.3 Existing functionalization transformations utilizing deprotonative zincation

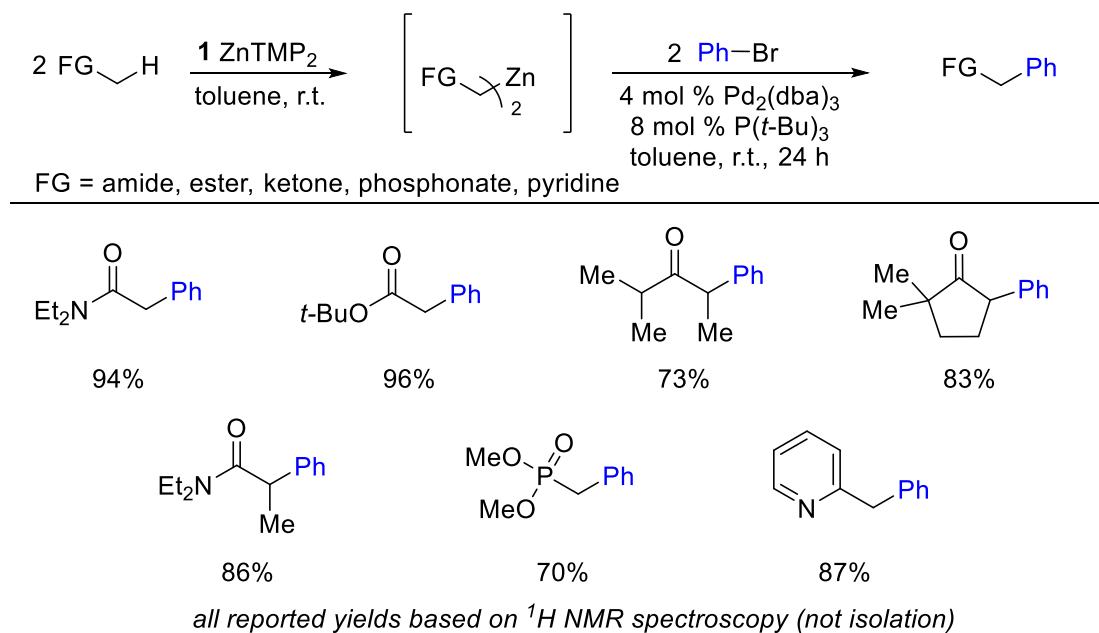
Deuteration has been used extensively to study metalation efficiency, however as there is very little functional difference between hydrogen and deuterium, deuteration will not be discussed. Various C–C and C–heteroatom bond forming reactions utilizing deprotonative zincation will be described.

1.3.1 Functionalization of sp^3 C–H bonds

TMP-Zinc bases have been used for the deprotonation of the acidic sp^3 C–H bonds α - to esters, amides, nitriles, phosphonates, and sulfones. Initially, these substrates have been used for transition metal-catalyzed cross-coupling and have also been used for electrophilic amination.

1.3.1.1 Carbon-carbon bond formation

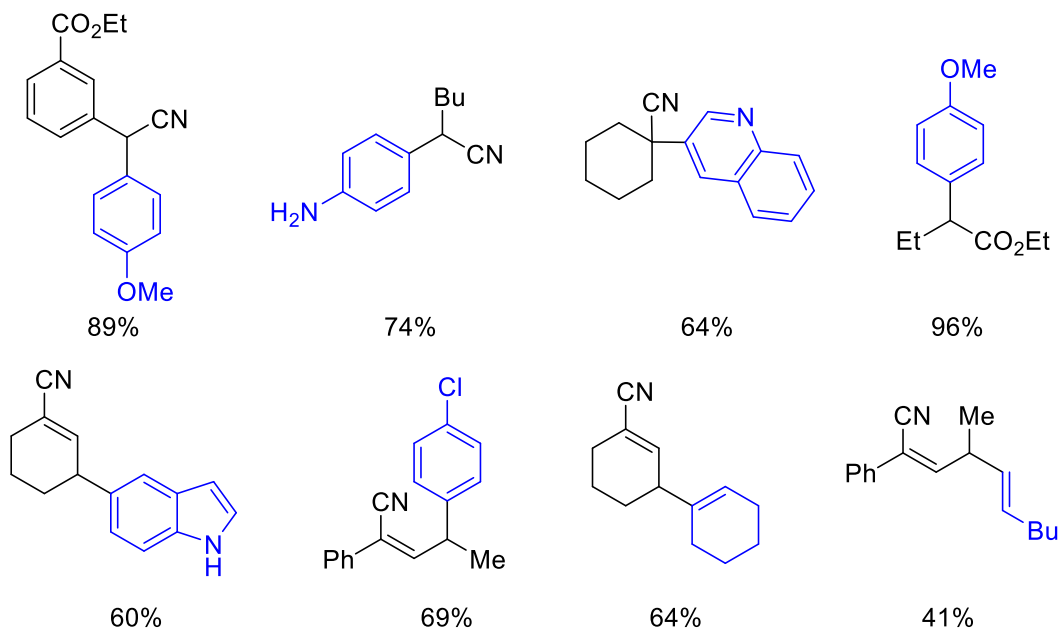
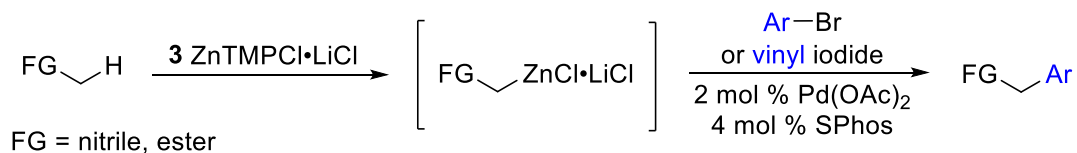
Some of the first examples of TMP-zinc bases for *in situ* zincation and functionalization utilized traditional palladium-catalyzed cross-coupling with aryl halides. With **1**, Hagadorn performed Negishi couplings of amides, esters, ketones, phosphonates and picoline with phenyl bromide, giving efficient α -phenylation (Scheme 2).⁵ However, all of the reported yields were based on ¹H NMR, not isolation and no catalyst optimization was performed.



Scheme 2: Palladium-catalyzed α -phenylation with ZnTMP₂

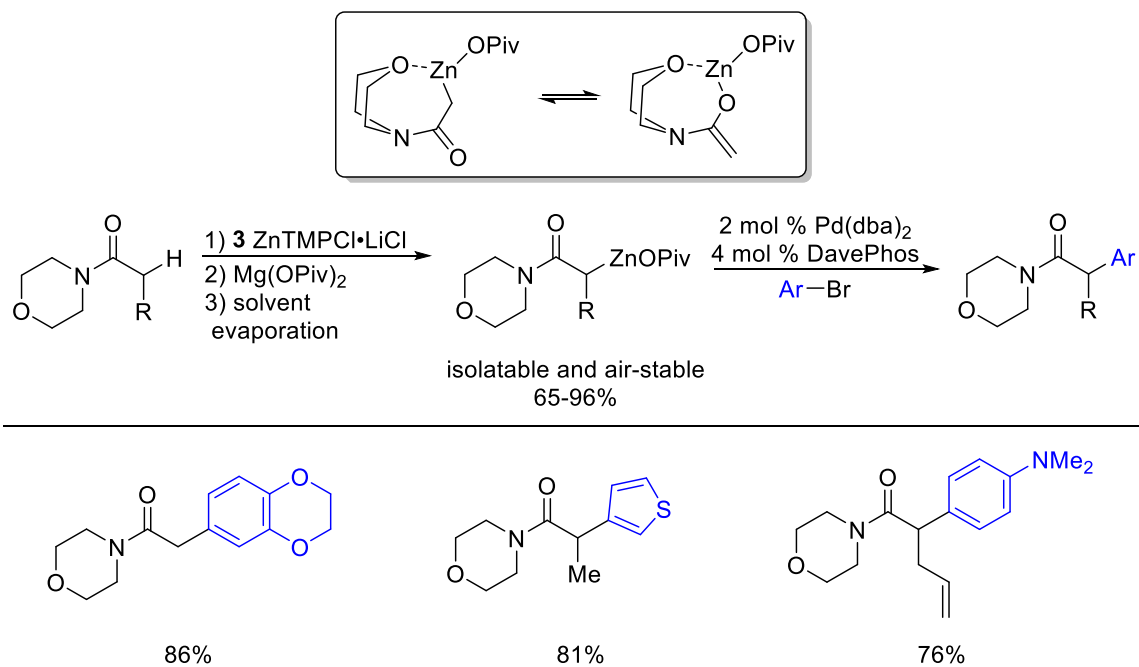
In a similar manner, Knochel further developed this palladium-catalyzed coupling utilizing his mono TMP-zinc base **3** (Scheme 3).¹⁶ Zincation was achieved α - to nitriles and esters and γ - to unsaturated nitriles and the organozinc chlorides underwent subsequent cross-coupling. The catalyst system was optimized to 2 mol% Pd(OAc)₂ and 4 mol%

SPhos, and cross-coupling with various aryl bromides and vinyl iodides was demonstrated.



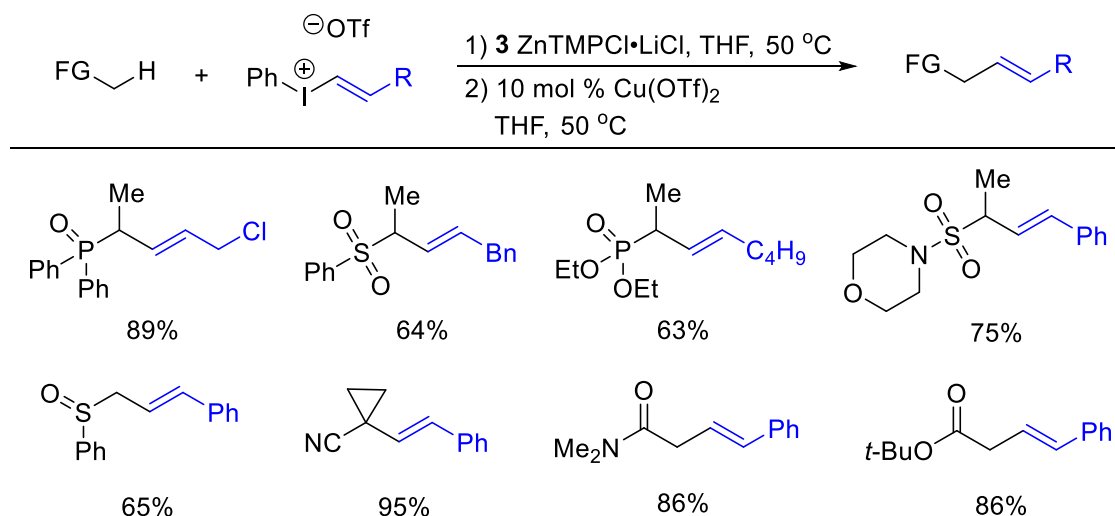
Scheme 3: Palladium-catalyzed α -arylation and vinylation

Later the same base **3** was used for the α -zincation of morpholino amides, which were subsequently transmetalated on to magnesium pivalate, generating zinc pivalate salts which were found to be isolable and air-stable (Scheme 4). Then the isolated intermediates were utilized for another palladium-catalyzed cross-coupling with aryl bromides.¹⁷



Scheme 4: Palladium-catalyzed arylation of stabilized zinc pivalate enolates

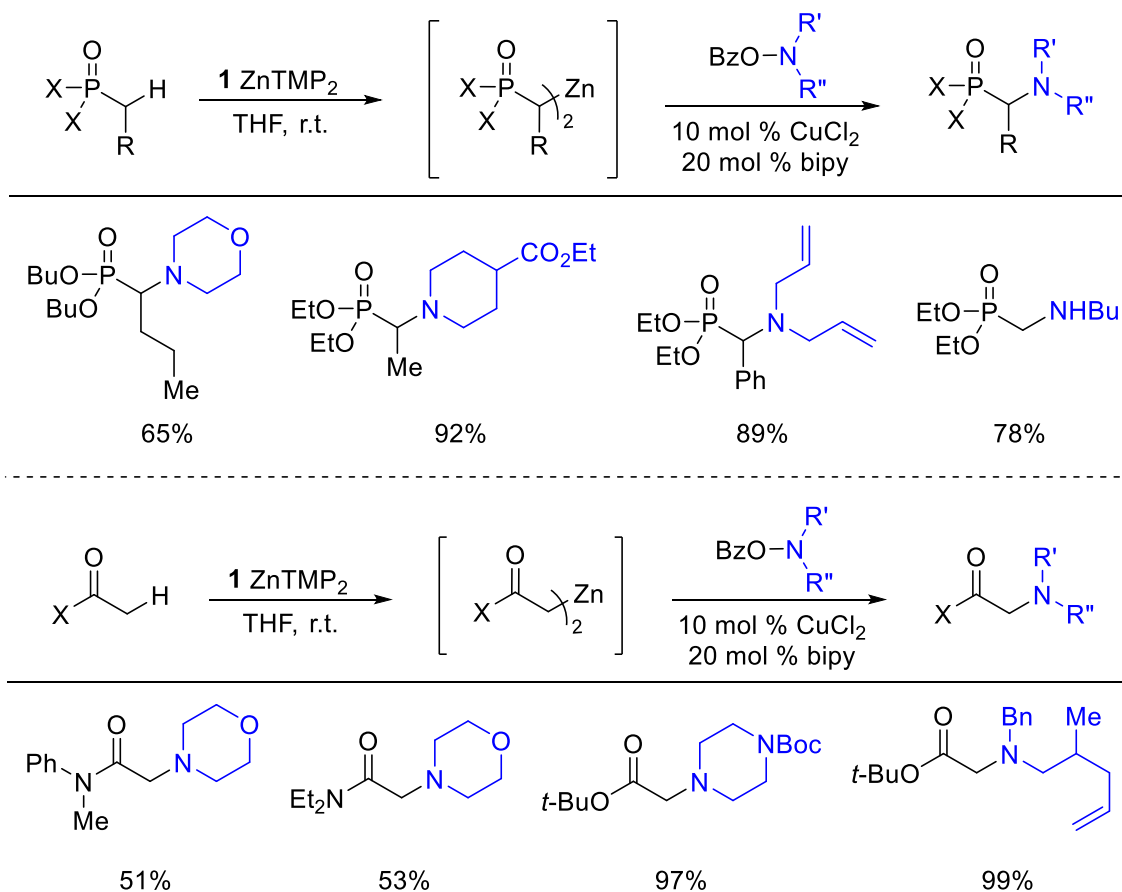
As an alternative to traditional palladium-catalyzed coupling with halides, our group has recently used deprotonative zincation with **3** for copper-catalyzed coupling with iodonium salts (Scheme 5). Phenyl vinyl iodonium triflate salts are air and moisture stable electrophiles and readily react with phosphones, phosphonates, sulfones, sulfonates, nitriles, amides and esters for alkenylation.¹⁸



Scheme 5: Copper-catalyzed alkenylation of sp^3 zinc intermediates generated by ZnTMPCl·LiCl with iodonium salts

1.3.1.2 Carbon–nitrogen bond formation

ZnTMP₂ (**1**) has also been used to achieve C–N bond formation with copper-catalyzed electrophilic amination using *O*-benzoyl hydroxylamines as an electrophilic amine source (Scheme 6). *O*-Benzoyl hydroxylamines are easily synthesized on a large scale, are air-stable and are easily handled.¹⁹ The bis-basic, lithium chloride free base (**1**) was found to be most effective for sp^3 amination, as lithium chloride appeared to hinder the reaction. Various phosphonates smoothly underwent amination under mild conditions with cyclic and acyclic secondary hydroxylamines and primary hydroxylamines.²⁰ Amides and esters could also undergo α -amination under similar conditions, however, this transformation was limited to unsubstituted substrates.²¹ Interestingly, the amide and ester zinc enolates also undergo acylation with the hydroxylamine electrophile when no copper catalyst is used.



Scheme 6: Copper-catalyzed electrophilic α -amination of phosphonates, esters, and amides with *O*-benzoyl hydroxylamines

1.3.2 Functionalization of sp^2 C–H bonds

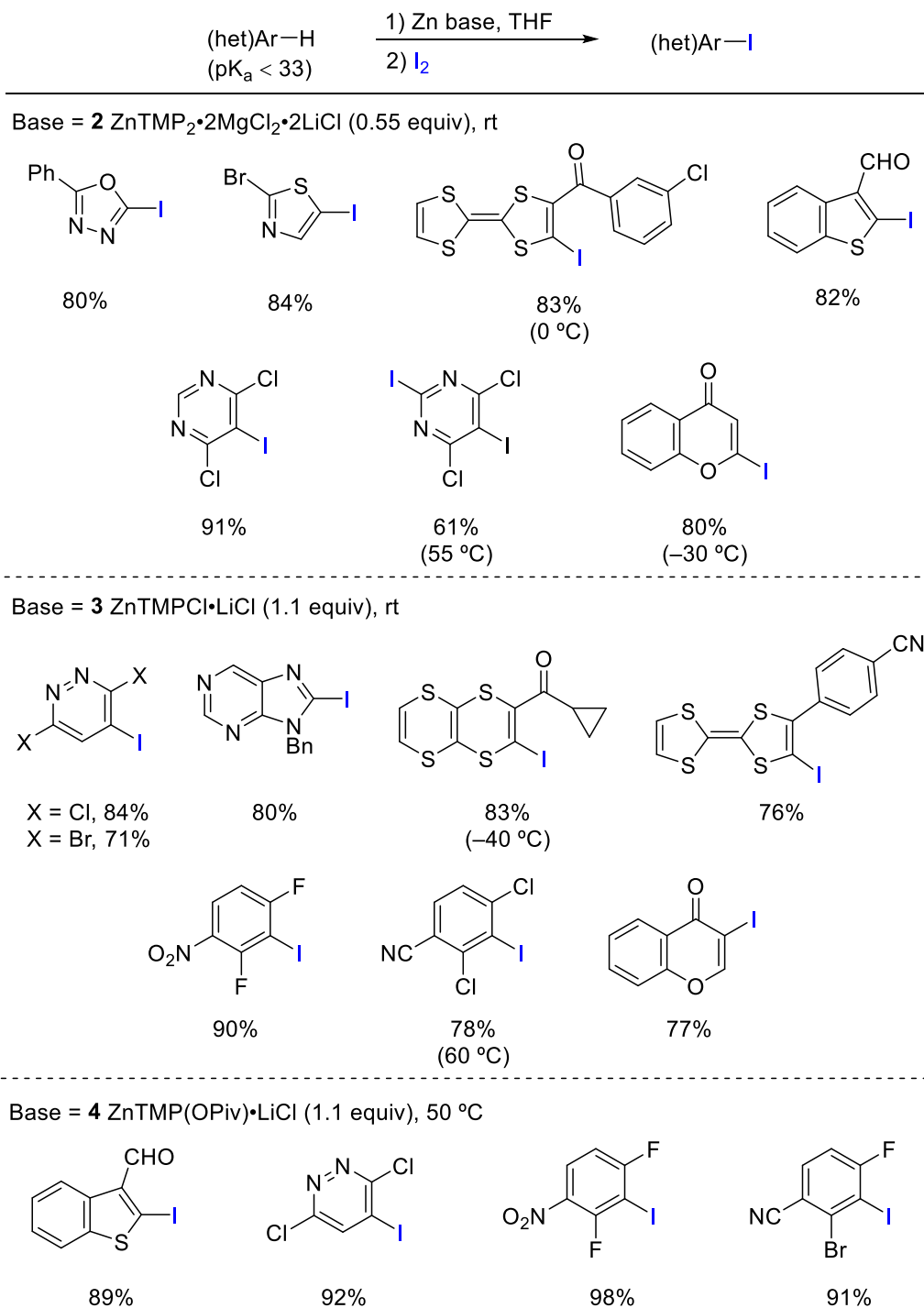
Zinc amide bases have been studied most extensively for the deprotonation of sp^2 C–H bonds, mostly arenes and heteroarenes. Much work has been done to develop selective zincation of important aryl and heteroaryl skeletons.

1.3.2.1 Carbon–halogen bond formation

The vast majority of halogenations that have been performed by deprotonative zincation have been iodination. It is well known that organozinc reagents readily react

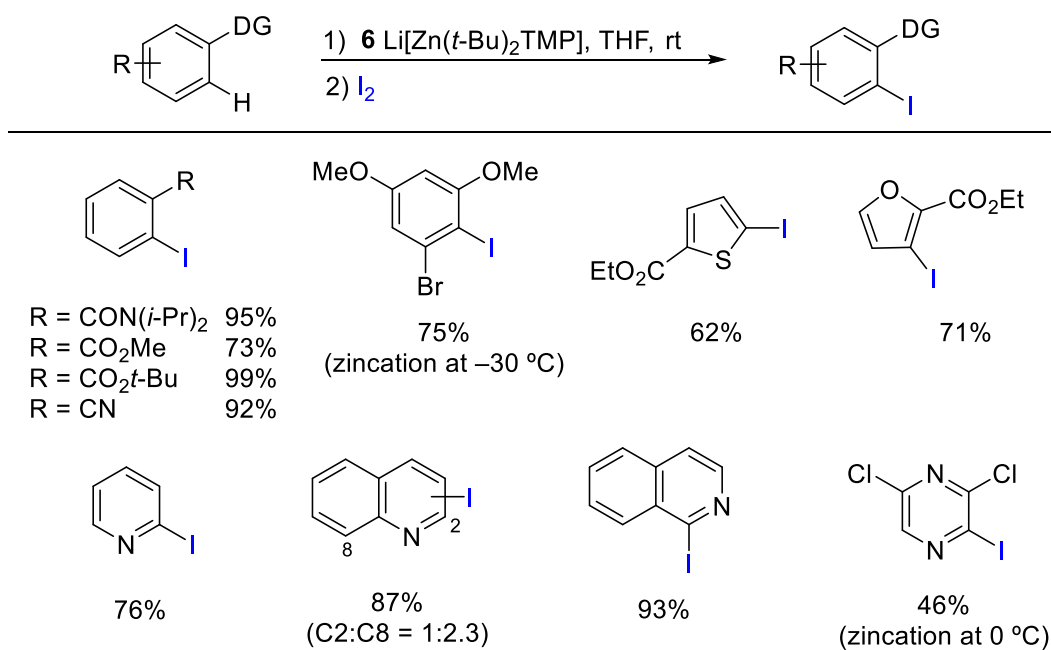
with iodine as an excellent electrophile, and aryl iodide products are highly useful synthetic intermediates. Iodination it has been reported to study the zincation of a variety of aryl and heteroaryl substrates, therefore, the scope for each base can easily be distinguished by comparing iodination.

Knochel reported iodination with different neutral zinc bases including **2**²², **3**^{3d, 22c, 22d, 23}, and **4**²⁴ (Scheme 7). Iodination of zincated arenes deprotonated by neutral zinc bases have showed high functional group compatibility including halides, carbonyls, nitriles, and even sensitive nitro and formyl groups. Moreover, various heteroarenes that contain nitrogen, oxygen, or sulfur atoms are compatible. Site-selectivity of zincation and iodination among neutral zinc bases (**2**, **3**, and **4**) is similar for most arenes and heteroarenes with the exception of chromones, quinolones, and thiochromones because the MgCl₂ in **2** acts as a Lewis acid that changes the coordination and regioselectivity.^{22c}



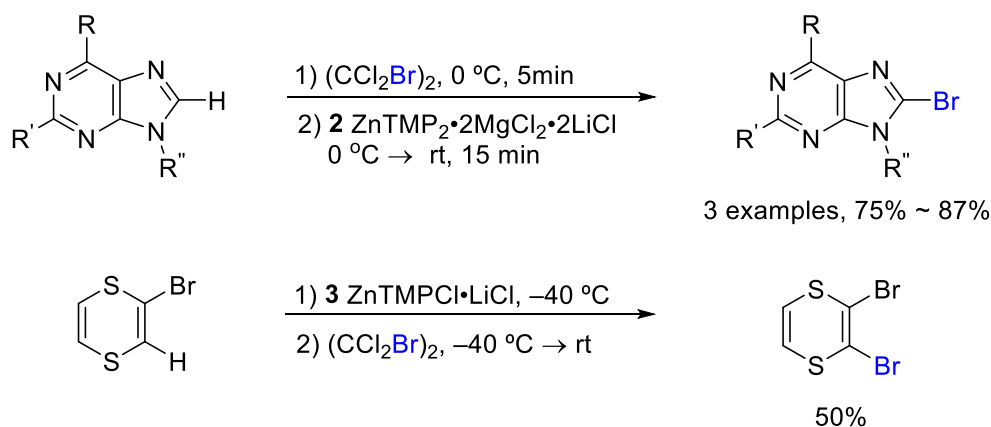
Scheme 7: Regioselective iodination of electron-deficient arenes and heteroarenes with neutral zinc bases

Lithium directed zincation with $\text{Li}[\text{Zn}(t\text{-Bu})_2\text{TMP}]$ (**6**) has been extensively explored via iodination (Scheme 8).^{13-14, 23g, 25} A wide variety of functional groups can direct zincation of unactivated arenes and heteroarenes. Amides, esters, nitriles and halides are all tolerated without elimination to benzyne, however, sensitive nitro and formyl groups are incompatible.



Scheme 8: Regioselective iodination of unactivated arenes and heteroarenes by directed zincation with $\text{Li}[\text{Zn}(t\text{-Bu})_2\text{TMP}]$

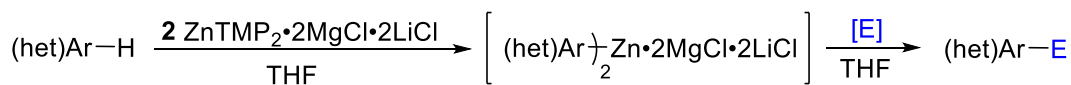
Several brominations have been reported by deprotonation with neutral zinc-amide bases.^{23c, 23e} Knochel reported bromination of purine derivatives^{23c} and 1,4-dithiins^{23e} with 1,2-dibromotetrachloroethane as the electrophilic bromination source (Scheme 9).



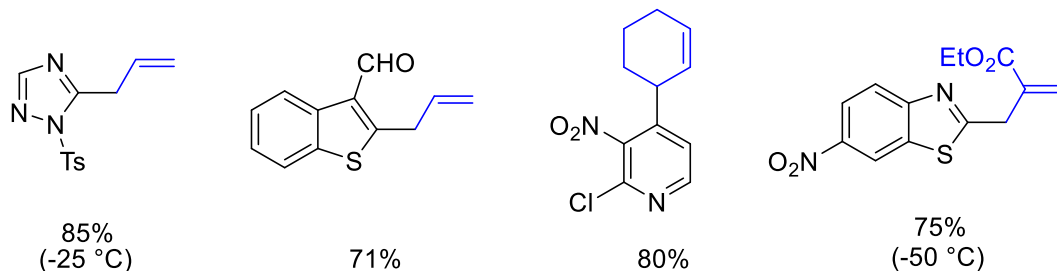
Scheme 9: Bromination of heteroarenes with neutral zinc bases

1.3.2.2 Carbon–carbon bond formation

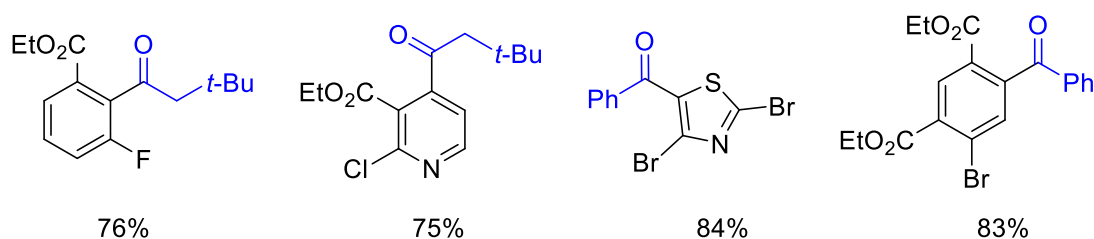
In his initial report of **2**, Knochel demonstrated several types of carbon–carbon bond-forming reactions, including allylation, acylation, and arylation (Scheme 10).⁶ For the allylation, a catalytic amount of $\text{CuCN} \cdot \text{LiCl}$ was necessary to achieve reaction with various allyl bromides and for acylation, stoichiometric copper was required with acyl chlorides. Additionally, Negishi couplings were performed in good yield with aryl iodides with 5 mol% $\text{Pd}(\text{dba})_2$ and 10 mol% tfp ligand. Later, a cobalt-catalyzed Negishi coupling with primary and secondary alkyl halides was developed.²⁶



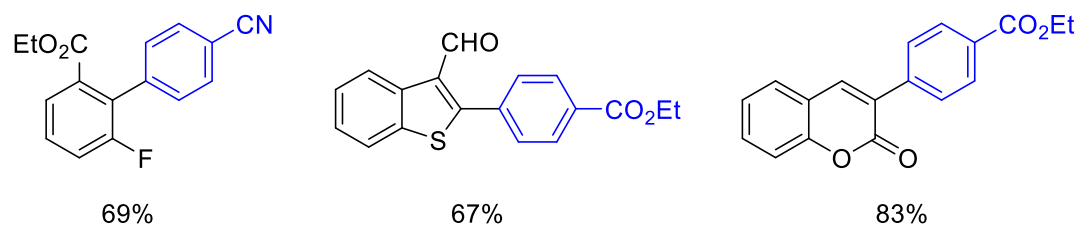
Cu-Catalyzed Allylation: [E] = allyl bromide, 5 mol% CuCN•2LiCl



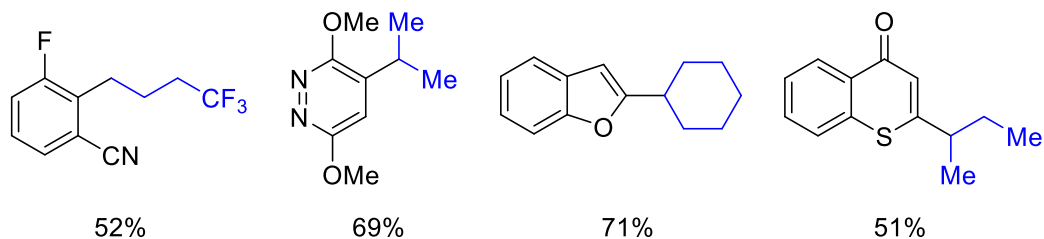
Cu-Mediated Acylation: [E] = acyl chloride, 1.1 equiv CuCN•2LiCl



Pd-Catalyzed Arylation: [E] = aryl iodide, 5 mol% [Pd(dba)₂] and 10 mol % tfp

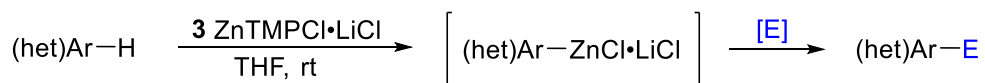


Co-Catalyzed Alkylation: [E] = 1° or 2° alkyl iodide, 20 mol % CoCl₂•2LiCl, 30 mol % TMEDA

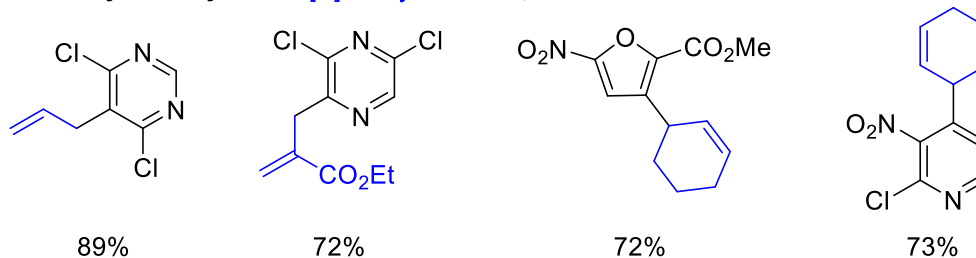


Scheme 10: Allylation, acylation, and arylation of aryl and heteroaryl zinc intermediates generated by ZnTMP₂•2MgCl₂•LiCl

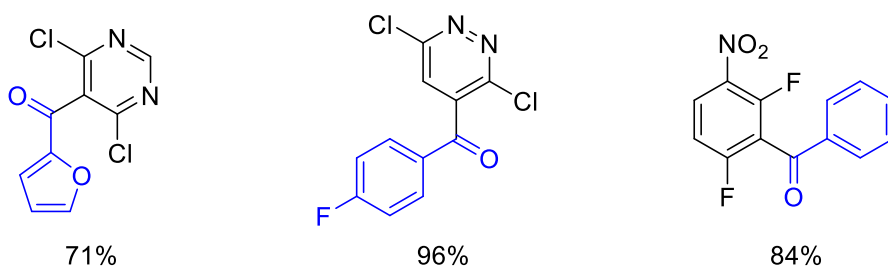
In a similar manner, Knochel utilized the mono base **3** for the same carbon–carbon bond forming reactions (allylation, acylation, and arylation), which could be used for more sensitive heteroaryl substrates including pyrimidines, pyridazines and pyrazines without requiring cryogenic temperatures (Scheme 11).⁷ A different phosphine ligand was used for arylations, and additionally, an example of alkynylation was also performed with iodination followed by Sonogashira conditions. These coupling reactions with **3** were also shown to be readily scalable to 50 mmol with equivalent if not improved yield.²⁷ The pivalate base **4** can also be used to generate air-stable, isolatable heteroarylzinc pivalates with similar scope and transformations (acylation, allylation and arylation) (Scheme 12).⁸



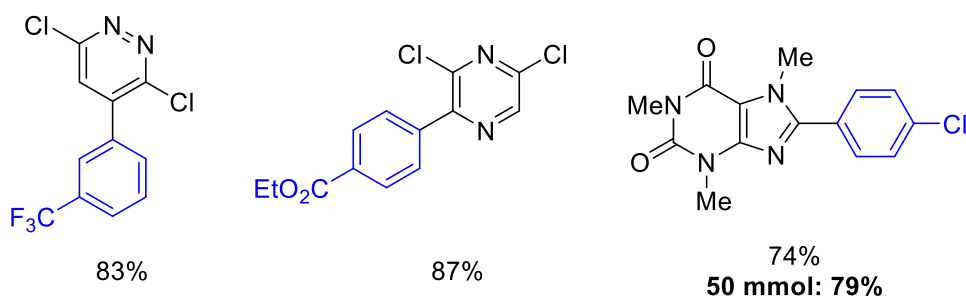
Cu-Catalyzed Allylation: [E] = allyl bromide, 5 mol % CuCN·LiCl



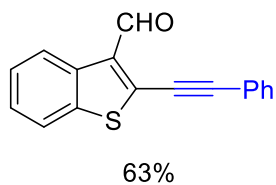
Cu-Mediated Acylation: [E] = acyl chloride, 1.1 equiv of CuCN·LiCl



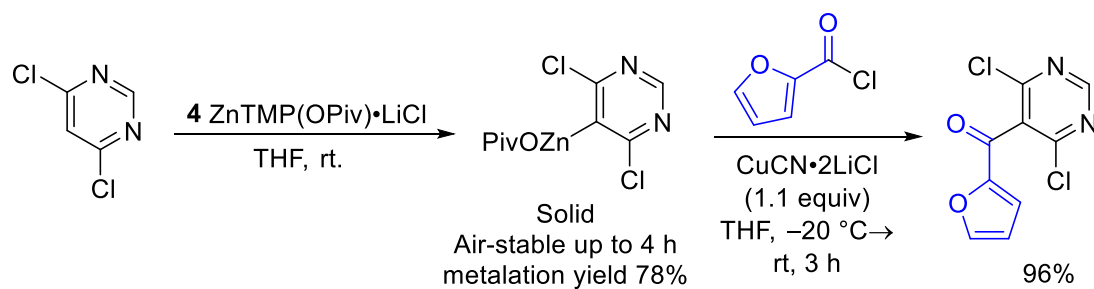
Pd-Catalyzed Cross Coupling: [E] = aryl iodide, 3 mol % Pd(dba)₂, 6 mol % P(o-furyl)₃



[E] = iodine; followed by 3 mol % Pd(dba)₂ and 6 mol % tfp, CuI, NEt₃; followed by alkyne

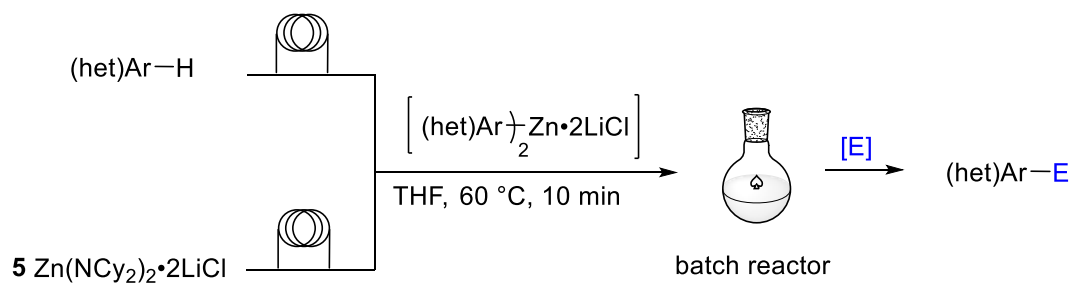


Scheme 11: Allylation, acylation, and arylation of sensitive aryl and heteroaryl zinc intermediates from ZnTMPCl·LiCl

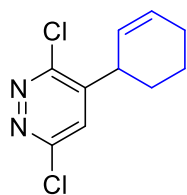


Scheme 12: Copper-mediated acylation of air-stable heteroaryl zinc pivalates generated by ZnTMP(OPiv)Cl·LiCl

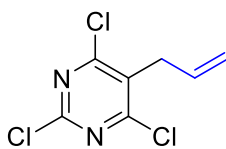
As TMP is fairly expensive as a stoichiometric reagent, Knochel recently discovered that dicyclohexylamine (NCy₂) can be used as an alternative with the base **5**, which gives excellent metalation under continuous flow conditions with elevated temperatures. Copper-catalyzed allylation and palladium-catalyzed arylations were performed, and for some substrates, different regioselectivity was observed in comparison to the TMP base (Scheme 13).



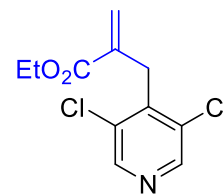
Allylation: [E] = allyl bromide, 5 mol % CuCN•2LiCl



86%

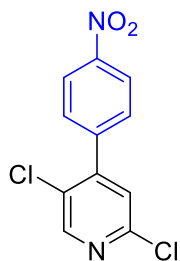


92%



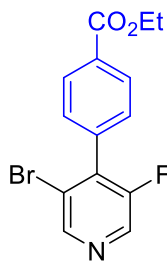
74%

Arylation: [E] = aryl iodide, 2 mol % Pd(dba)₂, 4 mol % tfp

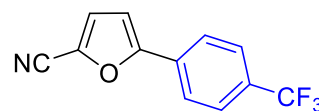


78%

different regioselectivity
than TMP base



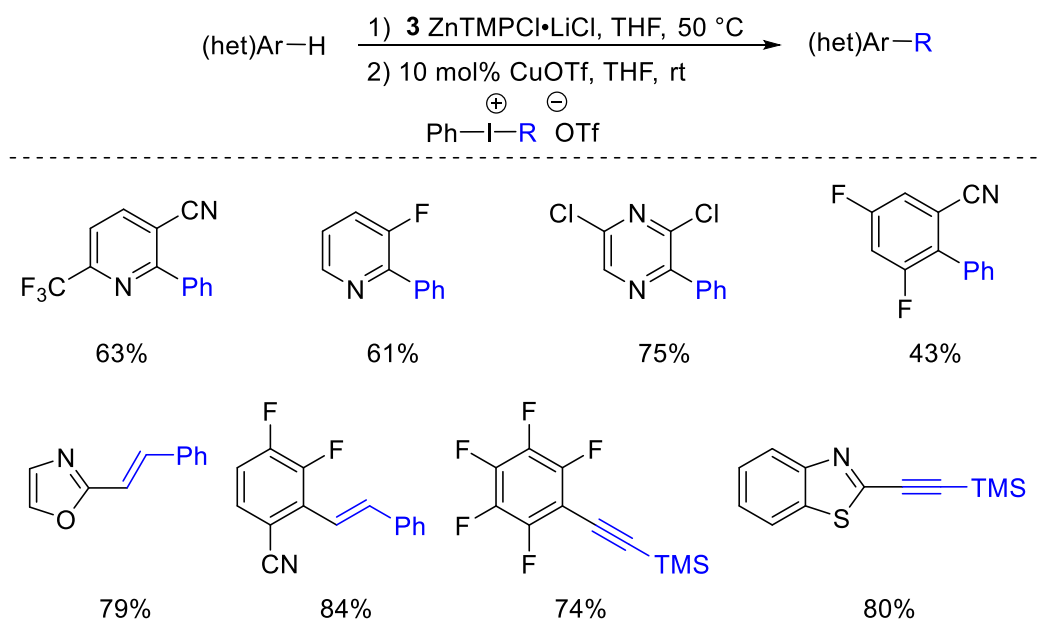
60%



64%

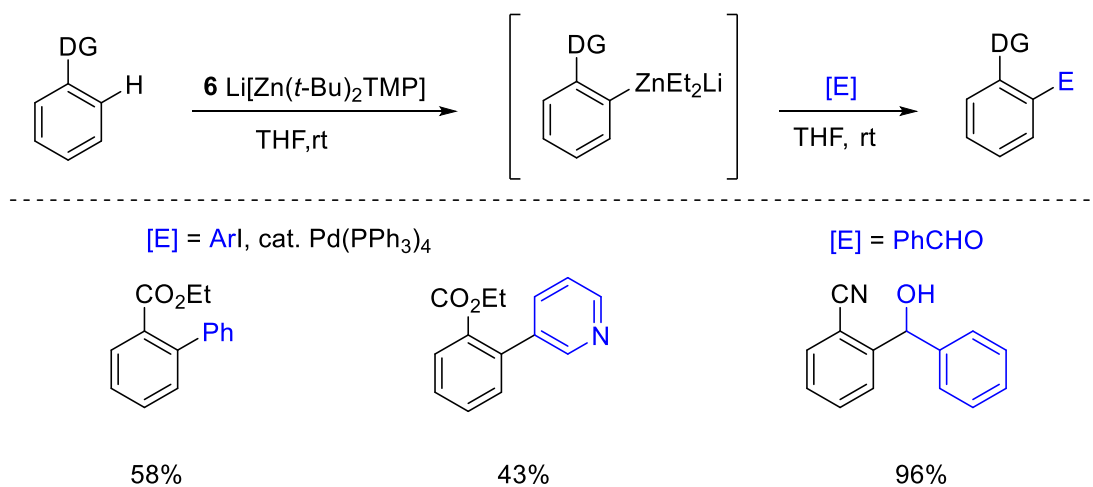
Scheme 13: High-temperature continuous flow zincation with Zn(NCy₂)₂•2LiCl for allylation and arylation

Cross-coupling can also be performed with copper instead of palladium as a catalyst with iodonium salts as the electrophile.²⁸ Using **3** for zincation of electron-deficient heteroarenes and arenes, arylation, vinylation and alkynylation can all be achieved with the corresponding phenyl triflate iodonium salts (Scheme 14).



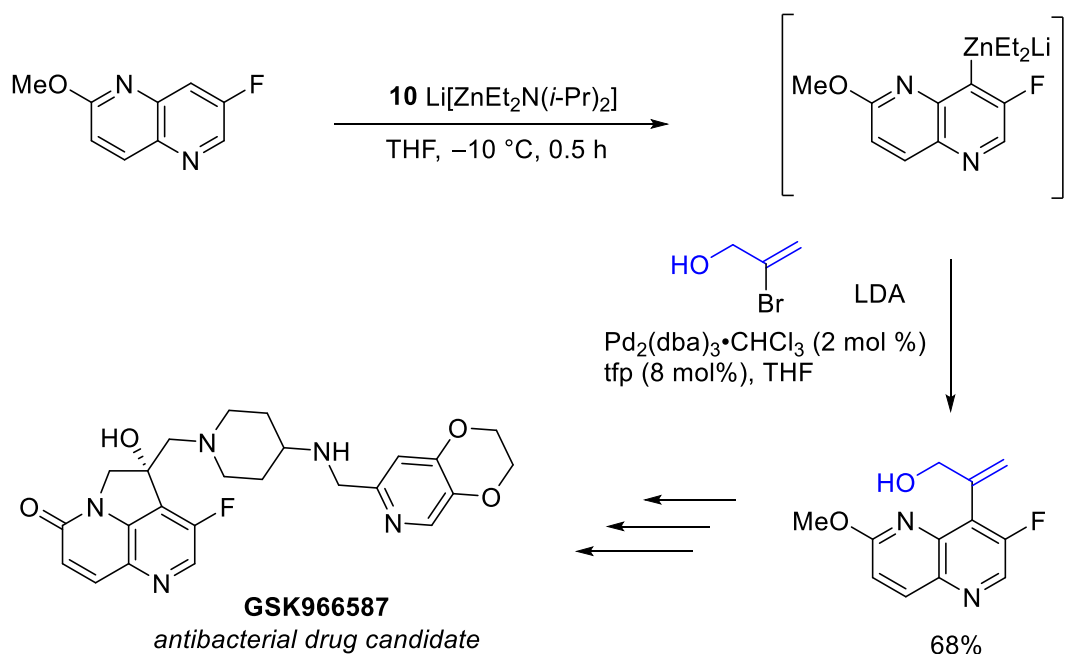
Scheme 14: Copper-catalyzed arylation, alkenylation and alkynylation of heteroaryl zinc intermediates with iodonium salts

There have been limited examples utilizing lithium zincate base **6** for Negishi coupling of less-activated arene and heteroarene substrates, as well as reaction with benzaldehyde, the latter of which does not occur with neutral zinc reagents (Scheme 15).¹⁰



Scheme 15: Carbon-carbon bond forming reactions with Li[Zn(*t*-Bu)₂TMP] for directed metalation

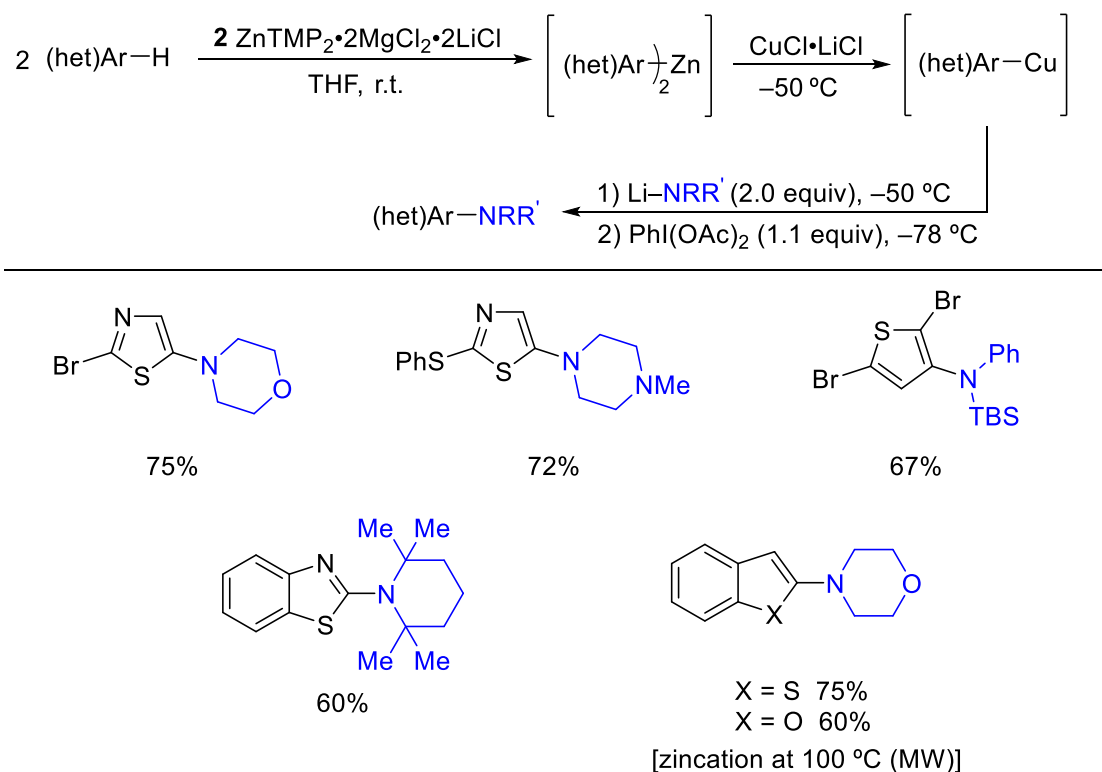
In order to synthesize an antibacterial drug candidate, GlaxoSmithKline utilized an analogous zincate base **10**, which could be synthesized from commercially available reagents to achieve selective *ortho*-metalation of 7-fluoro[1.5]naphthyridinone. The zincate intermediate could be trapped with iodine or undergo palladium-catalyzed Negishi coupling to directly access a key intermediate (Scheme 16).¹⁴



Scheme 16: Zincate-mediated *ortho*-metallation and Negishi coupling

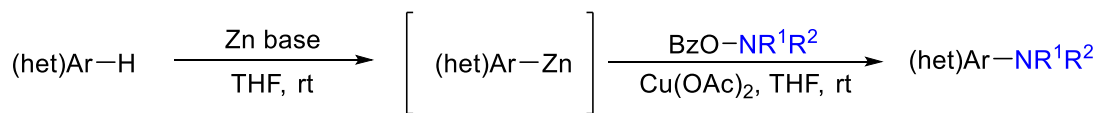
1.3.2.3 Carbon–nitrogen bond formation

Copper-mediated oxidative amination of heteroarenes has been reported by Knochel using **2** (Scheme 17).²⁹ Amination was achieved by transmetalation to a stoichiometric amount of copper chloride and addition of lithium amide followed by oxidation using (diacetoxyiodo)benzene. With this method, various heteroarenes have been explored such as thiazoles, benzothiazoles, thiophenes, benzofurans, benzothiophenes, but no arenes were reported.

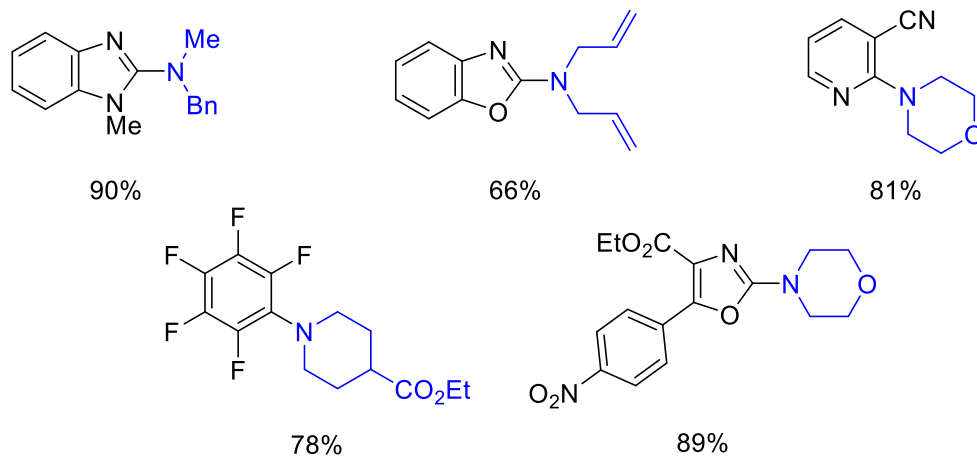


Scheme 17: Copper-mediated oxidative amination of heteroarenes

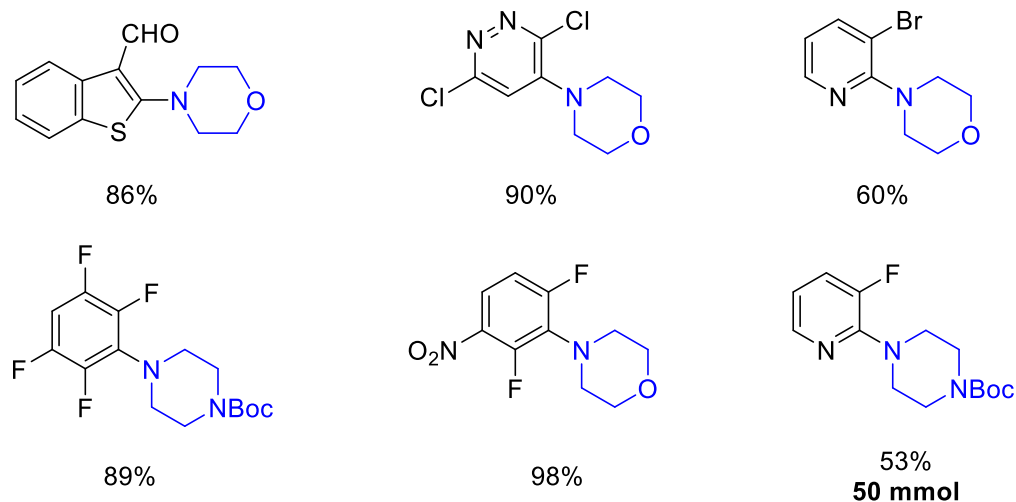
Our group reported copper-catalyzed electrophilic amination via deprotonative zincation of arenes and heteroarenes with neutral zinc-amide bases.³⁰ *O*-benzoylhydroxylamines were used as electrophilic nitrogen sources. Initially, amination using dibasic ZnTMP₂ (**1**) was first established, allowing for tertiary amination of a broad range of (hetero)arene substrates in good yields (Scheme 18, A). In later studies, this method was improved by using a monobasic **3**, requiring less copper catalyst and arene substrates while maintaining adequate yields (Scheme 18, B). Additionally, the reaction is easily scaled to 50 mmol to obtain over 7 g of aminated product.³¹ One limitation of the neutral zinc-amide base was its inability to deprotonate arenes with less acidic protons.



(A) base = **1** (1.0 equiv), Ar-H (2.1 equiv); BzO-NRR' (1.0 equiv), Cu(OAc)₂ (10 mol %)



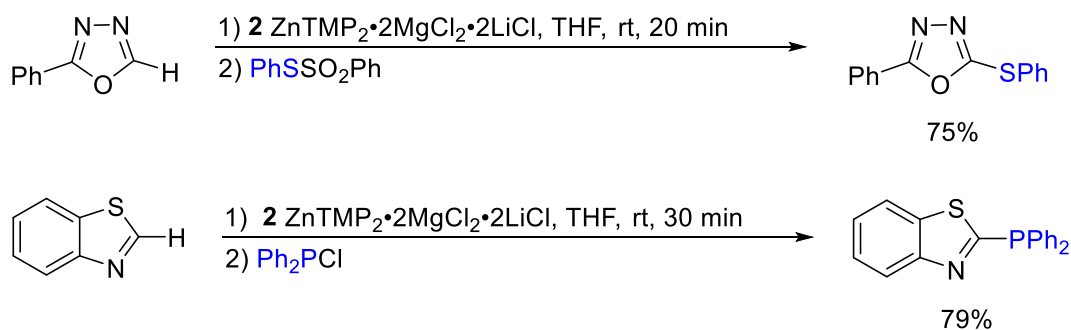
(B) base = **3** (1.0 equiv), Ar-H (1.0 equiv); BzO-NR¹R² (1.2 equiv), Cu(OAc)₂ (5 mol %)



Scheme 18: Copper-catalyzed electrophilic amination of arenes and heteroarenes by zincation with neutral zinc bases

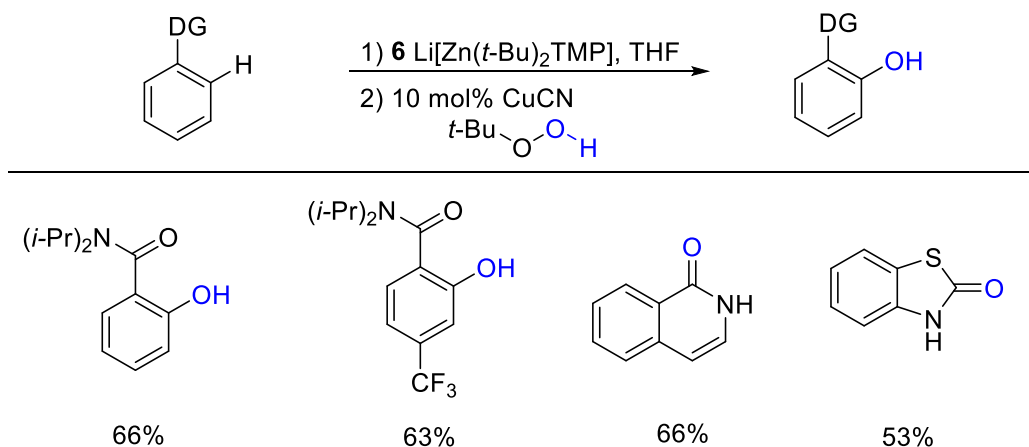
1.3.2.4 Carbon–oxygen, sulfur and phosphorous bond formation

A single example of both thiolation and phosphorylation were reported with **2** utilizing phenyl benzenethiosulfonate and chlorodiphenylphosphine as electrophiles (Scheme 19).⁶



Scheme 19: Thiolation and phosphorylation of heteroarenes with ZnTMP₂·2MgCl₂·2LiCl

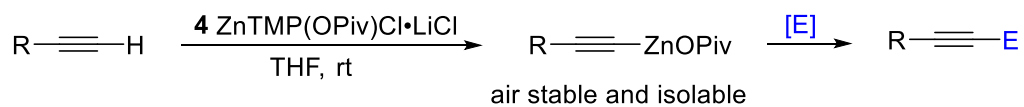
Recently, Uchiyama showed hydroxylation through deprotonative cupration with a stoichiometric cuprate base and *t*-butyl hydrogen peroxide. Several examples of hydroxylation were also performed with zincate base **6** and a copper catalyst (Scheme 20).³²



Scheme 20: Copper-catalyzed hydroxylation of zincates

1.3.3 Functionalization of *sp* C–H bonds

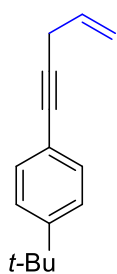
To the best of our knowledge, there is only one example of deprotonative zincation used for the functionalization of alkynes. Knochel used base **4** to generate air-stable and isolatable alkynyl zinc pivalates (Scheme 21).^{24b} The electrophilic transformations performed with these zinc reagents included copper-catalyzed allylation, aluminum-mediated addition to aldehydes and palladium-catalyzed coupling with aryl bromides.



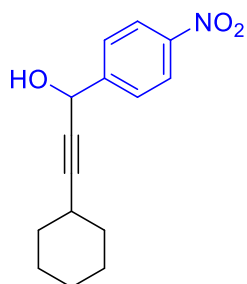
[E] = allyl bromide,
10 mol% CuCN·2LiCl

[E] = aldehyde,
1.0 equiv AlMe₃

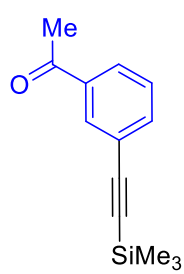
[E] = ArBr, 2 mol % Pd(dba)₂, 4 mol% DavePhos



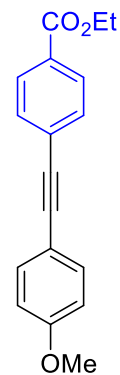
84%



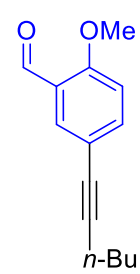
70%



89%



91%



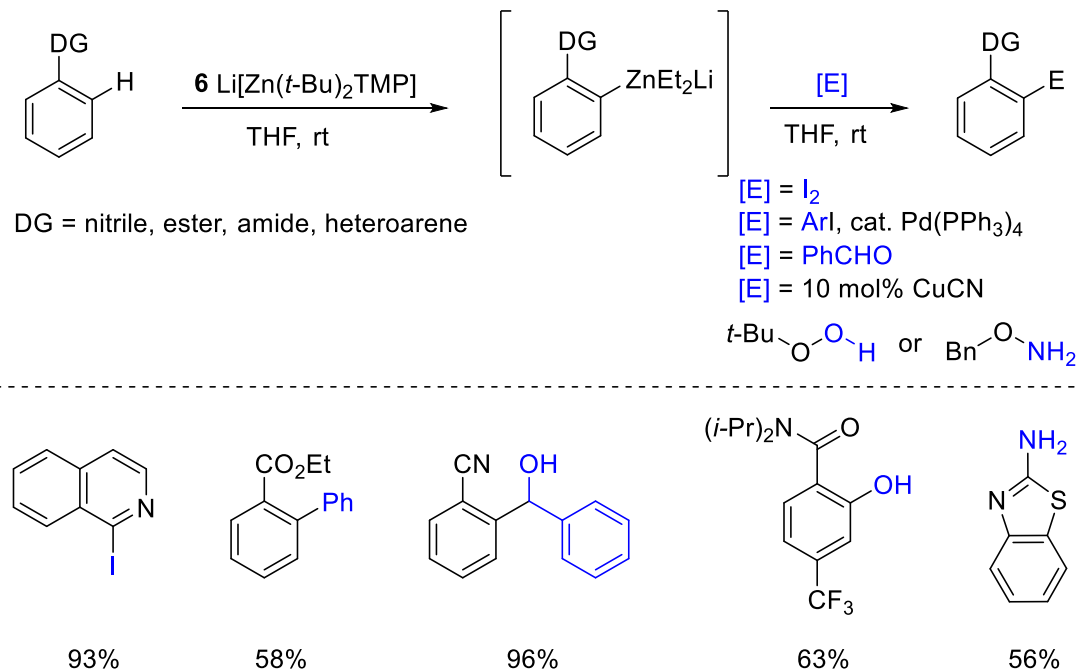
76%

Scheme 21: Deprotonative zincation to generate stable alkynyl zinc pivalates for coupling reactions

2. Design and development of lithium zincate bases

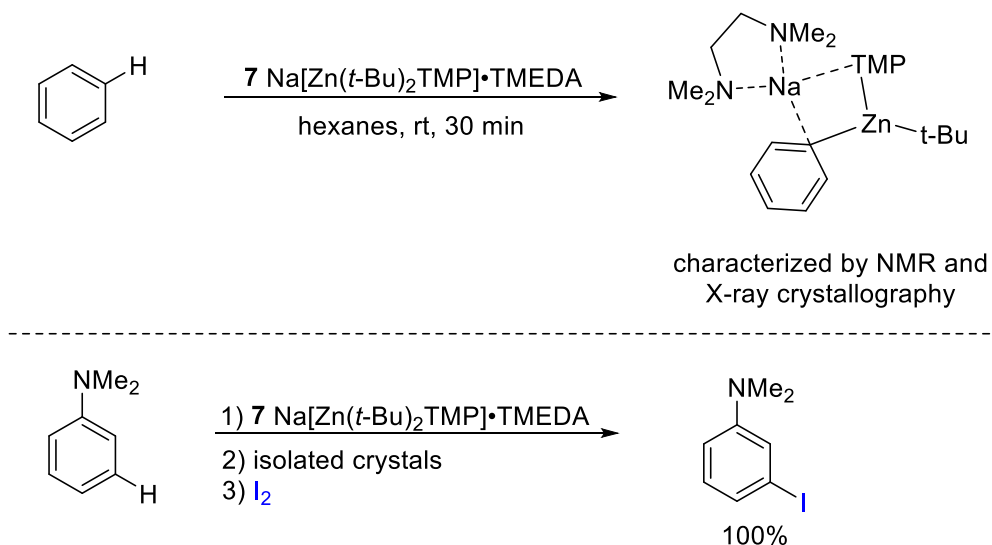
2.1 Existing knowledge of zincate base composition

In 1999, Kondo and Uchiyama first reported the base $\text{Li}[\text{Zn}(t\text{-Bu})_2\text{TMP}]$ (**6**) for the directed zincation of arenes and heteroarenes.¹⁰ In their initial report they demonstrated *ortho*-iodination of a variety of directing groups including nitriles, esters, amides, and heteroarenes, and also included two examples of palladium-catalyzed Negishi cross-coupling and one reaction with benzaldehyde. The mechanism of zincation with **6** was studied extensively³³ and the scope of these transformations has been further explored.^{23g} More recently, Uchiyama also used **6** for copper-catalyzed hydroxylation with *t*-butyl hydrogen peroxide and amination with primary benzyl hydroxylamine (Scheme 22).³²



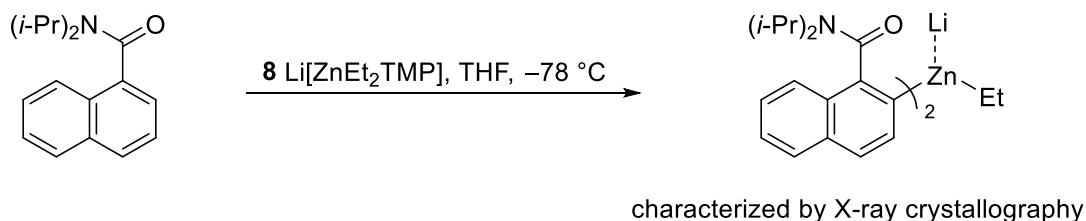
Scheme 22: Existing functionalization transformations with $\text{Li}[\text{Zn}(t\text{-Bu})_2\text{TMP}]$

Some work has been done to study the effect of the composition of zincate bases. A version of the di-*tert*-butyl base with sodium as the counterion (**7**) was synthesized and interestingly, had different reactivity than the lithium version.³⁴ The direct zincation of benzene was achieved with **7** and the *tert*-butyl ligand acted as a base instead of the TMP. *Meta*-functionalization has also been achieved with dimethylaniline using **7**, which is in direct contrast to *ortho*-metalation selectivity of lithium bases (Scheme 23).^{11b}



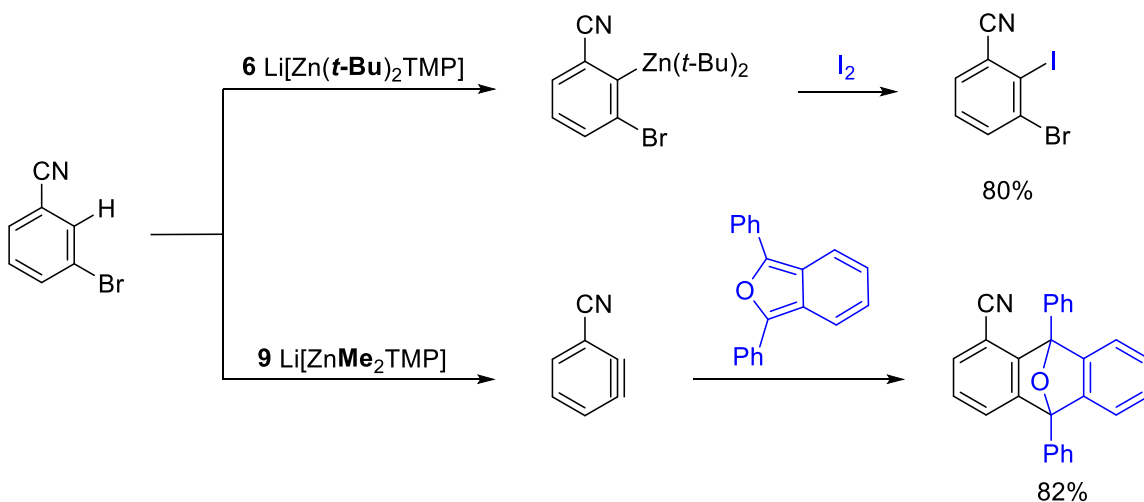
Scheme 23: Zincation using sodium base Na[Zn(*t*-Bu)₂TMP]•TMEDA

In one report, a diethyl version was synthesized and characterized and one example of zincation was demonstrated (Scheme 24).¹² This diethyl base has the advantage of using commercially available diethylzinc, however, the scope of its reactivity was underexplored.



Scheme 24: Singular example of zincation of *N,N*-diisopropyl-naphthamide with Li[ZnEt₂TMP]

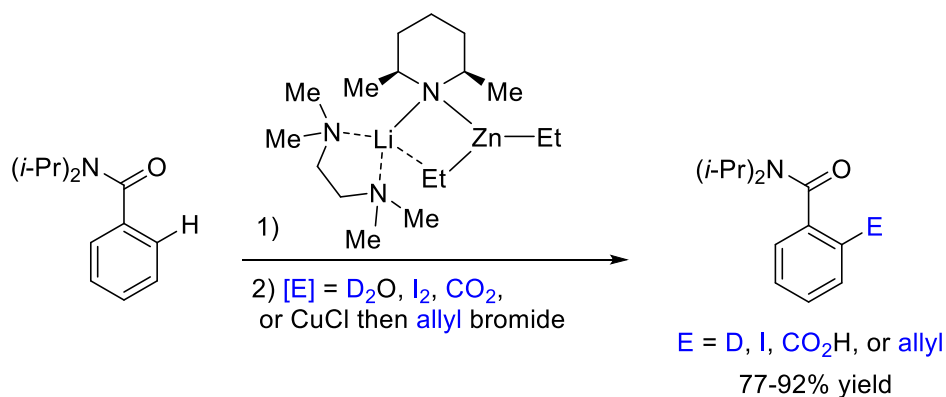
A dimethyl version of the zincate base (**9**) was also synthesized and found more prone to elimination to form benzyne (Scheme 25).^{13, 25c} Therefore, **9** was utilized for *ortho*-zincation and elimination of bromide or triflate as a leaving group; the benzyne intermediate could be trapped, such as with a diene electrophile.



Scheme 25: Generation of benzyne with Li[ZnMe₂TMP] by elimination

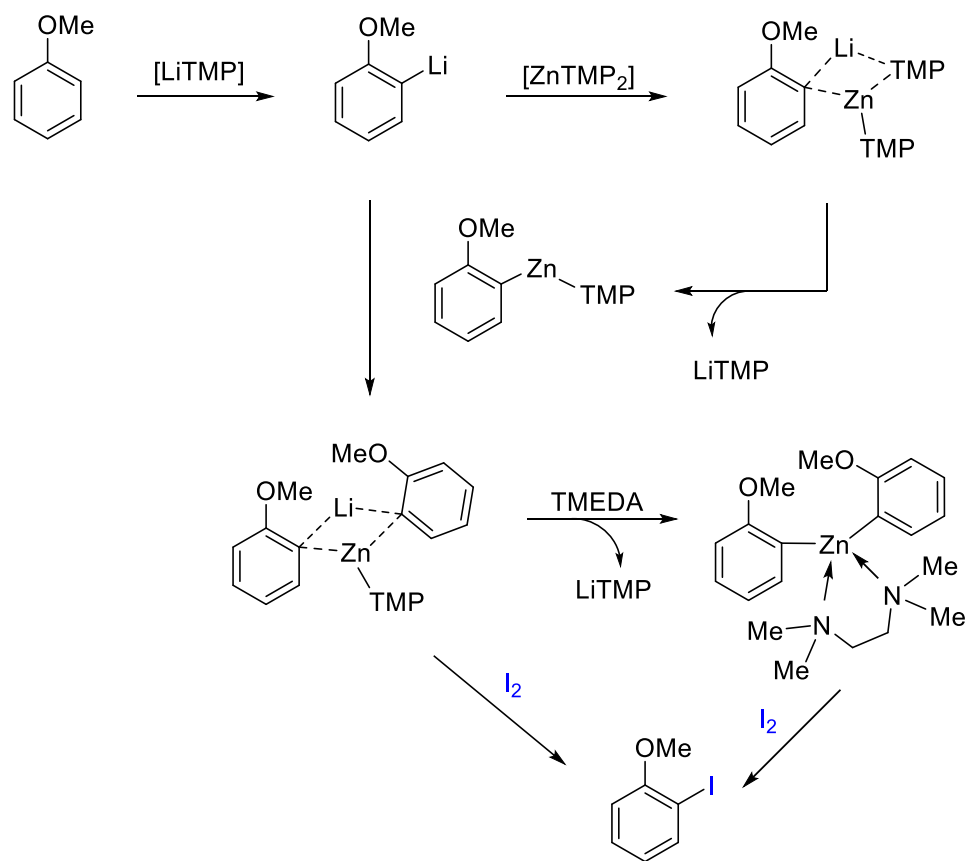
As an alternative to TMP, *cis*-DMP has been used in the synthesis of various lithium dialkylzincate bases for the metallation of *N,N*-diisopropylbenzamide. The base Li[ZnEt₂(*cis*-DMP)]•TMEDA was found most efficient for zincation and functionalization

was performed by deuteration, iodination, carbonylation, or copper-mediated allylation for this one substrate (Scheme 26).³⁵



Scheme 26: *cis*-DMP as an alternative amide base for lithium zincate functionalization

Additionally, mixed lithium amide zinc salt combinations have been studied for *ortho*-metalation. For example, Li[Zn(TMP)₃]•2LiCl•TMEDA (**11**), which was synthesized from a 3:1 ratio of LiTMP to ZnCl₂•TMEDA, could give improved *ortho*-metalation of various heterocycles and anisole in comparison to LiTMP or ZnTMP₂ bases alone.^{15b, 36} Mechanistic studies have shown that LiTMP and the LiCl released from the transmetalation and “salt elimination” reaction are the active species for metalation and the ZnTMP₂ is just a spectator (Scheme 27).^{15c}



Scheme 27: Proposed mechanism of metalation of anisole with lithium tri-amide zincate

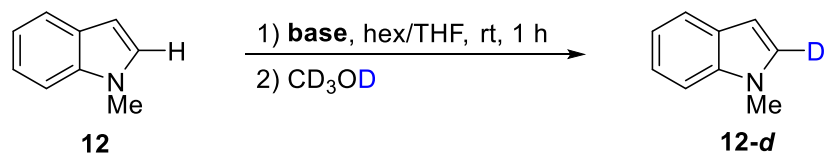
Lithium amide zincate bases show promise as useful reagents for deprotonative zincation, and their composition and deprotonation ability and scope are studied in this chapter.

2.2 Results and Discussion

2.2.1 Deprotonative zincation of arenes and heteroarenes with lithium diethyl zincate bases

2.2.1.1 Deprotonation studies and optimization of base stoichiometry of Li[ZnEt₂TMP]

Our group had previously studied neutral ZnTMP₂ (1) and ZnTMPCl•LiCl (3) for copper-catalyzed electrophilic amination^{20-21, 30-31} and cross coupling with iodonium salts^{18, 28}; however, the deprotonation abilities of those bases gave substrate limitations. Due to our interest in expanding the scope of such transformations involving C–H zincation to include less acidic and more unactivated arenes and heteroarenes, we examined the utility of previously reported lithium zincate base Li[ZnEt₂TMP] (8). We selected this base over the more extensively studied Li[Zn(*t*-Bu)₂TMP] (6) because its synthesis is more facile; commercially available ZnEt₂ can be used instead of Zn(*t*-Bu)₂ which must be synthesized and isolated from pyrophoric reagents. We were pleased to find that Li[ZnEt₂TMP] was able to metallate *N*-methylindole, a valuable substrate which could not be accessed with the neutral base ZnTMPCl•LiCl (Table 1). Metallation efficiency of heterocyclic compounds was determined by deuteration using CD₃OD to quench the zincate species, and deuterium incorporation was determined by ¹H NMR. Interestingly, the zincate base by itself only gave moderate deuteration of **12-d** (entry 2), but when 10 mol % LiTMP was added excellent deuteration was observed (entry 3). Therefore, for subsequent studies the base was prepared with 10 mol % excess LiTMP relative to ZnEt₂ (entry 4).

Table 1: Optimization of base composition for the deuteration of *N*-methylindole.^a

entry	base	12-d ^b (%)
1	ZnTMPCl•LiCl (1.5 equiv)	0
2	Li[ZnEt ₂ TMP] (1.0 equiv)	43
3	Li[ZnEt ₂ TMP] (1.0 equiv) + LiTMP (0.1 equiv)	89
4	LiTMP _{0.1} •Li[ZnEt ₂ TMP] (1.0 equiv)	89 ^c

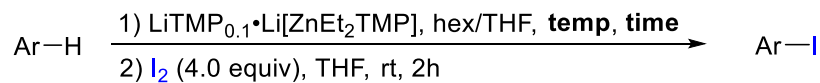
Work completed by Charles Hendrick. ^a Reactions run on 0.2 mmol scale in THF. ^b Yields determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard.

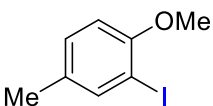
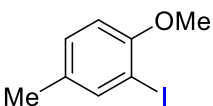
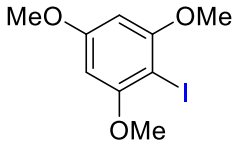
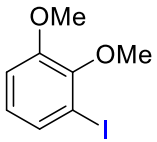
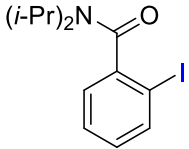
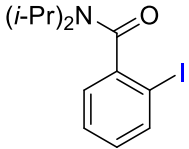
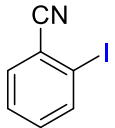
^c Base synthesized with 10 mol % excess LiTMP relative to ZnEt₂.

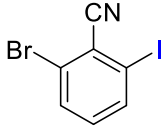
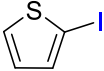
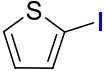
For aryl and some heteroaryl substrates, iodination was also used as a method for determining metalation efficiency and regioselectivity, as the products are useful synthetic intermediates. Excitingly, metalation and iodination could be observed *ortho* to methoxy groups for electron-rich substrates such as 4-methylanisole (**13**), however, excess base and longer reaction times were necessary for improved metalation (Table 2, entries 1-5). This trend held true for other electron rich methoxy-directed substrates such as **14** and **15**. The strongly coordinating diisopropylamide directing group gave efficient metalation at room temperature with 1.0 equivalent of base for 1 h (entry 8). Substrates with a strongly-coordinating and electron-withdrawing nitrile group only required 15 min for good deprotonation at room temperature (entries 10 and 12). Thiophene was able

to be deprotonated without dimetallation when only 1.0 equivalent of base was used with a reaction time limited to 1 h at room temperature (entries 13-15).

Table 2: Optimization of deprotonation conditions of aryl and heteroaryl substrates with Li[ZnEt₂TMP] by iodination.^a



entry	product	base (equiv)	temp (°C)	time (h)	yield ^b (%)
1		1.0	rt	14	18
2		1.0	60	3	35
3		1.0	60	14	34
4	13	2.0	60	3	64
5	13	2.0	70	3	70 (66)
6		2.0	70	3	67 (71)
7		2.0	70	3	60 (64)
8		1.0	rt	1	99 (91)
9		1.0	rt	3	90
10		1.0	rt	0.25	97 (72)
11	17	1.0	rt	1	60

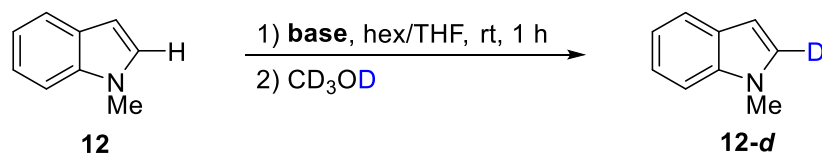
12		1.0	rt	0.25	91 (84)
13		1.0	rt	1	56 (63)
14		1.0	50	1	80 ^c
15	19	2.0	50	1	14 ^c

^a Reactions run on 0.2 mmol scale. ^b Yield determined by ¹H NMR spectroscopy with CH₂Br₂ used as quantitative internal standard. Isolated yield on a 3.0 mmol scale in parentheses. The optimal condition for each class of substrate is in bold. ^c Inseparable diiodination observed as major byproduct.

2.2.1.2 The development of novel Li[ZnEt₂NCy₂] and deprotonation studies of aryl and heteroaryl C–H bonds

After demonstrating that Li[ZnEt₂TMP] (**8**) can deprotonate a wide scope of non-activated arenes and heteroarenes, the composition of lithium zincate bases was further explored in relation to zincation efficiency. As TMP is somewhat expensive as a stoichiometric reagent, other sterically hindered and poorly nucleophilic amines were examined for a more economical alternative. Dicyclohexylamine³⁷ and diisopropylamine¹⁴ were used for the preparation of amidodialkylzincate bases Li[ZnEt₂NCy₂] and Li[ZnEt₂N(*i*-Pr)₂] (**10**), respectively. Lithium zincate bases were synthesized with 10 mol % excess lithium amide relative to diethylzinc, as was previously shown to give most efficient and consistent zincation. In the initial evaluation for their metalation efficacy of indole, Li[ZnEt₂NCy₂] showed better deuteration than Li[ZnEt₂N(*i*-Pr)₂] and only slightly less zincation than the originally studied TMP base (Table 3).

Table 3: Lithium amide diethyl zincate bases for the deuteration of *N*-methyl indole.^a

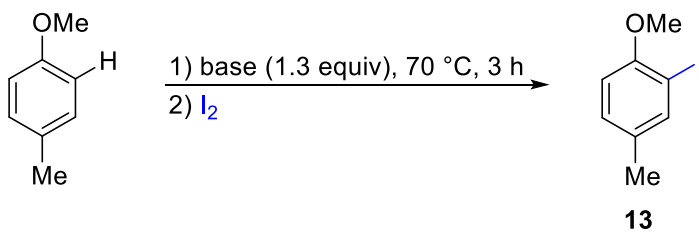


entry	base	12- <i>d</i> ^b (%)
1	Li[ZnEt ₂ TMP]	90
2	Li[ZnEt ₂ NCy ₂]	79
3	Li[ZnEt ₂ N(<i>i</i> -Pr) ₂]	66

^a Reactions run on a 0.2 mmol scale in THF with zincate bases prepared with lithium amide in 10 mol % excess relative to ZnEt₂. ^b Yield determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard.

For the zincation of less acidic 4-methylanisole, Li[ZnEt₂NCy₂] performed slightly better than the other zincate bases, giving a moderate yield of iodinated **13** (Table 4). Deuteration of indole confirmed that slight excess of lithium amide was necessary relative to diethylzinc to achieve good zincation, in the same trend that was observed with the Li[ZnEt₂TMP] base (Table 5).

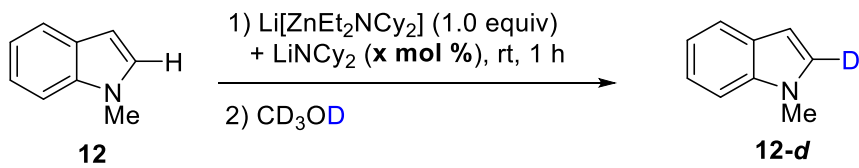
Table 4: Lithium amide diethyl zincate bases for the iodination of 4-methylanisole.^a



entry	base	13 ^b (%)
1	Li[ZnEt ₂ TMP]	51
2	Li[ZnEt ₂ NCy ₂]	56
3	Li[ZnEt ₂ N(<i>i</i> -Pr) ₂]	29

^a Reactions run on a 0.2 mmol scale in THF with zincate bases prepared with lithium amide in 10 mol % excess relative to ZnEt₂. ^b Isolated yields.

Table 5: Optimization of stoichiometry of Li[ZnEt₂NCy₂] for deuteration of *N*-methylindole.^a

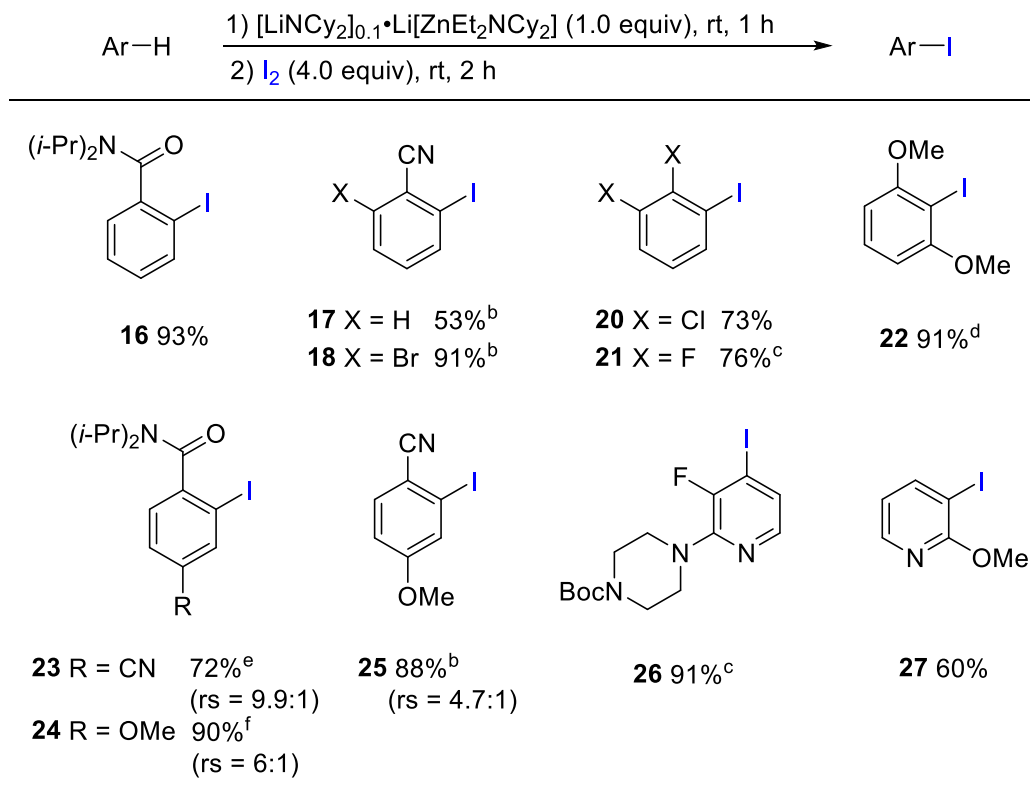


entry	LiNCy ₂ (mol %)	12- <i>d</i> ^b (%)
1	0	42
2	5	68
3	10	79
4	15	82
5	20	78

^a Reactions run on 0.2 mmol scale in THF. ^b Yields determined by ¹H NMR spectroscopy with CH₂Br₂ used as quantitative internal standard.

Encouraged by these results, $\text{Li}[\text{ZnEt}_2\text{NCy}_2]$ was examined for its metallation efficiency and selectivity for various arenes and heteroarenes by iodination. A wide variety of common Lewis basic moieties could direct zincation, including amide, nitrile, chloride, fluoride, and methoxy groups (Table 6). Most substrates could be smoothly deprotonated at room temperature after 1 h with 1.0 equivalent of base (standard zincation conditions). For nitrile directed substrates (compounds **17**, **18**, **23**), the zincative iodination was found more effective with 0.67 equivalents of base for a shorter time (15 min), than the standard zincation conditions, likely due to the instability of zincate intermediate. More electron-rich substrates, such as anisole, prefer longer deprotonation times with slightly elevated temperature for metalation (compounds **13** and **22**). Basic tertiary amines were well tolerated in **26** where exclusive metalation was observed at the 4-position of the pyridine and *ortho* to the fluorine atom.

Table 6: Iodination of arenes by zincation with Li[ZnEt₂NCy₂].^a



^a Isolated yields for reactions run on a 0.2 mmol scale in THF. ^b Reaction run with 0.67 equiv base and 15 min deprotonation. ^c Reaction run on 1.0 mmol scale. ^d Deprotonation run with 1.3 equiv of base for 3 h at 70 °C. ^e Deprotonation run with 0.67 equiv of base for 15 min at 0 °C. ^f Deprotonation run with 1.3 equiv of base for 3 h. rs = regioselectivity

To further investigate the regioselectivity of zincation, the iodination of **23** and **25** were studied under different deprotonation conditions. For 4-cyano-*N,N*-diisopropylbenzamide (Table 7), standard deprotonation conditions with 1.0 equiv of base at room temperature for 1 h (entry 2) gave a mixture of regioisomers with the iodine *ortho* to nitrile (**23'**) as the major product. Interestingly, some diiodinated product (**23''**) was observed, suggesting that some dizincated intermediate exists under these

conditions. The ratio of products was similar when more base was added and longer deprotonation times were tested (entry 1). When less base (0.67 equiv) was used, the diiodination disappeared, but full conversion was still observed. Shorter deprotonation times and/or lower deprotonation temperatures gave a switch in the regioselectivity and iodination was observed mostly *ortho* to the amide (**23**) with good regioselectivity and yield obtained at room temperature for 5 min or 0 °C for 15 min (entries 3 and 5). Therefore, **23'** appears to be the thermodynamically favorable product due to stabilization of nitrile group while **23** appears to be the kinetically favorable product, due to strong coordination of the amide directing group.

Table 7: Optimization of deprotonation condition and regioselectivity for 4-cyano-*N,N*-diisopropylbenzamide.^a

entry	base (equiv)	temp	time	23	23'	23''	rs (22a : 22a')
1	1.3	rt	3 h	35	57	10	1 : 1.6
2	1.0	rt	1 h	36	54	11	1 : 1.5
3	0.67	rt	5 min	90	10	--	9 : 1
4	0.67	rt	15 min	82	18	--	4.7 : 1
5	0.67	0	15 min	70	7	--	9.9 : 1 (72%)
6	0.67	-78	15 min	32	4	--	7.9 : 1

^a Reactions run on a 0.2 mmol scale following indicated deprotonation time and temperature. Yields determined by ¹H NMR with CH₂Br₂ as a quantitative internal standard. Isolated yield shown in parenthesis. rs = regioselectivity

For 4-methoxybenzonitrile, iodination occurs primarily *ortho* to the nitrile group (**25**) when the deprotonation is run at room temperature or 0 °C (Table 8, entries 1 and 2). However, when the deprotonation is kept at -78 °C, exclusive iodination *ortho* to the methoxy (**25'**) is observed, albeit in low conversion (entry 3). When the deprotonation is allowed to warm to 0 °C for an hour after the same 15 min at -78 °C, the regioselectivity reverts to **25** as the major regioisomer (entry 5). This suggests that deprotonation *ortho* to the methoxy is more kinetically favorable, but the intermediate with zincation *ortho* to the nitrile is more thermodynamically stabilized. The inversion of regioselectivity indicates that the zincation step is reversible, and an equilibrium may exist.

Table 8: Optimization of deprotonation conditions and study of regioselectivity for 4-methoxybenzonitrile.^a

entry	temp (°C)	25	25'	sm	rs (25 : 25')
1	rt	82	18	--	4.7 : 1 (88%)
2	0	82	18	--	4.7 : 1
3	-78	0	34	68	--
4 ^b	-78 to 0	13	62	31	1: 4.8
5 ^c	-78 to 0	81	18	--	5.1:1

^a Reactions run on a 0.2 mmol scale at indicated temperature. Yields determined by ¹H NMR with CH₂Br₂ as a quantitative internal standard. Isolated yield shown in parenthesis.

^b Deprotonation run at -78 °C for 15 min, then warmed up to 0 °C for an additional 15 min.

^c Deprotonation run at -78 °C for 15 min, then warmed up to 0 °C for an additional 1 h. sm = starting material. rs = regioselectivity.

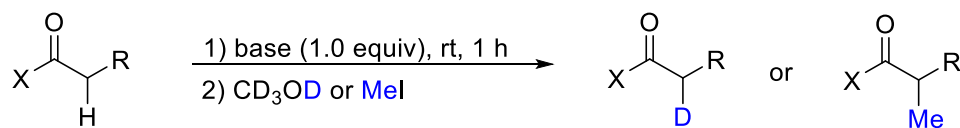
2.2.2 Deprotonative zincation of sp^3 C–H bonds

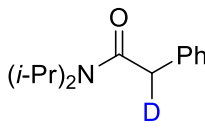
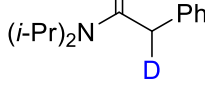
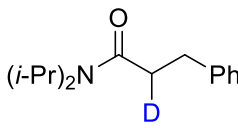
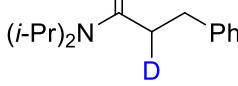
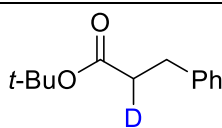
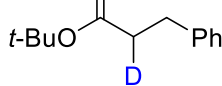
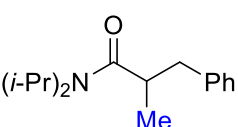
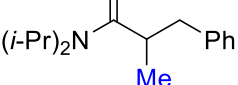
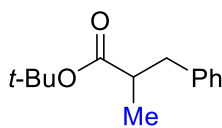
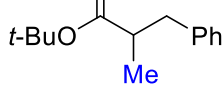
In addition to sp^2 C–H bonds of arenes and heteroarenes, the functionalization of sp^3 C–H bonds is highly desirable. Deprotonative zincation is an attractive strategy for this type of transformation and previous work has utilized neutral bases $ZnTMP_2$ (**1**)^{5, 21} and $ZnTMPCl \cdot LiCl$ (**3**)^{16, 18}; however, a limited scope of substrates and transformations have been reported. As lithium zincate bases had not yet been used for the functionalization of sp^3 C–H bonds, we were interested in investigating if these bases could expand the scope of substrates to be functionalized by deprotonative zincation. In particular, we were interested in examining the α -zincation of substituted amides and esters which could not be functionalized with $ZnTMP_2$ (**1**) in our previous studies.

Toward this goal, the deprotonation efficiency of various substituted esters and amides with neutral and lithium zincate bases was determined by either deuteration or methylation with methyl iodide (Table 9). The neutral $ZnTMPCl \cdot LiCl$ (**3**) only gave significant deprotonation for the more acidic benzyl amide substrate (entry 1) but still only about 63% deuteration whereas amides and esters with alkyl substituents did not give any significant deprotonation (entry 4 & 7). Lithium zincate base $Li[ZnEt_2NCy_2]$ gave excellent deprotonation efficiency of all amides and esters tested (entry 2, 5 & 8). Additionally, zinc-free lithium dicyclohexylamine ($LiNCy_2$) was also capable of full metallation (entry 3, 6 & 13). Monobasic and dibasic neutral dicyclohexylamine zinc bases gave little methylation (entries 9 & 10), however a tribasic lithium dicyclohexylamine

zincate base synthesized with a 3:1 ratio of LiNCy₂ to ZnCl₂ gave quantitative metalation (entry 11). Therefore, lithium containing zincate bases seem to have an improved scope and access to α -zincation, probably due to lithium coordination.

Table 9: Deprotonation study of amides and esters with lithium and zinc bases.^a

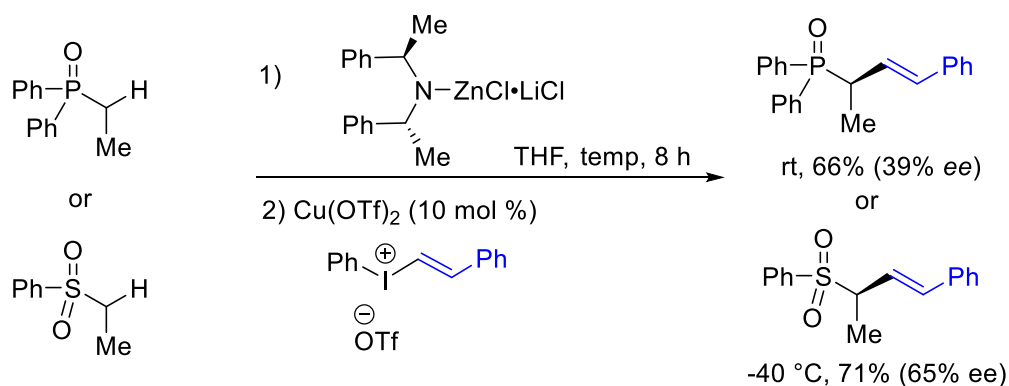


entry	product	base	yield ^b (%)
1		ZnTMPCLi•LiCl	63
2		Li[ZnEt ₂ NCy ₂]	100
3	28-d	LiNCy ₂	100
4		ZnTMPCLi•LiCl	0
5		Li[ZnEt ₂ NCy ₂]	100
6	29-d	LiNCy ₂	100
7		ZnTMPCLi•LiCl	0
8		Li[ZnEt ₂ NCy ₂]	100
	30-d		
9		Zn(NCy ₂)Cl•LiCl	0
10		Zn(NCy ₂) ₂ •2LiCl	30
11		Li[Zn(NCy ₂) ₃]•2LiCl	100 (96)
12	31	Li[ZnEt ₂ NCy ₂]	100 (96)
13		LiNCy ₂	100
14		Li[ZnMe ₂ NCy ₂]	100
15		Li[Zn(NCy ₂) ₃]•2LiCl	71 (21)
16	32	LiNCy ₂	71

^a Reactions run on a 0.2 mmol scale in THF with 0.2 mL CD₃OD or 8.0 equiv of iodomethane. ^b Yield determined by ¹H NMR with CH₂Br₂ used as quantitative internal standard. Isolated yield in parentheses.

2.2.3 Studies of chiral zincate base development towards enantioselective zincation

Enantioselective C–H functionalization is a highly desirable transformation. If the organozinc intermediate formed from zincation is configurationally stable and the stereochemistry is retained in the subsequent transformation, enantioselective zincation would be needed for enantioselective reaction development. Previously, a neutral zinc base made from a chiral amine, was able to give some enantioselectivity for the copper-catalyzed α -alkenylation of a phosphine oxide and sulfone (Scheme 28).¹⁸ Therefore, we were interested in testing the enantioselectivity of deprotonation for chiral lithium zincate bases.

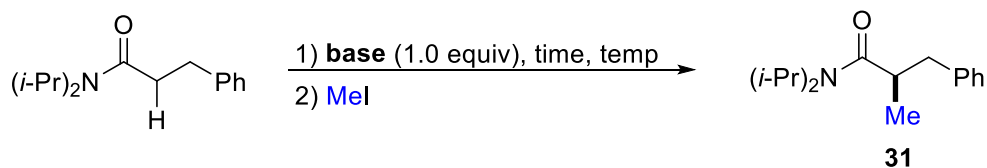


Scheme 28: Enantioselective alkenylation with chiral zinc base

Various chiral lithium zincate bases were tested using methylation with methyl iodide as measure of the enantioselectivity of metalation (Table 10). Chiral bases with diethyl zinc gave good metalation (entries 1-3), but very little enantioselectivity. A different version of zincate base was also tested, formed from a chiral lithium amide and bis diphenylamine zinc reagent made with lithium chloride. This base did not give any

deprotonation at room temperature or lower (entries 4-6). Finally, a tribasic lithium zincate was synthesized with 3:1 ratio of chiral lithium amide to zinc chloride, giving good methylation but little enantioselectivity even at low temperatures (entries 7-9). From these results, it appears that lithium zincate bases made from chiral amides are not able to provide enantioselective zincation as studied by methylation. It is possible that the *O*-enolate is directly formed over the *C*-enolate, or these two forms are in rapid equilibrium making stereocontrol impossible.

Table 10: Screen of chiral lithium zincate bases for enantioselective methylation.



entry	base	temp (°C)	time	yield ^b (%)	ee ^c (%)
1		rt	1 h	41	3.6
2		rt	1 h	95	4.0
3		rt	18 h	100	2.2
4		rt	1 h	0	--
5		0	1 h	0	--
6		-78	1 h	0	--
7		rt	1 h	94	3.0
8		0	1 h	82	3.8
9		-78	1 h	79	4.0

^a Reactions run on a 0.2 mmol scale in THF with 8.0 equiv of iodomethane. ^b Isolated yield given. ^c Enantioselectivity determined by chiral HPLC analysis.

2.3 Supplemental Information

2.3.1 General Information

General Procedures. Glassware was dried either by propane torch or for at least 12 h in an oven at 140 °C before cooling in a desiccator over Drierite. Optimization and condition

screening reactions were performed under N₂ using standard Schlenk techniques in 8-mL microwave tubes sealed with PTFE crimp-top caps. Reactions were stirred magnetically using Teflon-coated, magnetic stir bars. Thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with 0.25 mm of 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or exposure to KMnO₄ or vanillin stain. Organic solutions were concentrated in vacuo using a rotary evaporator. Column chromatography was performed with silica gel (60 Å, standard grade). Medium-pressure chromatography was performed using a Teledyne ISCO Combiflash system using Redisep Gold column cartridges.

Materials. All commercially available reagents were purchased in >98% purity and used as received unless otherwise noted. Anhydrous THF was obtained from an Innovative Technologies solvent purification system. 2,2,6,6-Tetramethylpiperidine and dicyclohexylamine were dried over CaH₂ and fractionally distilled under reduced pressure and stored under N₂. *n*-Butyl lithium was purchased as a 2.5 M solution in hexanes from Sigma-Aldrich and titrated prior to use with *N*-benzylbenzamide as an indicator.³⁸ The solution of diethylzinc (1.0 M in hexanes) was purchased from Sigma Aldrich and titrated with iodine in THF at 0 °C prior to use.

Instrumentation. Nuclear magnetic resonance spectra were recorded at ambient temperature on 400 MHz or 500 MHz spectrometers. All values for proton chemical shifts

are reported in parts per million (δ) and are referenced to the residual protium in CDCl_3 (δ 7.26). All values for carbon chemical shifts are reported in parts per million (δ) and are referenced to the carbon resonances in CDCl_3 (δ 77.0). All values for fluorine chemical shifts are reported in parts per million and are referenced to the fluorine resonance in CFCl_3 (δ 0.0) as an internal standard. NMR data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad), coupling constant (Hz), and integration. Infrared spectroscopic data are reported in wavenumbers (cm^{-1}) with selected peaks shown. High-resolution mass spectra were obtained using a liquid chromatography-electrospray ionization and time-of-flight mass spectrometer. Enantiomeric excesses were determined by chiral High Performance Liquid Chromatography (HPLC) analysis.

2.3.2 Experimental procedures

Standard Procedure for Lithium Zincate Base $\text{Li}(\text{NR}_2)_{0.1} \cdot \text{Li}[\text{ZnEt}_2(\text{NR}_2)]$ Synthesis. The appropriate amine (3.3 mmol, 1.1 equiv) in a 25-mL RBF with stir bar was cooled to -78 °C by dry ice/acetone bath under N_2 and stirred until the amine was frozen. To the flask, was added dropwise *n*-butyl lithium (2.5 M solution in hexanes, 3.3 mmol, 1.1 equiv) at -78 °C and the mixture was stirred vigorously for 10 min. Diethylzinc (3.0 mL, 1.0 M solution in hexanes, 3.0 mmol, 1.0 equiv) was added dropwise. The resulting white slurry was allowed to stir at -78 °C for 5 min and then warmed up to room temperature followed by the addition of anhydrous THF (3 mL) and titration.

Standard Procedure for Tribasic Lithium Zincate $\text{Li}[\text{Zn}(\text{NR}_2)_3] \cdot 2\text{LiCl}$ Synthesis. The appropriate amine (6.0 mmol, 3.0 equiv) in a 25-mL round bottom flask with a stir bar was cooled to $-78\text{ }^\circ\text{C}$ by dry ice/acetone bath under N_2 and stirred until the amine was frozen. To the flask, was added dropwise *n*-butyl lithium (2.4 mL, 2.5 M solution in hexanes, 6.0 mmol, 3.0 equiv) at $-78\text{ }^\circ\text{C}$ and the mixture was stirred vigorously for 15 min. In a separate pear flask was added ZnCl_2 (272.6 mg, 2.0 mmol, 1.0 equiv) which was flame dried under vacuum, cooled under N_2 , and dissolved in THF (1.0 mL). The ZnCl_2 solution was added dropwise via syringe to the lithium amide at $-78\text{ }^\circ\text{C}$. The resulting white slurry was allowed to stir at $-78\text{ }^\circ\text{C}$ for 5 min and then warmed up to room temperature and titrated before use.

Standard titration. A 15-mL round bottom flask was charged with a stir bar, benzoic acid (approx. 60 mg) and 4-(phenylazo)diphenylamine (approx. 2 mg). The flask was placed under N_2 via sequential vacuum purge/ N_2 backfill (3 times) followed by the addition of THF (1.0 mL). The flask was cooled down to $0\text{ }^\circ\text{C}$ by ice/water bath and was added dropwise the solution of base until the endpoint of the presumed tribasic zinc complex (i.e., 3.1 equivalents of basic moieties per mole of complex) was observed, as indicated by a persistent dark orange-red color change, providing the concentration of active base.

General Protocol for Optimization of Zincation. To a solution of the arene substrate (0.2 mmol) in THF was added freshly prepared and titrated base (0.20 mmol, 1.0 equiv unless otherwise indicated) to a final concentration of 0.2M. The resulting mixture was stirred at

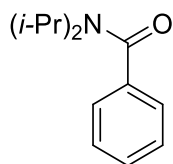
room temperature for 1 h (unless otherwise noted) before electrophile addition. **For deuteration:** To the reaction was added d_4 -methanol (0.2 mL) in a single portion and the resulting mixture stirred at room temperature for 2 h. The reaction was then filtered through a plug of silica (approx. 3 mL) and washed with ethyl acetate (approx. 10 mL). The filtrate was concentrated by rotary evaporation. Crude yields were obtained by ^1H NMR analysis using dibromomethane (7.0 μL , 0.1 mmol) as a quantitative internal standard. **For iodination:** To a separate pear-shape flask was added iodine (0.203 g, 0.8 mmol, 4 equiv) before flushing with N_2 for 15 min and dissolving in THF (1.0 mL). This solution was then added dropwise, slowly, to the room temperature reaction mixture before stirring for at least 2 h. The crude reaction was then diluted in ethyl acetate (15 mL), washed with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) followed by brine (10 mL), dried over Na_2SO_4 , filtered, then concentrated by rotary evaporation. Purification was performed by silica gel flash column chromatography.

For methylation: To the room temperature reaction was added iodomethane (75 μL , 1.6 mmol, 8.0 equiv). After stirring for 2 h, the reaction was then filtered through a plug of silica and washed with ethyl acetate (approx. 10 mL). The filtrate was concentrated by rotary evaporation and the crude was purified by silica gel flash column chromatography.

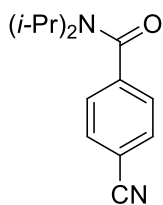
Procedure for determining enantioselectivity of methylation of 31. Analysis was performed on a Shimadzu Prominence HPLC with a Phenomenex Lux Cellulose 1 column

(5 μ L), *i*-PrOH/hexanes =10/90, 0.5 mL/min, λ = 220 nm, retention time: 7.8 minutes (minor) and 8.8 minutes (major).

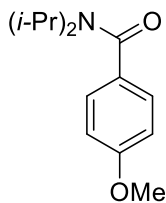
2.3.3 Preparation of starting materials



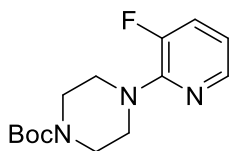
***N,N*-Diisopropylbenzamide.** Precursor for **16** prepared according to literature procedure.³⁹



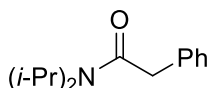
4-Cyano-*N,N*-diisopropylbenzamide. Precursor for **23** prepared following literature procedure.⁴⁰



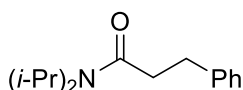
***N,N*-Diisopropyl-4-methoxybenzamide.** Precursor for **24** prepared following literature procedure.⁴⁰



tert-Butyl-4-(3-fluoropyridin-2-yl)piperazine-1-carboxylate. Precursor for **26** prepared according to literature procedure.³¹

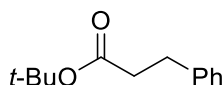


N,N-Diisopropyl-2-phenylacetamide (28). Prepared following literature procedure.⁴¹



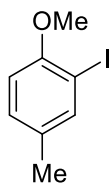
N,N-Diisopropyl-3-phenylpropanamide (29). To 3-phenylpropionic acid (3.00 g, 20.0 mmol, 1.0 equiv) in DCM (100 mL) with DMF (4 drops) was added oxalyl chloride (1.86 mL, 22.0 mmol, 1.1 equiv) dropwise via syringe. Upon stirring at room temperature for 3 h, the reaction was cooled to 0 °C, followed by dropwise addition of diisopropylamine (3.36 mL, 24.0 mmol, 1.2 equiv) and triethylamine (3.62 mL, 26.0 mmol, 1.3 equiv). The reaction was stirred at 0 °C for 2 h, then room temperature for 15 h and was worked up by filtration through a plug of silica (50 mL) and rinsing with ethyl acetate (100 mL). Following concentration by rotary evaporation, the crude was redissolved in ethyl acetate (75 mL), washed with saturated aqueous sodium bicarbonate (2 x 75mL) and brine (75 mL), dried over sodium sulfate, filtered and concentrated. Purification by medium pressure chromatography (hexanes to 30% ethyl acetate–hexanes) gave **28** as a pale yellow

oil (4.29 g, 18.4 mmol, 92% yield); $R_f = 0.45$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3): 7.31–7.26 (m, 2H), 7.24–7.17 (m, 3H), 3.92 (quint, $J = 6.8$ Hz, 1H), 3.58–3.39 (br s, 1H), 2.98–2.92 (m, 2H), 2.61–2.54 (m, 2H), 1.39 (d, $J = 6.8$ Hz, 6H), 1.13 (d, $J = 6.7$ Hz, 6H). $^1\text{H NMR}$ matched literature spectra.⁴²

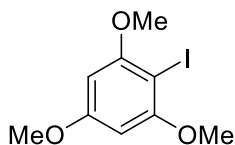


tert-Butyl 3-phenylpropanoate (30). Prepared following literature procedure.⁴³

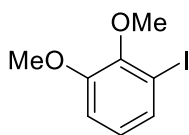
2.3.4 Characterization of compounds



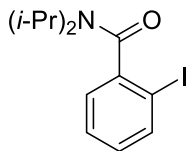
2-Iodo-4-methylanisole (13). Prepared according to standard iodination procedure with 1.3 equiv of $[\text{LiNCy}_2]_{0.1} \cdot \text{Li}[\text{ZnEt}_2\text{NCy}_2]$ at 70 °C for 3 h for the deprotonation step. Purification by medium pressure chromatography (hexanes to 5% ethyl acetate–hexanes) gave **13** a yellow oil (27.9 mg, 0.112 mmol, 56%); $R_f = 0.35$ (5% ethyl acetate–hexanes) $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.60 (d, $J = 2.1$ Hz, 1H), 7.10 (dd, $J = 8.6, 2.1$ Hz, 1H), 6.72 (d, $J = 8.3$ Hz, 1H), 3.85 (s, 3H), 2.26 (s, 3H). $^1\text{H NMR}$ matched literature spectra.⁴⁴



2-Iodo-1,3,5-trimethoxybenzene (14). Prepared according to standard iodination procedure on a 3.0 mmol scale with 2.0 equiv of $\text{LiTMP}_{0.1} \bullet \text{Li}[\text{ZnEt}_2\text{TMP}]$ at 70 °C for 3 h for the deprotonation step. Purification by flash chromatography (50% dichloromethane–hexanes) gave **14** as a yellow solid (0.630 g, 2.14 mmol, 71%). ^1H NMR (400 MHz, CDCl_3) δ 6.14 (s, 2H), 3.87 (s, 6H), 3.83 (s, 3H). ^1H NMR matched literature spectra.⁴⁵

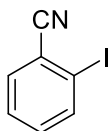


1-Iodo-2,3-dimethoxybenzene (15). Prepared according to standard iodination procedure on a 3.0 mmol scale with 2.0 equiv of $\text{LiTMP}_{0.1} \bullet \text{Li}[\text{ZnEt}_2\text{TMP}]$ at 70 °C for 3 h for the deprotonation step. Purification by flash chromatography (50% dichloromethane–hexanes) gave **15** as a peach solid (0.5073 g, 1.92 mmol, 64%). ^1H NMR (400 MHz, CDCl_3) δ 7.34 (d, $J = 7.9$ Hz, 1H), 6.88 (d, $J = 8.2$ Hz, 1H), 6.80 (t, $J = 8.2$ Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H). ^1H NMR matched literature spectra.⁴⁶

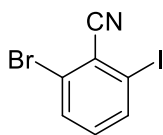


2-Iodo-N,N-diisopropylbenzamide (16). Prepared according to standard iodination procedure with 1.0 equiv of $[\text{LiNCy}_2]_{0.1} \bullet \text{Li}[\text{ZnEt}_2\text{NCy}_2]$. Purification by flash column

chromatography (20% ethyl acetate–hexanes) gave **16** as a as an off-white solid (61.7 mg, 0.186 mmol, 93%); $R_f = 0.41$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.80 (d, $J = 8.0$ Hz, 1H), 7.34 (td, $J = 7.5, 1.1$ Hz, 1H), 7.13 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.01 (td, $J = 7.6, 7.4, 1.6$ Hz, 1H), 3.57 (dq, $J = 13.7, 6.9$ Hz, 1H), 3.50 (dq, $J = 13.4, 6.7$ Hz, 1H), 1.59 (d, $J = 6.8$ Hz, 3H), 1.55 (d, $J = 6.9$ Hz, 3H), 1.26 (d, $J = 6.7$ Hz, 3H), 1.05 (d, $J = 6.7$ Hz, 3H). $^1\text{H NMR}$ matched literature spectra.⁴⁷

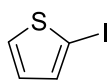


2-Iodobenzonitrile (17). Prepared according to standard iodination procedure with 0.67 equiv of $[\text{LiNCy}_2]_{0.1} \bullet \text{Li}[\text{ZnEt}_2\text{NCy}_2]$ for 15 mins on a 3.0 mmol scale for the deprotonation step. Purification by medium pressure chromatography (hexanes to 5% ethyl acetate–hexanes) gave **17** as an off-white solid (361.7 mg, 1.58 mmol, 53%); $R_f = 0.33$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.92 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.62 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.46 (td, $J = 7.8, 1.2$ Hz, 1H), 7.29 (td, $J = 7.8, 1.7$ Hz, 1H). $^1\text{H NMR}$ matched literature spectra.⁴⁸

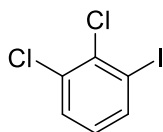


2-Bromo-6-iodobenzonitrile (18). Prepared according to standard iodination procedure with 0.67 equiv of $[\text{LiNCy}_2]_{0.1} \bullet \text{Li}[\text{ZnEt}_2\text{NCy}_2]$ for 15 min for the deprotonation step. Purification by medium pressure chromatography (hexanes to 5% ethyl acetate–hexanes)

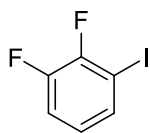
gave **18** as an off-white solid (55.8 mg, 0.181 mmol, 91%); $R_f = 0.35$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.87 (d, $J = 8.0$ Hz, 1H), 7.67 (d, $J = 8.1$ Hz, 1H), 7.12 (t, $J = 8.1$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 138.2, 134.2, 132.5, 126.3, 118.1, 105.0, 99.6; FTIR (thin film): 3073, 2927, 2227, 1541, 1420, 1190, 774 cm^{-1} ; Compound did not ionize by HRMS-ESI; GC-MS (m/z) Calcd for ($\text{C}_7\text{H}_3\text{BrIN}$): 306.9; found: 306.8.



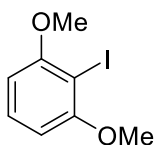
2-Iodothiophene (19). Prepared according to standard iodination procedure on a 3.0 mmol scale with 1.0 equiv of $\text{LiTMP}_{0.1}\cdot\text{Li}[\text{ZnEt}_2\text{TMP}]$ for 30 mins for the deprotonation step. Purification by flash column chromatography (50% dichloromethane–hexanes) gave **19** as a gold liquid (0.400 g, 1.90 mmol, 64%); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.36 (dd, $J = 5.4, 1.2$ Hz, 1H), 7.25 (dd, $J = 3.6, 1.2$ Hz, 1H), 6.81 (dd, $J = 5.4, 3.6$ Hz, 1H). $^1\text{H NMR}$ matched literature spectra.^{15b}



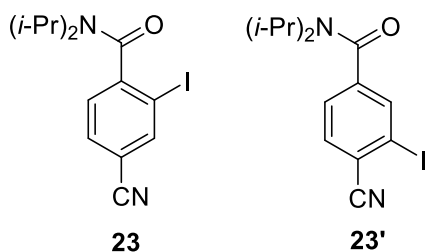
1,2-Dichloro-3-iodobenzene (20). Prepared according to standard iodination procedure with 1.0 equiv of $[\text{LiNCy}_2]_{0.1}\cdot\text{Li}[\text{ZnEt}_2\text{NCy}_2]$ at a 0.2 mmol scale and a 3.0 mmol scale. Purification by medium pressure chromatography (hexanes) gave **20** as clear oil (39.5 mg, 73% on 0.2 mmol scale and 603.4 mg, 74% for 3.0 mmol scale); $R_f = 0.78$ (5% ethyl acetate–hexanes) $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.77 (d, $J = 8.0$ Hz, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 6.89 (t, $J = 8.0$ Hz, 1H). $^1\text{H NMR}$ matched literature spectra.⁴⁷



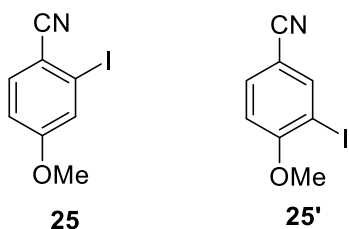
1,2-Difluoro-3-iodobenzene (21). Prepared according to standard iodination procedure with 1.0 equiv of $[\text{LiNCy}_2]_{0.1} \bullet \text{Li}[\text{ZnEt}_2\text{NCy}_2]$ on a 1.0 mmol scale. Purification by medium pressure chromatography (hexanes) gave **21** as clear oil (182.4 mg, 0.76 mmol, 76%); $R_f = 0.75$ (hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.50 (td, $J = 6.4, 1.3$ Hz, 1H), 7.15 (q, $J = 8.3$ Hz, 1H), 6.87 (q, $J = 7.8$ Hz, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 151.2 (dd, $J_{\text{C-F}} = 62.6, 13.9$ Hz), 149.2 (dd, $J_{\text{C-F}} = 68.9, 14.2$ Hz), 133.9 (d, $J_{\text{C-F}} = 4.0$ Hz), 125.8 (m), 117.5 (d, $J_{\text{C-F}} = 17.4$ Hz), 82.4 (d, $J_{\text{C-F}} = 21.5$ Hz); $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -116.8 (m), -133.9 (m); FTIR (thin film), cm^{-1} 3086, 2930, 22454, 2285, 1922, 1847, 1773, 1588, 1473, 1289, 868, 765; Compound did not ionize by HRMS-ESI; GC-MS (m/z) Calcd for ($\text{C}_6\text{H}_3\text{F}_2\text{I}$): 239.9; found: 240.0.



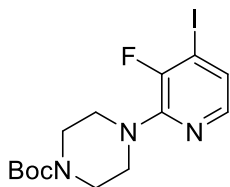
2-Iodo-1,3-dimethoxybenzene (22). Prepared according to standard iodination procedure with 1.3 equiv of $[\text{LiNCy}_2]_{0.1} \bullet \text{Li}[\text{ZnEt}_2\text{NCy}_2]$ at 70 °C for 3 h for the deprotonation step. Purification by medium pressure chromatography (hexanes to 5% ethyl acetate–hexanes) gave **22** as a white solid (48.1 mg, 0.182 mmol, 91%); $R_f = 0.45$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.24 (t, $J = 8.2$ Hz, 1H), 6.49 (d, $J = 8.2$ Hz, 2H), 3.87 (s, 6H). $^1\text{H NMR}$ matched literature spectra.⁴⁷



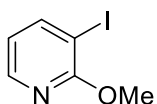
4-Cyano-2-iodo-*N,N*-diisopropylbenzamide (23) and 4-cyano-3-iodo-*N,N*-diisopropylbenzamide (23'). Prepared according to standard iodination procedure with 0.67 equiv of $[\text{LiNCy}_2]_{0.1} \cdot \text{Li}[\text{ZnEt}_2\text{NCy}_2]$ for 15 min at 0 °C for the deprotonation step. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **23** and **23'** as white solid (51.4 mg, 0.144 mmol, 72%) as a 9:1 mixture of regioisomers. **23** was separately isolated by flash column chromatography (dichloromethane to 1% methanol–dichloromethane) as a white solid (49.1 mg, 0.138 mmol, 69%); $R_f = 0.32$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.10 (d, $J = 1.6$ Hz, 1H), 7.66 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.22 (d, $J = 7.8$ Hz, 1H), 3.53 (quin, $J = 6.8$ Hz, 1H), 3.46 (quin, $J = 6.6$ Hz, 1H), 1.58 (d, $J = 6.8$ Hz, 3H), 1.55 (d, $J = 6.8$ Hz, 3H), 1.29 (d, $J = 6.6$ Hz, 3H), 1.08 (d, $J = 6.6$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 168.0, 148.3, 142.4, 131.8, 126.0, 116.5, 113.2, 92.2, 51.3, 46.2, 20.7, 20.6, 20.4, 19.8; FTIR (thin film): 2977, 2929, 2236, 1630, 1437, 1337, 1044 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{14}\text{H}_{18}\text{IN}_2\text{O}]^+$ ($[\text{M}+\text{H}]^+$): 357.0458; found: 357.0457. **23'** was isolated in a mixture of regioisomers with **23** as a white solid (57.6 mg, 0.162 mmol, 81%); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.83 (d, $J = 1.5$ Hz, 1H), 7.62 (d, $J = 8.0$ Hz, 1H), 7.35 (dd, $J = 7.9, 1.6$ Hz, 1H), 3.53 (quin, $J = 6.8$ Hz, 1H), 3.46 (quin, $J = 6.6$ Hz, 1H), 1.58 (d, $J = 6.8$ Hz, 3H), 1.55 (d, $J = 6.8$ Hz, 3H), 1.29 (d, $J = 6.6$ Hz, 3H), 1.08 (d, $J = 6.6$ Hz, 3H).



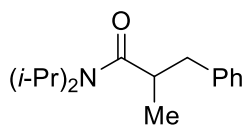
2-Iodo-4-methoxybenzonitrile (25) and 3-iodo-4-methoxybenzonitrile (25'). Prepared according to standard iodination procedure with 1.0 equiv of $[\text{LiNCy}_2]_{0.1} \cdot \text{Li}[\text{ZnEt}_2\text{NCy}_2]$ for 15 min for the deprotonation step. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **25** and **25'** as a 4.7:1 mixture of isomers as a pale yellow solid (45.6 mg, 0.180 mmol, 88%); **25** was isolated by medium pressure chromatography (hexanes to 5% ethyl acetate–hexanes) for a pure sample as a white solid (4.5 mg, 0.017 mmol, 9%) $R_f = 0.29$ (10% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.51 (d, $J = 8.7$ Hz, 1H), 7.41 (d, $J = 2.5$ Hz, 1H), 6.94 (dd, $J = 8.7, 2.5$ Hz, 1H), 3.85 (s, 3H). $^1\text{H NMR}$ matched literature spectra⁵⁰; **25'** was isolated by medium pressure chromatography (hexanes to 5% ethyl acetate–hexanes) for a pure sample as a white solid (4.1 mg, 0.016 mmol, 8%) $R_f = 0.21$ (10% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.05 (d, $J = 2.0$ Hz, 1H), 7.63 (dd, $J = 8.6, 2.0$ Hz, 1H), 6.85 (d, $J = 8.6$ Hz, 1H), 3.95 (s, 3H). $^1\text{H NMR}$ matched literature spectra.⁵¹



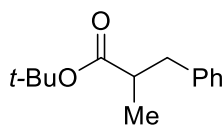
tert-Butyl 4-(3-fluoro-4-iodopyridin-2-yl)piperazine-1-carboxylate (26). Prepared according to standard iodination procedure with 1.0 equiv of $[\text{LiNCy}_2]_{0.1} \bullet \text{Li}[\text{ZnEt}_2\text{NCy}_2]$ on a 1.0 mmol scale. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **26** as an off-white solid (370.2 mg, 91%); $R_f = 0.53$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.61 (d, $J = 5.1$ Hz, 1H), 7.12 (dd, $J = 5.1, 3.6$ Hz, 1H), 3.53 (dd, $J = 6.6, 3.6$ Hz, 4H), 3.43 (dd, $J = 6.6, 3.6$ Hz, 4H), 1.47 (s, 9H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 154.7, 150.8, 149.4 (d, $J_{\text{C-F}} = 8.9$ Hz), 143.1 (d, $J_{\text{C-F}} = 6.8$ Hz), 125.5 (d, $J_{\text{C-F}} = 2.3$ Hz), 92.8, 79.9, 47.5 (d, $J_{\text{C-F}} = 5.6$ Hz), 43.2, 28.4; FTIR (thin film): 2974, 2927, 2856, 1689, 1574, 1415, 1163, 944, 731 cm^{-1} ; $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ 108.9 (d, $J = 3.7$ Hz); HRMS-ESI (m/z) Calcd for $[\text{C}_{14}\text{H}_{20}\text{FIN}_3\text{O}_2]^+$ ($[\text{M}+\text{H}]^+$): 408.0587; found: 408.0579.



3-Iodo-2-methoxypyridine (27). Prepared according to standard procedure with 1.0 equiv of $[\text{LiNCy}_2]_{0.1} \bullet \text{Li}[\text{ZnEt}_2\text{NCy}_2]$. Purification by medium pressure chromatography (hexanes to 10% ethyl acetate–hexanes) gave **27** as a yellow oil (28.0 mg, 0.119 mmol, 60%); $R_f = 0.67$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.11 (dd, $J = 4.8, 1.7$ Hz, 1H), 8.02 (dd, $J = 7.5, 1.7$ Hz, 1H), 6.64 (dd, $J = 7.5, 4.8$ Hz, 1H), 3.98 (s, 3H). $^1\text{H NMR}$ matched literature spectra.⁴⁷



***N,N*-Diisopropyl-2-methyl-3-phenylpropanamide (31).** Prepared following standard methylation procedure with 1.0 equiv of Li[ZnEt₂NCy₂]. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **31** as a clear oil (49.3 mg, 0.20 mmol, 100%); *R_f* = 0.54 (20% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.26–7.21 (m, 2H), 7.19–7.13 (m, 3H), 3.92–3.78 (br s, 1H), 3.64–3.22 (br s, 1H), 3.02 (dd, *J* = 13.0, 8.2 Hz, 1H), 2.93–2.83 (m, 1H), 2.61 (dd, *J* = 13.0, 6.1 Hz, 1H), 1.32 (d, *J* = 6.0 Hz, 3H), 1.26 (d, *J* = 6.7 Hz, 3H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H); ¹³C (125 MHz, CD₃Cl) δ 174.8, 140.4, 129.1, 128.0, 125.9, 45.5, 40.7, 39.7, 39.1, 27.9, 21.3, 20.7, 20.4, 18.3; FTIR (thin film): cm⁻¹ 2965, 2930, 1629, 1440, 1149; HRMS-ESI (*m/z*) Calcd for [C₁₆H₂₆NO]⁺ ([M+H]⁺): 248.2009; found 248.2013.



***tert*-Butyl 2-methyl-3-phenylpropanoate (32).** Prepared following standard methylation procedure with 1.0 equiv Li[Zn(NCy₂)₃]•2LiCl. Purification by medium pressure chromatography (hexanes to 10% ethyl acetate–hexanes) gave **32** as a clear oil (9.1 mg, 0.041 mmol, 21%). *R_f* = 0.95 (20% ethyl acetate–hexanes); ¹H NMR (CDCl₃, 400 MHz): δ 7.29-7.25 (m, 2H), 7.22-7.08 (m, 3H), 3.00-2.93 (m, 1H), 2.66-2.59 (m, 2H), 1.37 (s, 9H), 1.12 (d, *J* = 6.4 Hz, 3H); ¹³C (CDCl₃, 125 MHz): δ 175.5, 139.7, 129.0, 128.2, 126.1, 80.0, 42.3, 39.8,

28.0, 17.0; FTIR (thin film): cm^{-1} 2975, 2932, 1725, 1147; HRMS-ESI (m/z) Calcd for $[\text{C}_{14}\text{H}_{24}\text{NO}_2]^+$ ($[\text{M}+\text{NH}_4]^+$): 238.1802; found 238.1802.

3. Copper-catalyzed electrophilic amination of aryl and heteroaryl zincates

3.1 Direct C–H amination of unactivated arenes and heteroarenes

Developing general and rapid access to diversely functionalized aminoarenes is important as they are highly valuable skeletons widely found in ligands, natural products, and pharmaceuticals (Figure 2).⁵² Recent developments in direct C–H amination provide an attractive strategy that streamlines the synthesis of aminoarenes without the need for prefunctionalization of arene precursors (Scheme 29).⁵³

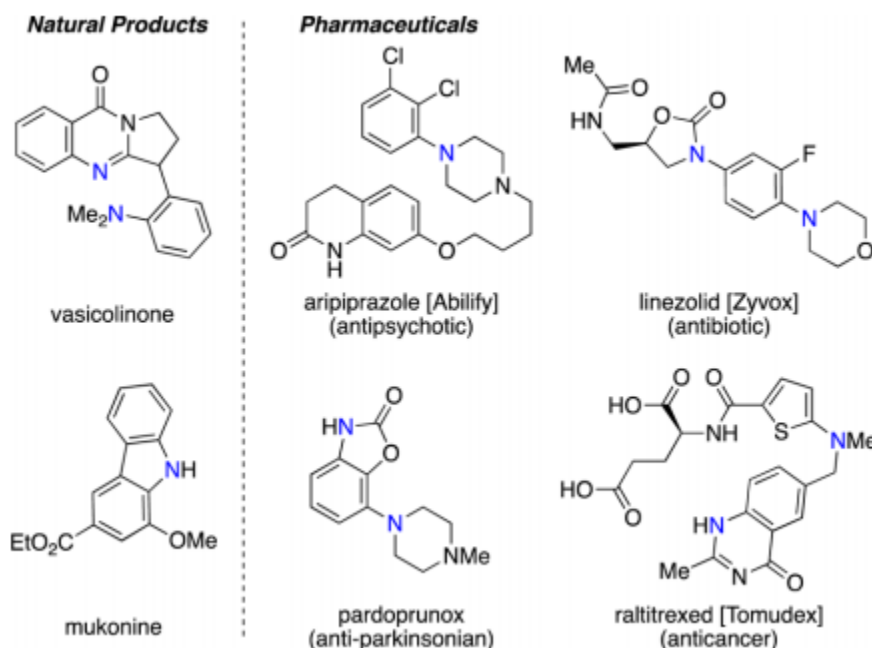
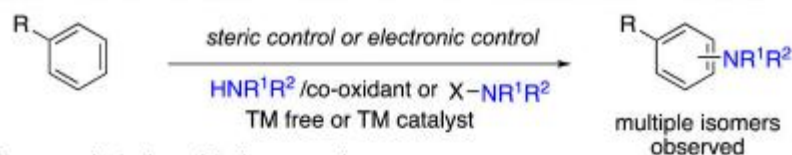


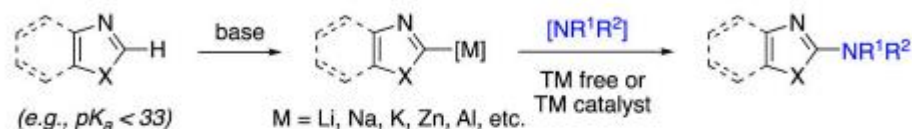
Figure 2: Representative examples of functionalized aminoarenes in natural products and pharmaceuticals

(I) **Innate approaches (independent of arenes):** ideal yet remains challenging



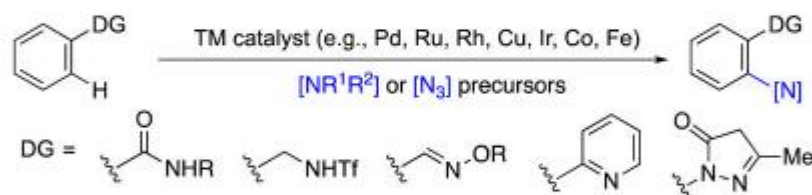
(II) **Arene-substrate guided approaches**

electron-deficient, activated arenes: selective deprotonation of the acidic C–H bonds



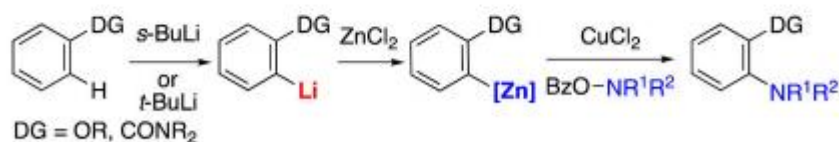
simple, non-activated arenes

(a) via transition-metal (TM) catalyzed C–H activation by directing group (DG) assistance

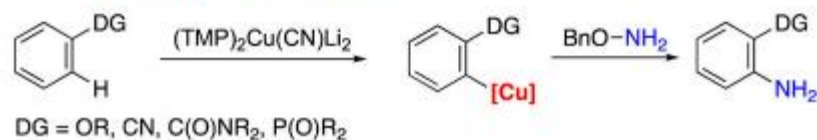


(b) via selective C–H deprotonative metalation

Selective ortho-lithiation, transmetalation and amination (2004)



Selective ortho-cupration and amination (2016)



Scheme 29: Existing approaches for arene C–H amination

To achieve selective C–H amination reactions, an innate approach that is independent of arene substrates would be an ideal strategy. While notable progress has been achieved by steric or electronic control (Scheme 29, I), unambiguous selectivity remains challenging in many cases where reactions give multiple isomers of aminated

arenes.⁵⁴ Among arene substrate-guided strategies, selective amination of electron-deficient arenes has been commonly achieved via directed metalation of acidic aromatic C–H bonds.^{29c, 30, 55} Simple, nonactivated arenes, however, are more challenging, though such aminoarenes constitute one of the most common amine skeletons of well-recognized importance. Toward this end, transition-metal-catalyzed selective C–H amination reactions have been elegantly achieved by directing-group-assisted C–H activation (Scheme 29, II, a).⁵⁶ Yet, this sophisticated strategy is limited by the need of specific directing groups on the arene substrates for facilitating the C–H activation step. Alternatively, selective *ortho*-metallation represents a more general strategy for a much broader scope of arenes bearing diverse directing moieties (Scheme 29, IIb). The Johnson group reported selective arene C–H amination by *ortho*-lithiation, transmetalation to arylzinc species, and Cu-catalyzed electrophilic amination with hydroxylamines.^{19, 57} In this one-pot reaction, the formation of the key arylzinc intermediate relies on the initial lithiated intermediates, which intrinsically hinders the utility of this transformation by their instability and incompatibility with sensitive functional groups (e.g., halides, carbonyl).⁵⁸ Recently, selective C–H amination has also been reported via deprotonative cupration for the preparation of primary anilines.³²

In an effort to develop rapid access to important and novel nitrogen-containing skeletons, our group has been interested in the development of selective C–H amination by using deprotonation zincation (Scheme 29, II). In our previous work, neutral zinc

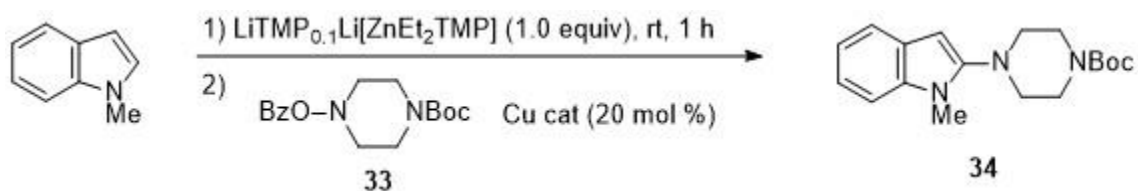
amide bases, ZnTMP₂ (**1**) and ZnTMPCl•LiCl (**3**) could enable copper-catalyzed amination with *O*-benzoyl hydroxylamines under mild conditions.^{30, 55f} However, the scope of this transformation is restricted to acidic and highly activated arenes and heteroarenes (generally with a pK_a < 33), due to limitations of zincation. Given the wide scope of substrates which could be deprotonated by *ortho*-directed zincation, lithium zincate bases were a promising alternative to expand this amination strategy to unactivated arenes and heteroarenes.

3.2 Results and Discussion

To optimize the efficiency of the electrophilic amination of lithium zincate intermediates, we utilized *N*-methylindole as a model substrate. As previously demonstrated, neutral base ZnTMPCl•LiCl (**3**) could not achieve deprotonation but lithium zincate base Li[ZnEt₂TMP] (**8**) could provide zincation (see Chapter 2, Table 1). It was found that 10 mol % excess LiTMP greatly improved zincation efficiency and reproducibility, therefore LiTMP_{0.1}•Li[ZnEt₂TMP] was used for zincation for the rest of these studies. *O*-Benzoyl *N*-Boc piperazine hydroxylamine **33** was used as a model electrophile, due to the common presence of piperazine in bioactive molecules, and copper catalysts were screened (Table 11). In the absence of a catalyst, no aminated indole was observed (entry 1). When different copper salts were used (entries 2–7), the desired amine **34** was formed, with Cu(OAc)₂, Cu(OTf)₂, and Cu(eh)₂ among the most effective catalysts (entries 5–7). The reactions were more efficient with an increased amount of

hydroxylamine **33** (entries 8–10), with Cu(eh)₂ emerging as the best copper source (entry 10), which was then chosen as the standard conditions in our studies.

Table 11: Screen of copper catalysts for amination of *N*-methylindole.^a



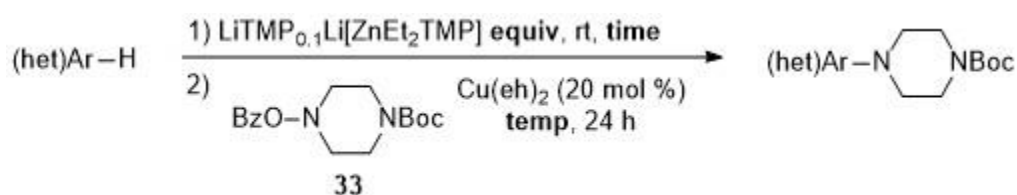
entry	equiv of 33	catalyst	34 ^b (%)
1	1.5	none	0
2	1.5	CuI	7
3	1.5	CuCl ₂	23
4	1.5	Cu(acac) ₂	46
5	1.5	Cu(OAc) ₂	53
6	1.5	Cu(OTf) ₂	49
7	1.5	Cu(eh) ₂	49
8	2.0	Cu(OAc) ₂	79
9	2.0	Cu(OTf) ₂	81
10	2.0	Cu(eh) ₂	85 (77) ^c

Work by Charles Hendrick. ^a Reactions run on a 0.2 mmol scale in THF at rt for 24 h for amination step. ^b Yields determined by ¹H NMR spectroscopy with CH₂Br₂ used as quantitative internal standard. ^c Isolated yield.

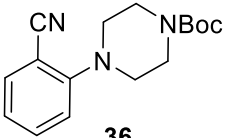
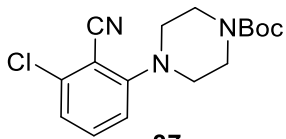
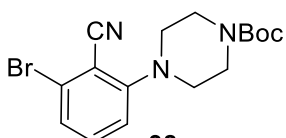
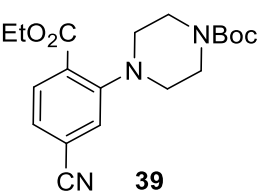
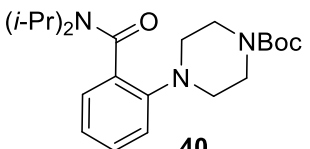
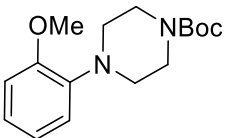

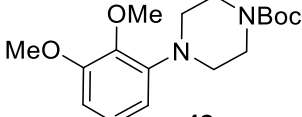
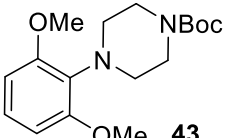
Next, the substrate scope was explored, and optimization was performed for certain substrates (Table 10). For thiophene, less base and a shorter 30 min deprotonation helped to eliminate diamination and gave excellent yield of **35**. As previously optimized for zincation, more electron-deficient substrates with nitrile directing groups only

required 0.67 equivalent of base and 15 min for the deprotonation step. Under standard amination conditions, benzonitrile, 2-chlorobenzonitrile and 2-bromobenzonitrile gave **36-38** with regioselective amination *ortho* to the nitrile. The amination also gave good yield for a larger 3.0 mmol scale reaction (entry 4), highlighting the practicality of this method. The same reaction conditions gave amination of ethyl 4-cyanobenzoate to provide **39** with regioselective amination *ortho* to the ester, which was confirmed by X-ray crystal structure. The stronger electron-withdrawing nature of the ester presumably stabilizes the zincate intermediate in that position. For more electron rich arenes, such as those with amide and methoxy directing groups, increasing the amount of **33** to 3.0 equivalents and the temperature to 50 °C improved the amination efficiency to give **40-43**. When 1,3-dimethoxy groups are present, zincation and amination occurs at the 2 position (**43**) as both methoxy groups can coordinate in cooperative manner.

Table 12: Scope and optimization of amination of aryl and heteroaryl zincates.^a



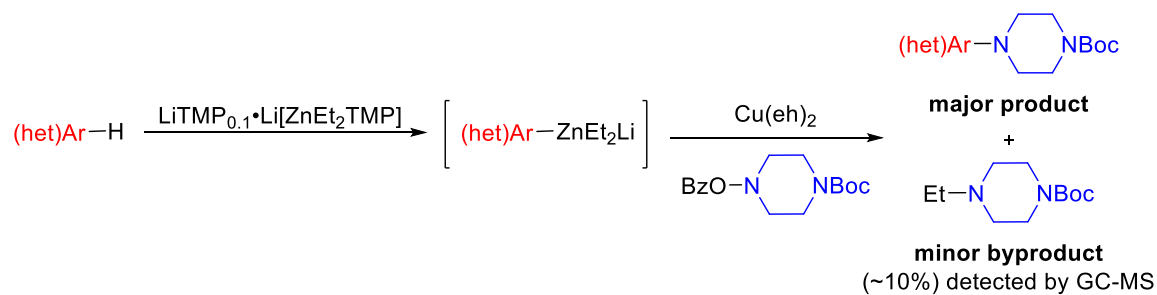
entry	product	base equiv	time	equiv of 33	amination temp (°C)	yield ^b (%)
1	 35	0.67	30 min	2.0	rt	96 (95)

2		0.67	15 min	2.0	rt	95 (58)
3		0.67	15 min	2.0	rt	87 (75)
4		0.67	15 min	2.0	rt	100 (83) (73) ^c
5		0.67	15 min	2.0	rt	61 (54)
6				2.0	rt	56 (39)
7		1.0	1 h	3.0	rt	60
8				3.0	50	78 (55)
9				2.0	rt	21 (17)
10		1.3	3 h	3.0	rt	43
11				3.0	50	55 (41)
12		1.3	3 h	2.0	rt	38 (34)
13		1.3	3 h	3.0	50	50 (39)
14		1.3	3 h	3.0	50	(46)

^a Reactions run on a 0.2 mmol scale. ^b Yields determined by ¹H NMR spectroscopy with CH₂Br₂ used as quantitative internal standard. Isolated yield in parenthesis. ^c Reaction run on a 3.0 mmol scale with 10 mol % Cu(eh)₂.

Additionally, heteroarenes such as isoquinoline, pyridine, and pyrimidines could also undergo amination. A range of secondary hydroxylamines could give efficient amination of *N*-methylindole including acyclic and 5,6, and 7-membered cyclic amines. Trifluoromethyl, fluoryl, and dichloryl moieties could also direct zincation and amination, and the last stage amination of (-)-nicotine and *N*-Boc protected sertraline was achieved.⁵⁹

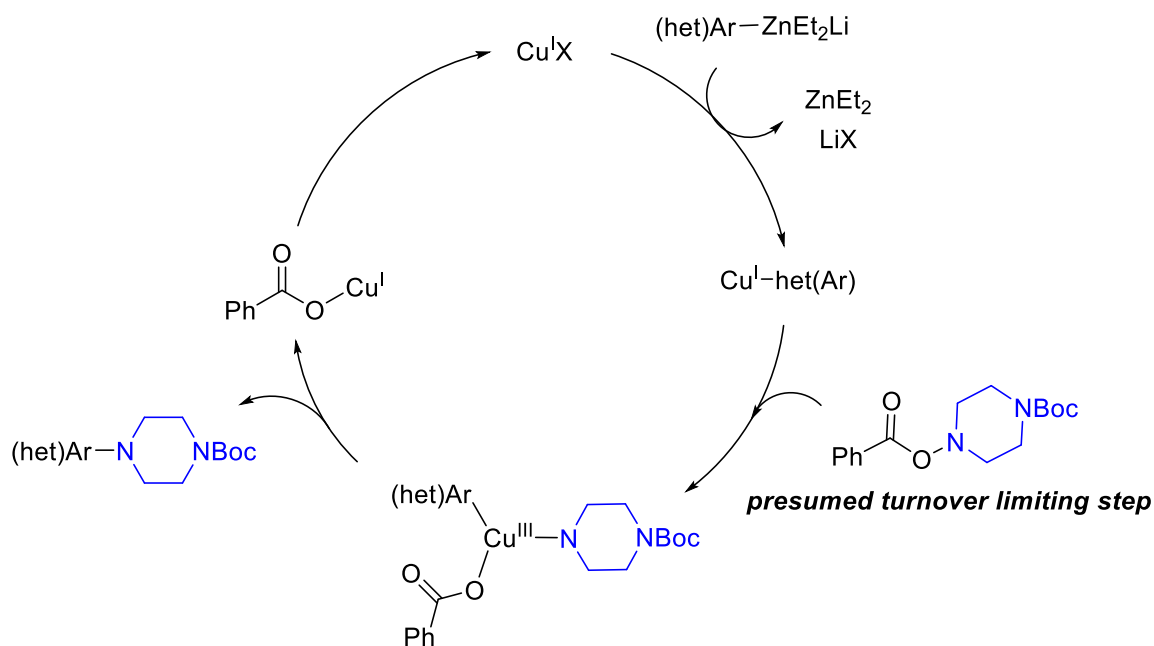
Small, but detectable amounts of ethyl amination were observed as a byproduct of the amination reaction (Scheme 30). Transmetalation of the aryl or heteraryl reagent from zinc to copper appears to be favorable, but ethyl transmetalation can occur. Indeed, direct copper-catalyzed electrophilic amination of diethylzinc has been reported.¹⁹



Scheme 30: Ethyl amination observed as minor byproduct

For more electron-deficient arenes and heteroarenes, such as nitrile, ester, and halogen-containing substrates, the amination proceeded smoothly, generally with better yields and the hydroxylamine was consumed within several hours. However, electron-rich arenes such as methoxy and amide directed substrates generally had lower efficiency and required more hydroxylamine and higher amination temperatures. Interestingly, the hydroxylamine was not fully consumed after 24 h in these cases, even though

hydroxylamine degradation occurs relatively quickly in the presence of copper without organozinc reagent. Therefore, this seems to suggest that transmetalation of the (hetero)arylzincate to copper may occur first, followed by the oxidative addition of the hydroxylamine, which may be the turnover limiting step and slower with more electron-rich aryl reagents (Scheme 31). Therefore, increasing the amount of hydroxylamine and amination temperature could help to promote this oxidative addition step. Additional experiments would be necessary to more definitively identify the mechanism.



Scheme 31: Proposed mechanism for electrophilic amination of aryl zincates

3.3 Supplemental Information

3.3.1 General Information

General Information. Glassware was dried either by propane torch or for at least 12 h in an oven at 140 °C before cooling in a desiccator over Drierite. Electrophilic aminations were performed under N₂ using standard Schlenk techniques in 8-mL microwave tubes sealed with PTFE crimp-top caps. Reactions were stirred magnetically using Teflon-coated, magnetic stir bars. Thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with 0.25 mm of 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or exposure to KMnO₄ or vanillin stain. Organic solutions were concentrated in vacuo using a rotary evaporator. Column chromatography was performed with silica gel (60 Å, standard grade). Medium-pressure chromatography was performed using a Teledyne ISCO Combiflash system using Redisep Gold column cartridges.

Materials. All commercially available reagents were purchased in >98% purity and used as received unless otherwise noted. Anhydrous THF was obtained from an Innovative Technologies solvent purification system. 2,2,6,6-Tetramethylpiperidine was dried over CaH₂ and fractionally distilled under reduced pressure and stored under N₂. Isoquinoline and *N*-methylindole were fractionally distilled under reduced pressure and stored under N₂. *n*-Butyl lithium was purchased as a 2.5 M solution in hexanes from Sigma-Aldrich and

titrated prior to use. Diethylzinc (ZnEt₂) was purchased from Sigma-Aldrich as 1.0 M solution in hexanes and titrated prior to use with iodine in THF at 0 °C.

Instrumentation. Nuclear magnetic resonance spectra were recorded at ambient temperature (unless otherwise stated) on 400 MHz or 500 MHz spectrometers. All values for proton chemical shifts are reported in parts per million (δ) and are referenced to the residual protium in CDCl₃ (δ 7.26). All values for carbon chemical shifts are reported in parts per million (δ) and are referenced to the carbon resonances in CDCl₃ (δ 77.0). All values for fluorine chemical shifts are reported in parts per million and are referenced to the fluorine resonance in CFCl₃ (δ 0.0) as an internal standard. NMR data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad), coupling constant (Hz), and integration. Infrared spectroscopic data are reported in wavenumbers (cm⁻¹) with selected peaks shown. High-resolution mass spectra were obtained using a liquid chromatography-electrospray ionization and time-of-flight mass spectrometer.

3.3.2 Experimental procedures

Synthesis of LiTMP_{0.1}•Li[ZnEt₂TMP]. 2,2,6,6-Tetramethylpiperidine (0.56 mL, 3.3 mmol, 1.1 equiv) in a 25-mL RBF with stir bar was cooled to -78 °C by dry ice/acetone bath under N₂ and stirred until the amine was frozen. To the flask, was added dropwise *n*-butyl lithium (2.5 M solution in hexanes, 3.3 mmol, 1.1 equiv) at -78 °C. The resulting biphasic mixture was allowed to briefly warm outside the bath (roughly 30 seconds, permitting stir

bar rotation), and cooled back to $-78\text{ }^{\circ}\text{C}$. The mixture was stirred vigorously for 10 min and diethylzinc (1.0 M solution in hexanes, 3.0 mmol, 1.0 equiv) was added dropwise. The resulting white slurry was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 5 min and then warmed up to room temperature over 45 min followed by the addition of anhydrous THF (2.4 mL). With this sequence, the title complex was formed as a homogenous pale yellow solution, reproducibly in the range of 0.33–0.36 M solution in hexanes/THF upon titration against benzoic acid described below.

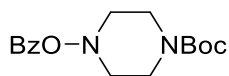
Standard titration: A 15-mL round bottom flask was charged with a stir bar, benzoic acid (approx. 60 mg) and 4-(phenylazo)diphenylamine (approx. 2 mg). The flask was placed under N_2 via sequential vacuum purge/ N_2 backfill (3 times) followed by the addition of THF (1.0 mL). The flask was cooled down to $0\text{ }^{\circ}\text{C}$ by ice/water bath and was added dropwise the solution of $\text{LiTMP}_{0.1}\cdot\text{Li}[\text{ZnEt}_2\text{TMP}]$ until the endpoint of the presumed tribasic zinc complex (i.e., 3.1 equivalents of basic moieties per mole of complex) was observed, as indicated by a persistent dark orange-red color change, providing the concentration of active $\text{LiTMP}_{0.1}\cdot\text{Li}[\text{ZnEt}_2\text{TMP}]$.

Standard Amination Procedure. To a solution of arene substrate (0.20 mmol, 1.0 equiv) in THF (to give a final concentration of 0.2 M) was added dropwise freshly titrated $\text{LiTMP}_{0.1}\cdot\text{Li}[\text{ZnEt}_2\text{TMP}]$ solution (0.20 mmol, 1.0 equiv). The resulting aryl zincate mixture was allowed to stir for 1 h at room temperature. A pear-shape flask containing hydroxylamine (0.40 mmol, 2.0 equiv) and $\text{Cu}(\text{eh})_2$ (14 mg, 0.04 mmol, 0.2 equiv) was

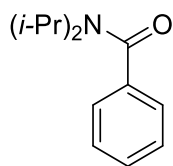
purged under vacuum and backfilled with N₂ three times, and then added THF (1 mL). The mixture of hydroxylamine and Cu(eh)₂ in THF was subsequently added dropwise to the stirring aryl zincate mixture, resulting in a final reaction concentration of 0.1 M. The resulting reaction mixture was allowed to stir at room temperature for 24 h and then was quenched by the addition of isopropanol (approx. 0.2 mL). The crude reaction mixture was filtered through a plug of silica gel (approx. 3 mL) and washed with ethyl acetate (approx. 10 mL). The filtrate was concentrated by rotary evaporation under reduced pressure. Purification of aminated products was performed by silica column chromatography, acid/base extraction, or a combination thereof.

Aqueous Extraction Procedure. The crude material was dissolved in dichloromethane (15 mL), washed rapidly with aqueous solution of HCl (1.0 M, 3 × 5 mL) and brine (5 mL), dried over Na₂SO₄, filtered, and concentrated by rotary evaporation under reduced pressure.

3.3.3 Preparation of starting materials

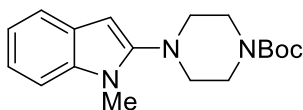


***tert*-Butyl 4-(benzoyloxy)piperazine-1-carboxylate (33).** Prepared according to literature procedure.³¹

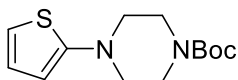


***N,N*-Diisopropylbenzamide.** Precursor for **40** prepared according to literature procedure.³⁹

3.3.4 Characterization of compounds

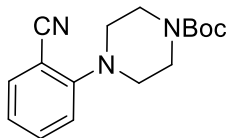


***tert*-Butyl 4-(1-methyl-1H-indol-2-yl)piperazine-1-carboxylate (34).** Synthesized by standard amination procedure. Purification by medium-pressure column chromatography (hexanes to 5% ethyl acetate–hexanes) gave **34** as a white solid (48.2 mg, 77%). $R_f = 0.33$ (25% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.50 (d, $J = 7.6$ Hz, 1H), 7.23 (d, $J = 7.6$ Hz, 1H), 7.17–7.13 (m, 1H), 7.10–7.06 (m, 1H), 5.93 (s, 1H), 3.63–3.61 (m, 7H), 2.97 (t, $J = 4.8$ Hz) 1.51 (s, 9H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3 , 50 °C): δ 154.7, 149.8, 135.5, 128.4, 127.5, 120.4, 119.6, 119.4, 108.7, 87.4, 79.9, 52.4, 28.9, 28.4; FTIR (thin film), cm^{-1} 2972, 1687, 1547, 1417, 1121, 744; HRMS-ESI (m/z) Calcd for ($\text{C}_{16}\text{H}_{26}\text{N}_3\text{O}_2$) ($[\text{M}+\text{H}]^+$): 316.2020; found: 316.2018.

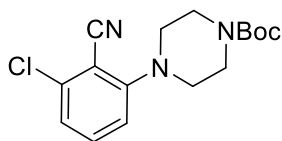


***tert*-Butyl 4-(thiophen-2-yl)piperazine-1-carboxylate (35).** Synthesized by standard amination procedure with 0.67 equiv of base and a 30 min deprotonation. Purification by

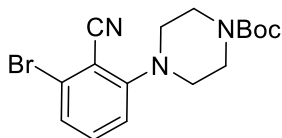
flash column chromatography (hexanes to 10% ethyl acetate–hexanes) gave **35** as a yellow solid (50.9 mg, 95%). $R_f = 0.59$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 6.78 (t, $J = 5.6$ Hz, 1H), 6.64 (d, $J = 5.6$ Hz, 1H), 6.16 (d, $J = 4.0$ Hz, 1H), 3.56 (t, $J = 4.4$ Hz, 4H), 3.08 (t, $J = 4.4$ Hz, 4H), 1.47 (s, 9H); ^{13}C (CDCl_3 , 100 MHz): δ 159.1, 154.5, 126.0, 113.1, 106.6, 79.8, 51.9, 43.2, 28.4; FTIR (thin film): cm^{-1} 2974, 2823, 1690, 1242, 1223, 1079, 665; HRMS-ESI (m/z) Calcd for ($\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}_2\text{S}$) ($[\text{M}+\text{H}]^+$): 269.1318 ; found 269.1325.



tert-Butyl 4-(2-cyanophenyl)piperazine-1-carboxylate (36). Synthesized by standard amination procedure with 0.67 equiv of base and a 15 min deprotonation. Purification by medium pressure column chromatography (hexanes to 20% ethyl acetate–hexanes) gave **36** as a yellow oil (33.2 mg, 58%). $R_f = 0.39$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.57 (dd, $J = 7.7, 1.7$ Hz, 1H), 7.49 (ddd, $J = 8.2, 7.5, 1.7$ Hz, 1H), 7.04 (td, $J = 7.6, 1.0$ Hz, 1H), 6.99 (d, $J = 8.3$ Hz, 1H), 3.64 (m, 4H), 3.15 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ 155.4, 154.6, 134.2, 133.6, 122.1, 118.8, 118.0, 106.4, 79.8, 51.4, 43.8, 28.3; FTIR (thin film): cm^{-1} 974, 2219, 1689, 1595, 1417, 1162, 758; HRMS-ESI (m/z) Calcd for ($\text{C}_{16}\text{H}_{21}\text{N}_3\text{NaO}_2$) ($[\text{M}+\text{Na}]^+$): 310.1526; found 310.1531.

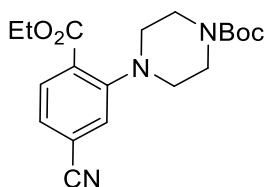


tert-Butyl 4-(3-chloro-2-cyanophenyl)piperazine-1-carboxylate (37). Synthesized by standard amination procedure with 0.67 equiv of base and a 15 min deprotonation. Purification by medium pressure column chromatography (hexanes to 20% ethyl acetate–hexanes) gave **37** as a yellow oil (48.3 mg, 75%). $R_f = 0.29$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.39 (t, $J = 8.2$ Hz, 1H), 7.08 (d, $J = 8.1$ Hz, 1H), 6.88 (d, $J = 8.4$ Hz, 1H), 3.64–3.61 (m, 4H), 3.16–3.14 (m, 4H), 1.47 (s, 9H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 157.7, 154.9, 138.6, 134.0, 123.1, 117.2, 115.4, 107.7, 80.3, 51.8, 44.1, 28.6; FTIR (thin film): cm^{-1} 2974, 2927, 2857, 1685, 1417, 1237, 1161, 944, 729; HRMS-ESI (m/z) Calcd for ($\text{C}_{16}\text{H}_{20}\text{ClN}_3\text{NaO}_2^+$) ($[\text{M}+\text{Na}]^+$): 344.11363; found: 344.11355.



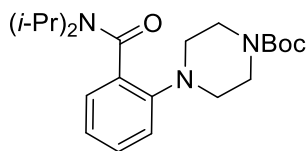
tert-Butyl 4-(3-bromo-2-cyanophenyl)piperazine-1-carboxylate (38). Synthesized by standard amination procedure with 0.67 equiv of base and a 15 min deprotonation step. Purification by medium-pressure column chromatography (hexanes to 20% ethyl acetate–hexanes) gave **38** as a yellow solid (60.7 mg, 83%). Synthesized on a 3 mmol scale using 10 mol % $\text{Cu}(\text{eh})_2$ afforded **38** as a yellow solid (803.2 mg, 73%). $R_f = 0.26$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.33 (t, $J = 8.1$ Hz, 1H), 7.27 (d, $J = 8.0$ Hz, 1H), 6.4 (d, $J = 8.0$ Hz, 1H), 3.65–3.62 (m, 4H), 3.17–3.14 (m, 4H), 1.48 (s, 9H); $^{13}\text{C NMR}$

(CDCl₃, 100 MHz): δ 157.6, 154.5, 133.9, 126.8, 126.0, 117.5, 116.3, 109.7, 79.9, 51.4, 43.7, 28.3;
FTIR (thin film): cm⁻¹ 2967, 2810, 1690, 1613, 1247, 1161, 736; HRMS-ESI (m/z) Calcd for
(C₁₆H₂₀BrN₃NaO₂) ([M+Na]⁺): 388.0632 ; found 388.0631.



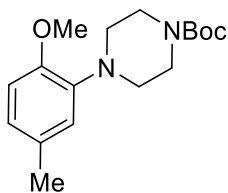
***tert*-Butyl 4-(5-cyano-2-(ethoxycarbonyl)phenyl)piperazine-1-carboxylate (39).**

Synthesized by standard amination procedure with 0.67 equiv of base and a 15 min deprotonation step. Purification by medium-pressure column chromatography (hexanes to 20% ethyl acetate–hexanes) gave **39** as a yellow oil (38.9 mg, 54%). R_f = 0.29 (20% ethyl acetate– hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, J = 7.9 Hz, 1H), 7.26 (dd, J = 7.9, 1.5 Hz, 1 H), 7.23 (d, J = 1.5 Hz, 1 H), 4.36 (q, J = 7.1, 2H), 3.57 (t, J = 5.0 Hz, 4H), 3.01 (t, J = 5.0 Hz, 4H), 1.47 (s, 9H), 1.38 (t, J = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 166.5, 154.7, 152.0, 131.9, 129.1, 124.7, 122.7, 118.0, 115.8, 80.0, 61.6, 52.0, 43.7, 28.4, 14.2; FTIR (thin film), cm⁻¹ 2977, 2231, 1693, 1414, 1169; HRMS-ESI (m/z) Calcd for (C₁₉H₂₆N₃O₄) ([M+H]⁺): 360.19178; found: 360.19188. Regioselectivity confirmed by X-Ray crystallography.



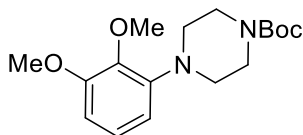
***tert*-Butyl 4-(2-(diisopropylcarbamoyl)phenyl)piperazine-1-carboxylate (40).**

Synthesized by standard amination procedure with 3.0 equiv of **33** and the amination step at 50 °C. Purification by medium-pressure column chromatography (dichloromethane to 5% isopropanol-dichloromethane) gave **40** as a white solid (43.2 mg, 55%). $R_f = 0.27$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.28 (m, 1H), 7.12 (dd, $J = 7.5, 1.9$ Hz, 1H), 7.07 (td, $J = 7.4, 7.3, 1.0$ Hz, 1H), 7.01 (dd, $J = 8.1, 1.1$ Hz, 1H), 3.56–3.42 (m, 6H), 3.31 (m, 2H), 2.71 (m, 2H), 1.56 (d, $J = 2.8$ Hz, 3H), 1.54 (d, $J = 2.8$ Hz, 3H), 1.46 (s, 9H), 1.18 (d, $J = 6.7$ Hz, 3H), 0.97 (d, $J = 6.7$ Hz, 3H); ^{13}C (CDCl_3 , 100 MHz) : δ 170.0, 154.6, 148.4, 135.1, 128.9, 126.6, 123.7, 119.1, 79.5, 52.2, 50.4, 45.3, 28.2, 20.5, 20.3, 20.2; FTIR (thin film): cm^{-1} 2966, 2810, 1690, 1614, 1209, 736; HRMS-ESI (m/z) Calcd for ($\text{C}_{22}\text{H}_{36}\text{N}_3\text{O}_3$) ($[\text{M}+\text{H}]^+$): 390.2752 ; found 390.2797.

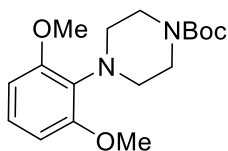


***tert*-Butyl 4-(2-methoxy-5-methylphenyl)piperazine-1-carboxylate (41).** Synthesized by standard amination procedure with 1.3 equiv of base and a 3 h deprotonation and the amination step at 50 °C with 3.0 equiv of **33**. Purification by aqueous workup procedure followed by medium-pressure column chromatography (hexanes to 20% ethyl

acetate–hexanes) gave **41** as a yellow oil (25.3 mg, 41%). $R_f = 0.35$ (25% ethyl acetate–hexanes); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 6.82–6.72 (m, 3H), 3.84 (s, 3H), 3.60 (m, 4H), 2.99 (m, 4H), 2.28 (s, 3H), 1.48 (s, 9H); ^{13}C (CDCl_3 , 125 MHz): δ 154.8, 150.3, 141.1, 130.4, 123.3, 119.4, 111.7, 79.6, 55.6, 50.8, 44.1, 28.5, 20.7; FTIR (thin film): cm^{-1} 2970, 1690, 1450, 1238, 1166, 1001, 731; HRMS-ESI (m/z) Calcd for ($\text{C}_{17}\text{H}_{27}\text{N}_2\text{O}_3$) ($[\text{M}+\text{H}]^+$): 307.2017; found 307.2025.



tert-Butyl 4-(2,3-dimethoxyphenyl)piperazine-1-carboxylate (42). Synthesized by standard amination procedure with 1.3 equiv of base, the deprotonation for 3 h, and the amination step at 50 °C with 3.0 equiv of **33**. Purification by aqueous workup procedure followed by medium-pressure column chromatography (hexanes to 20% ethyl acetate–hexanes) gave **42** as a colorless oil (25.1 mg, 39%); $R_f = 0.41$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 6.98 (t, $J = 8.2$ Hz, 1H), 6.63 (d, $J = 8.3$, 1H), 6.54 (d, $J = 8.2$ Hz, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 3.57 (m, 4H), 3.05 (m, 4H), 1.48 (s, 9H); ^{13}C (CDCl_3 , 125 MHz) : δ 154.9, 153.7, 146.1, 142.2, 123.9, 111.4, 107.2, 79.6, 59.5, 56.1, 50.7, 44.3, 28.5; FTIR (thin film): cm^{-1} 2974, 2822, 1690, 1417, 1284, 1001, 729; HRMS-ESI (m/z) Calcd for ($\text{C}_{17}\text{H}_{27}\text{N}_2\text{O}_4$) ($[\text{M}+\text{H}]^+$): 323.1966 ; found 323.1971.



tert-Butyl 4-(2,6-dimethoxyphenyl)piperazine-1-carboxylate (43). Synthesized by standard amination procedure with 1.3 equiv of base, the deprotonation for 3 h, and the amination step at 50 °C with 3.0 equiv of **33**. Purification by aqueous workup procedure followed by medium-pressure column chromatography (hexanes to 10% ethyl acetate–hexanes) gave **43** as a colorless oil (29.5 mg, 46%). $R_f = 0.22$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.00 (t, $J = 8.2$ Hz, 1H), 6.54 (d, $J = 8.2$ Hz, 2H), 3.80 (s, 6H), 3.50 (t, $J = 4.8$ Hz, 4H), 3.08 (t, $J = 4.8$ Hz, 4H), 1.48 (s, 9H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3 , 50 °C): δ 157.1, 155.1, 129.6, 124.6, 105.9, 79.2, 56.1, 50.5, 45.0, 28.5; FTIR (thin film), cm^{-1} 2976, 1701, 1646, 1414, 1374, 1231, 996; HRMS-ESI (m/z) Calcd for ($\text{C}_{17}\text{H}_{27}\text{N}_2\text{O}_4$) ($[\text{M}+\text{H}]^+$): 323.1965; found: 323.1965.

4. Direct silylation and borylation of aryl and heteroaryl zincates

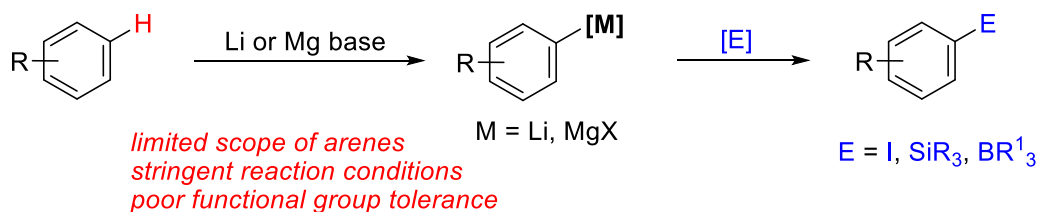
4.1 Methods for C–H silylation and borylation

Aromatic silanes and boronates are among the most versatile and valuable intermediates widely used in organic synthesis, materials, pharmaceuticals, and biologically important molecules. Silanes are highly useful, air-stable and easily handled synthetic intermediates⁶⁰ and boronic acids and boronate esters are extremely valuable due to their stability and utility in the robust Suzuki cross-coupling reaction which is commonly used in total synthesis, medical chemistry and the manufacturing of pharmaceuticals.⁶¹ General approaches for the direct silylation and borylation of C–H bonds are highly desirable to avoid the need for prefunctionalization (Scheme 32). Aryl lithium and Grignard reagents are known to undergo catalyst-free silylation and borylation by direct reaction with silicon or boron electrophiles (Scheme 32, A). The requisite organolithium and magnesium reagents are often generated by metal-halogen exchange, or deprotonative metalation. However, the substrate scope and functional group compatibility is inherently limited with lithiation or magnesiation and low temperatures and stringent reaction conditions are required.

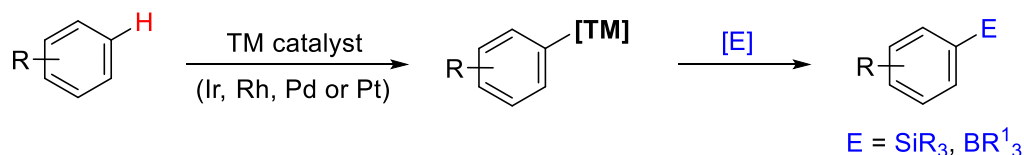
As an alternative, several elegant approaches have been reported via transition metal-catalyzed C–H activation (Scheme 32, B).⁶² Arene silylation reactions have been reported with Pt,⁶³ Rh,⁶⁴ Ir⁶⁵ and even potassium-based⁶⁶ catalysts. Additionally, directing-group assisted *ortho*-borylation has been achieved with Ir,⁶⁷ and Pd⁶⁸ and

sterically-controlled borylation can be performed with Ir⁶⁹ and Pt⁷⁰, where functionalization occurs at the most sterically accessible position. Recently, C–H borylation by earth abundant transition metal catalysts such as Co,⁷¹ Ni,⁷² and Fe⁷³ have been developed extensively with their potential economic and environmental advantages and metal-free borylations have also been established.⁷⁴ In many cases, regioselectivity, generality, and functional group compatibility remains a challenge for many transition metal C–H activation strategies.

(A) Catalyst-free C–H functionalization via deprotonative *ortho*-metalation



(B) Transition metal-catalyzed C–H silylation and borylation – *sterically-controlled*



Scheme 32: Approaches for C–H silylation and borylation

Ortho-directed metallation provides access to different regioselectivity than sterically-controlled transition metal-catalyzed reactions. As lithium zincate intermediates have many advantages over lithium and magnesium reagents, utilizing deprotonative zincation for the direct silylation and borylation of C–H bonds would be desirable. Several limited reports have suggested that lithium zincates may be able to

undergo these transformations, however, existing zinc-mediated silylation and borylation has not been performed by C–H zincation. For example, a zinc-catalyzed silylation of aryl magnesium halides has been reported, presumably through a magnesium zincate intermediate,⁷⁵ which gives promise for the silylation of lithium zincates generated through deprotonative zincation. Additionally, a borylation of aryl halides has been reported proceeding through a presumed borylzincate intermediate, involving zinc insertion into the carbon-halogen bond.⁷⁶ Therefore, we were interested in developing silylation and borylation of aryl and heteroaryl zincates generated by deprotonative zincation with a lithium amide zincate base.

4.2 Results and Discussion

Given the known reactivity of organolithium and organomagnesium nucleophiles with chlorosilane reagents, lithium zincate reagents generated by deprotonative zincation were tested with readily available chlorotrimethylsilane (TMSCl) as an electrophile to generate trimethyl silanes. For the deprotonative zincation, the novel base Li[ZnEt₂NCy₂] was utilized, as efficient zincation of a wide variety of substrates had previously been established (see Chapter 2). The silylation of *N*-methylindole to give **44** was used to examine the effect of the composition of zincate base (Table 13). When stoichiometric quantities of LiNCy₂ and ZnEt₂ were used to synthesize the base, moderately good silylation was observed (entry 1). For zincate bases made with slight excess of *n*-butyl lithium (entry 2) or LiNCy₂ relative to ZnEt₂ (entry 4), excellent silylation was observed,

whereas excess ZnEt₂ inhibited reactivity (entry 3). For subsequent reactions, lithium zincate bases were synthesized with 10 mol % excess LiNCy₂ relative to ZnEt₂. Silylation yields were consistently higher than deuteration yields (see Table 5), suggesting that zincation is in equilibrium and can continue during the silylation step and the trapping of TMSCl may drive the zincation forward.

Table 13: Optimization of zincate base composition by silylation of *N*-methylindole.^a

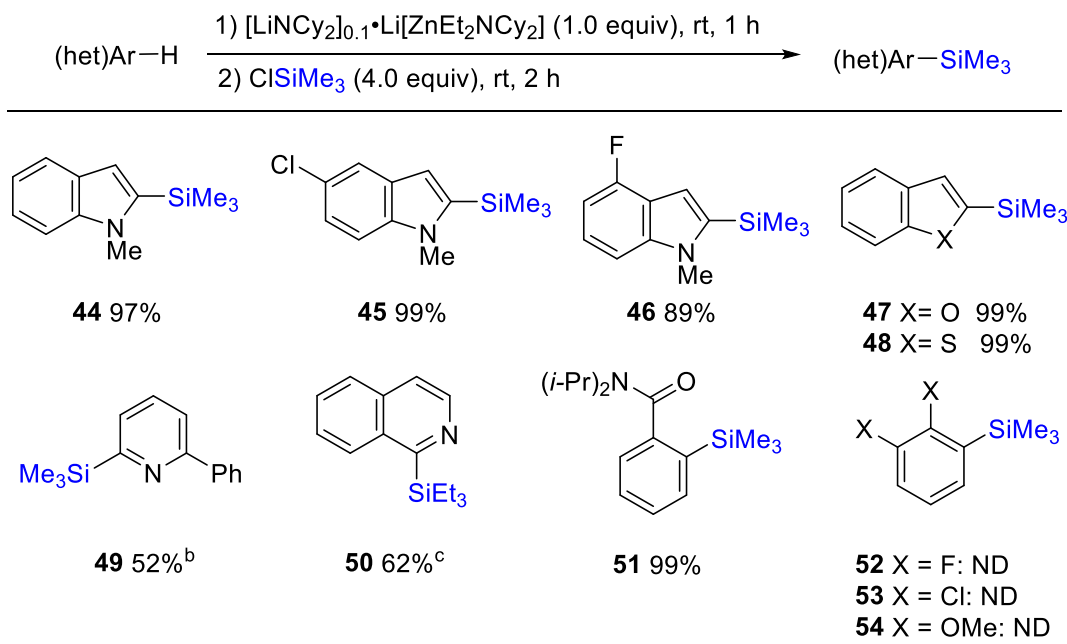
entry	zincate base composition			44 ^b (%)
	Cy ₂ NH (equiv)	<i>n</i> -BuLi (equiv)	ZnEt ₂ (equiv)	
1	1.0	1.0	1.0	83
2	1.0	1.1	1.0	92
3	1.0	1.1	1.2	32
4	1.1	1.1	1.0	100 (97)

^a Reactions run on a 2.0 mmol scale in THF. Zincate base complex was prepared following the standard procedure using the indicated stoichiometry from dicyclohexylamine, *n*-butyl lithium, and diethylzinc. ^b Yields determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard. Isolation yield shown in parentheses.

Encouragingly, heteroaryl and many aryl zincates smoothly underwent silylation without the need for additional transition metal catalyst (Table 14). Different heteroaryl substrates, such as indole, benzofuran, benzothiophene, and pyridine formed trimethylsilyl derivatives **44-49**, with good tolerance of fluoride and chloride functional groups. For the reaction of isoquinoline, the chlorotrimethylsilylated product from TMSCl was not stable toward isolation, whereas the triethylsilylated product **50** from TESCl was

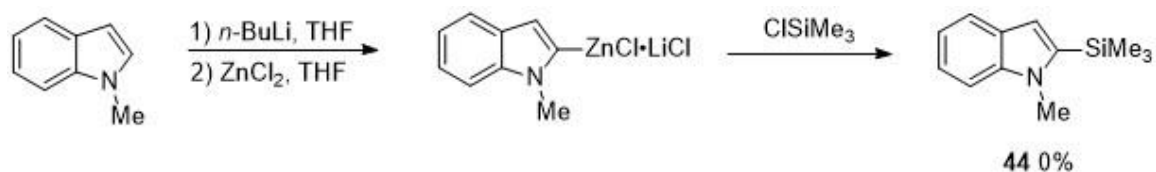
isolated in 62% yield after column chromatography. An amide as a strongly coordinating directing group effectively promoted *ortho*-silylation to provide **51** in 99% yield. Halo- and methoxy- substituted arenes **52–54**, failed to provide silylation products, but the reason for this lack of reactivity remains unclear as the corresponding zincative iodination products were formed successfully.

Table 14: Scope of simple heteroaryl and amide directed silylation of lithium zincates.^a



^a Isolated yields shown for reactions run on 0.2 mmol scale in THF. ^b Deprotonation run for 2 h with 1.3 equiv of base. ^c ClSiEt₃ used instead of ClSiMe₃. ND = not detected.

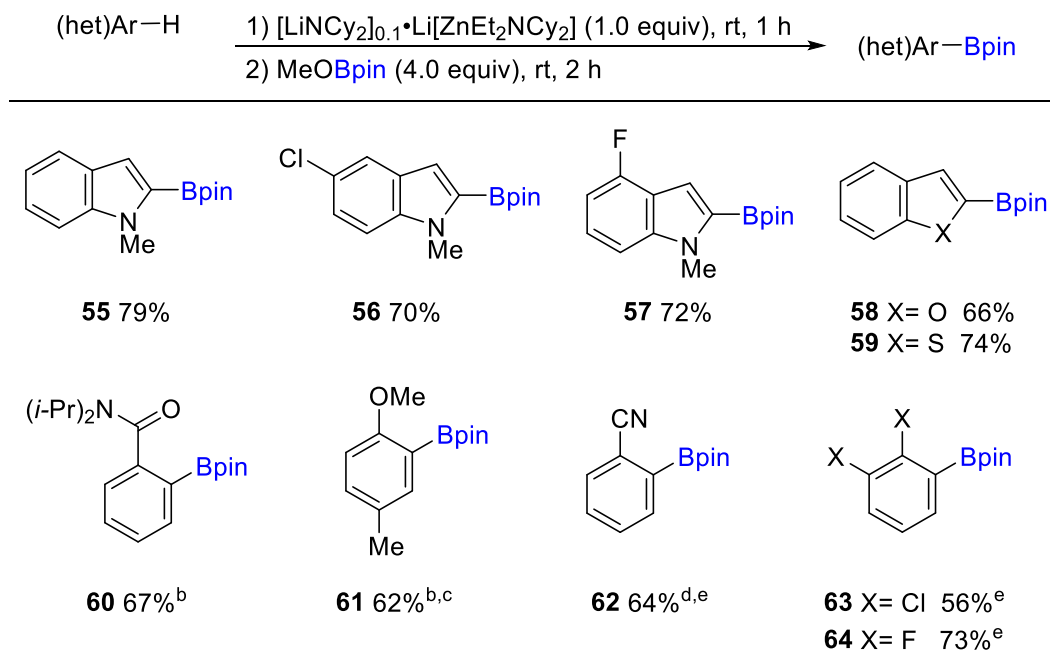
It is of note that the neutral arylzinc complex was not effective in forming silylated products, indicating that the more nucleophilic lithium zincate is necessary for silylation (Scheme 33).



Scheme 33: Ineffective silylation of neutral *N*-methylindole zinc chloride reagent

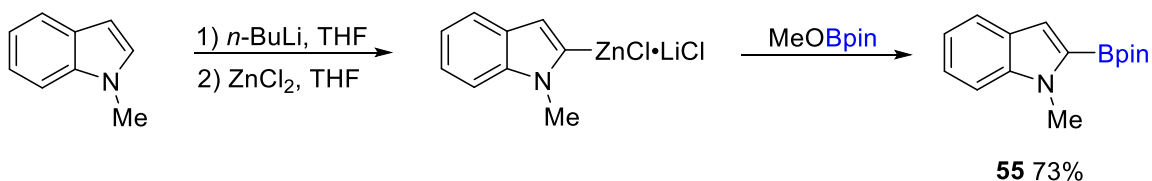
To examine the potential of zincate borylation, several boron reagents were screened, and we were pleased to find that aryl and heteroaryl lithium zincates could react without a transition metal catalyst. Ultimately, commercially available methoxy pinacol boronate ester (MeOBpin) was chosen as the ideal electrophile as it directly generates the stable pinacol boronate esters which can be isolated by chromatography (Table 15). Various directing groups and heteroarenes work well, however, more electron-rich substrates require lower borylation temperatures and short reaction times to avoid decomposition of the product under the reaction conditions (compounds **60** and **61**). Alternatively, more electron-deficient substrates such as halides and nitriles required longer borylation times at room temperature with more electrophile (compounds **62–64**).

Table 15: Borylation of heteroaryl and aryl zincates.^a



^a Isolated yields shown for reactions run on 0.2 mmol scale in THF. ^b Borylation run at 0 °C for 30 min. ^c Deprotonation run for 3 h at 70 °C with 1.3 equiv of base. ^d Deprotonation run for 15 min with 0.67 equiv of base. ^e Borylation run with 8.0 equiv of MeOBpin for 24 h.

Interestingly, when the neutral arylzinc reagent was tested under these standard borylation conditions a similar yield was observed (Scheme 34). This suggests that MeOBpin is a better electrophile than TMSCl and does not require a more nucleophilic lithium zincate reagent. However, lithium amide zincate bases provide advantage to this borylation method by giving increased access to C–H bonds through deprotonative zincation without the need for strong alkyl lithium bases.



Scheme 34: Borylation of neutral *N*-methylindole zinc chloride reagent

We next examined arenes bearing multiple potential directing groups to explore the generality and regioselectivity of Li[ZnEt₂NCy₂]-mediated C–H functionalization extensively (Table 16). When 1,2-dihalosubstituted arenes were tested, *ortho*-selective borylation was observed adjacent to fluorine or chlorine (entries 1 and 2), the more electronegative atom with the stronger activating inductive effect, compared to bromine. Encouragingly, bromine was well tolerated and no bromide zinc exchange was observed, making this method orthogonal to traditional Pd or Ni cross-coupling chemistry. The reactions with 2-bromobenzonitrile and 2-methoxybenzonitrile selectively led to the aryl derivatives at the *ortho*-position to the nitrile group, which is more strongly coordinating than bromo or methoxy groups (entries 3–6). For 3-methoxybenzonitrile, 2-borylation occurs selectively, neighboring to both directing groups (entry 7). For 4-methoxybenzonitrile, borylation was observed with the 2-substituted product as the major separable regioisomer **71** (entry 9). It is of note that iridium catalyzed borylation gives much poorer regioselectivity (2:1) for this substrate,⁷⁷ and that LiTMP (with the reaction run at -78 °C) gives the opposite regioselectivity (1:2.3).⁷⁸

Table 16: Regioselective silylation and borylation with multiple directing groups.^a

$(\text{het})\text{Ar}-\text{H} \xrightarrow[2) \text{ [E] (4.0 equiv), rt, 2 h}]{1) [\text{LiNCy}_2]_{0.1} \cdot \text{Li}[\text{ZnEt}_2\text{NCy}_2] (1.0 \text{ equiv}), \text{rt, 1 h}}$
 $(\text{het})\text{Ar}-\text{E}$

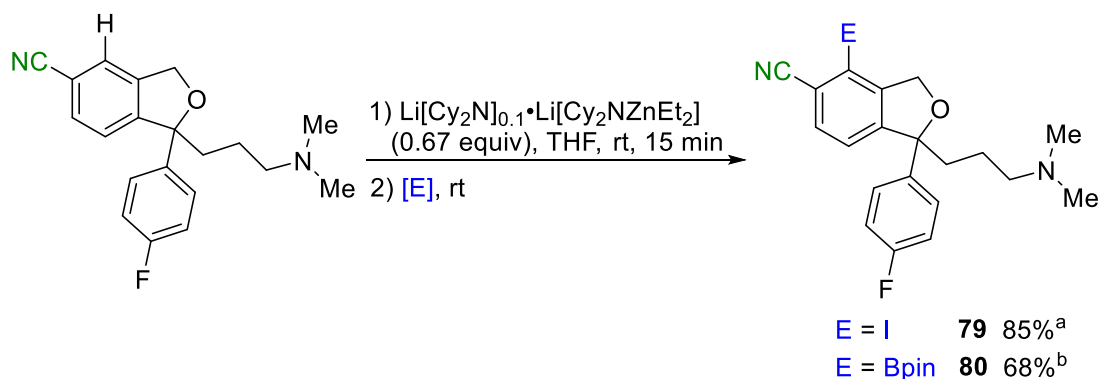
entry	substrate	electrophile	product	yield ^b
1		MeOBpin		65 X = Cl 41% ^c
2				66 X = F 41% ^c
3		I ₂		18 E = I 91% ^d
4		ClSiMe ₃		67 E = SiMe ₃ 58% ^e
5		MeOBpin		68 E = Bpin 40% ^{c,d}
6		MeOBpin		69 63% ^d
7		MeOBpin		70 45% ^d
8		I ₂		25 X = CN 88% ^f
9		MeOBpin		71 X = CN 43% ^d
10		MeOBpin		72 X = F 53% ^c
11		I ₂		23 E = I 72% ^g
12		ClSiMe ₃		73 E = SiMe ₃ 49% ^d
13		MeOBpin		74 E = Bpin 50% ^d
14		I ₂		24 E = I 90% ^h
15		ClSiMe ₃		75 E = SiMe ₃ 99% ^h
16		MeOBpin		76 E = Bpin 23% ^{h,i}
17		I ₂		27 E = I 60%
18		ClSiMe ₃		77 E = SiMe ₃ 57%
19		MeOBpin		78 E = Bpin 42% ⁱ

^a Reactions run on 0.2 mmol scale in THF. ^b Isolated yields shown for rs = regioselectivity, determined by ¹H NMR of crude reaction mixture. Major isomer shown. ^c Run with 8.0 equiv of MeOBpin. ^d Deprotonation run with 0.67 equiv of base for 15 min. ^e Deprotonation run with 0.67 equiv of base and in the presence of 4.0 equiv of ClSiMe₃ (*in situ* silylation). ^f Deprotonation run with for 15 min ^g Deprotonation run with 0.67 equiv of base for 15 min at 0 °C. ^h Deprotonation run with 1.3 equiv of base for 3 h. ⁱ Borylation run at 0 °C for 1 h.

We next examined additional 1,4-disubstituted arene substrates. The borylation of 4-fluoroanisole formed only **72**, suggesting the inductive influence of the fluoride is more significant than the coordination of the methoxy group (entry 10). In the reactions of 4-cyano-*N,N*-diisopropylbenzamide and 4-methoxy-*N,N*-diisopropylbenzamide (entries 11–16), selective formation of **73–76** indicate a stronger directing effect of the amide over nitrile and methoxy groups. Traditional directed *ortho*-lithiation with *s*-BuLi/TMEDA gives the same regioselectivity for **75**, albeit in lower yield.⁷⁹ Interestingly, the iodination of both substrates gave a mixture of two isomers (entries 11 and 14) while the borylation and silylation reactions only formed one isomer (entries 12–13 and 15–16), suggesting that the higher level of selectivity may result from differing reactivity of the two zincate isomers in the silylation and borylation step. For the iodination of **23**, the regioselectivity improved with shorter reaction times and lower temperatures, suggesting the strong coordination of the amide directing group provides more kinetically favorable deprotonation, but the nitrile gives better thermodynamic stabilization. In the case of 2-methoxypyridine **27** and **77–78**, the preferential zincative functionalization was observed for the methoxy over the pyridine nitrogen as a directing group (entry 17–19), which is

the same regioselectivity observed with LDA or LiTMP.⁸⁰ These representative examples offer a framework for identifying suitable substrates and predicting the regioselective outcome of zincation-mediated silylation and borylation reactions.

We applied the zincate-mediated functionalization for the synthesis of novel analogs of citalopram, a commonly prescribed antidepressant drug of the selective serotonin reuptake inhibitor (SSRI) class (Scheme 35). Under standard conditions, citalopram underwent selective metalation at the *ortho*-position of the nitrile group and provided iodination and borylation products **79** and **80** in 85% and 68% yields, respectively. The regioselectivity may be influenced by the coordination of the ether. It is worth noting that this deprotonative approach well tolerates the presence of the commonly problematic basic amine and sensitive benzylic ether groups.



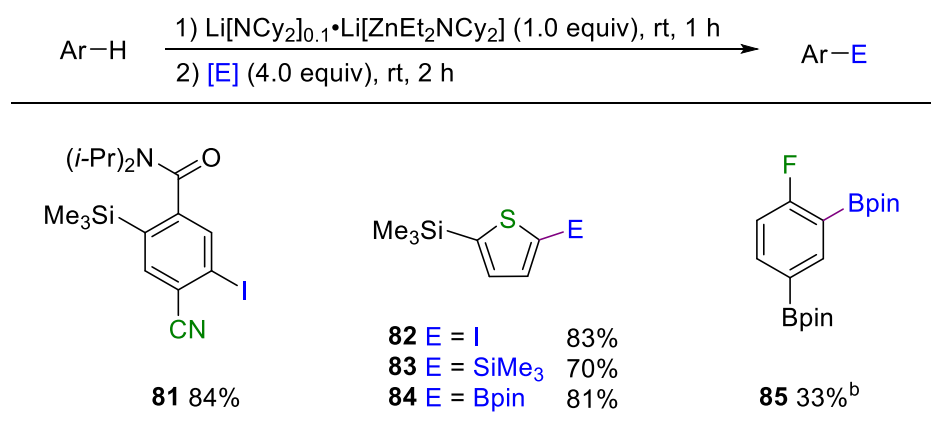
Isolated yields given for reactions run on a 0.1 mmol scale. ^a Reaction run with 4.0 equiv of iodine for 2 h. ^b Reaction run with 8.0 equiv of MeOBpin for 24 h.

Scheme 35: Late stage functionalization of citalopram

Finally, secondary functionalization of silylated and borylated substrates was explored (Table 17). Several silanes and a boronate substrate could be functionalized,

however, aryl iodides were not tolerated and underwent zinc-iodine exchange. Other boronates tested did not undergo zincation, perhaps due to the base attacking the existing boronate. 4-Cyano-*N,N*-diisopropylbenzamide undergo initial silylation *ortho*- to the amide, and this silylated product can be zincated and iodinated *ortho*- to the nitrile and *para*- to the trimethylsilyl (**81**). This structure was confirmed by X-ray crystallography.

Table 17: Secondary functionalization of aryl silanes and boronates.^a



^a Isolated yields given for reactions run on a 0.2 mmol scale. ^b Borylation run with 8.0 equiv MeOBpin for 24 h.

4.3 Supplemental Information

4.3.1 General Information

General Information. Glassware was dried either by propane torch or for at least 12 hours in an oven at 140 °C before cooling in a desiccator over Drierite. All small-scale reactions were performed under a N₂ atmosphere using standard Schlenk techniques in 8-mL microwave tubes sealed with PTFE crimp-top caps. Other reactions were run in round bottom flasks sealed with rubber septa. Thin-layer chromatography (TLC) was

performing using aluminum plates pre-coated with 0.25 mm of 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or exposure to vanillin stain. Organic solutions were concentrated *in vacuo* using a rotary evaporator. Column chromatography was performed with silica gel (60 Å, standard grade). Medium-pressure chromatography was performed using a Teledyne ISCO Combiflash system using Redisep Gold column cartridges.

Materials. All commercially available reagents were purchased in >95% purity and used as received unless otherwise noted. Anhydrous THF was obtained from an Innovative Technologies solvent purification system. Dicyclohexylamine was dried over calcium hydride and fractionally distilled under reduced pressure and stored under N₂. *n*-Butyl lithium was purchased as a 2.5 M solution in hexanes from Sigma-Aldrich and titrated prior to use with *N*-benzylbenzamide as an indicator.³⁸ The solution of diethylzinc (1.0 M in hexanes) was purchased from Sigma Aldrich and titrated with iodine in THF at 0 °C prior to use. Chlorotrimethylsilane and 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane were stored under N₂.

Instrumentation. Nuclear magnetic resonance spectra were recorded at ambient temperature (unless otherwise stated) on 400 MHz or 500 MHz spectrometers. All values for proton chemical shifts are reported in parts per million (δ) and are referenced to the residual protium in CDCl₃ (δ 7.26). All values for carbon chemical shifts are reported in parts per million (δ) and are referenced to the carbon resonances in CDCl₃ (δ 77.0). All

values for fluorine chemical shifts are reported in parts per million and are referenced to the fluorine resonance in CFCl_3 (δ 0.0) as an internal standard. NMR data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad), coupling constant (Hz), and integration. Infrared spectroscopic data was acquired on a Thermo FTIR instrument and are reported in wavenumbers (cm^{-1}) with selected peaks. High-resolution mass spectra were obtained using a liquid chromatography-electrospray ionization and time-of-flight mass spectrometer.

4.3.2 Experimental procedures

Standard Procedure A: Preparation of $[\text{LiNCy}_2]_{0.1}\text{Li}[\text{ZnEt}_2\text{NCy}_2]$. An oven-dried 25-mL round-bottom flask was charged with a stir bar, purged by vacuum, and refilled with N_2 three times. To the flask was added dicyclohexylamine (0.44 mL, 2.2 mmol, 1.1 equiv), which was cooled down to -78 °C in a dry ice/acetone bath. To the frozen dicyclohexylamine was added dropwise a solution of *n*-butyl lithium in hexanes (0.81 mL, 2.70 M, 2.2 mmol, 1.1 equiv). After 15 minutes a solution of diethylzinc in hexanes (1.87 mL, 1.07 M, 2.0 mmol, 1.0 equiv) was added dropwise at -78 °C, resulting in the immediate formation of white solid. The mixture was allowed to warm up to room temperature and was dissolved upon the addition of THF (2 mL). With this sequence, the complex of $[\text{LiNCy}_2]_{0.1}\text{Li}[\text{ZnEt}_2\text{NCy}_2]$ was formed as a homogenous clear to pale yellow solution, reproducibly in the range of 0.33–0.37 M solution in hexanes/THF upon titration.

Standard titration.⁶ A 15-mL round-bottom flask with stir bar was charged with benzoic acid (approx. 60 mg) and 4-(phenylazo)diphenylamine (approx. 2 mg) and placed under N₂ via sequential vacuum purge/nitrogen backfill (3 times). To the flask, was added THF (1.0 mL) and cooled to 0 °C by ice/water bath. To the resulting solution at 0 °C, was added a solution of [LiNCy₂]_{0.1}Li[ZnEt₂NCy₂] complex until the endpoint was observed, as indicated by a persistent dark orange-red color change. The titration results indicate the tribasic nature of this zinc complex (i.e., 3.1 equivalents of basic moieties per mole of complex). The concentration of active [LiNCy₂]_{0.1}Li[ZnEt₂NCy₂] ranges typically from 0.33–0.37 M.

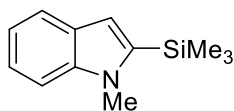
Standard Procedure B: Iodination of Arenes via Deprotonative Zincation. To a vacuum purged and N₂-flushed 8-mL microwave tube containing a solution of arene substrate (0.20 mmol, 1.0 equiv) in THF (to a final concentration of 0.2 M) was added dropwise the solution of [LiNCy₂]_{0.1}Li[ZnEt₂NCy₂] (0.20 mmol, 1.0 equiv). The zincation reaction mixture was allowed to stir at room temperature for 1 h. Separately, iodine (203.0 mg, 0.80 mmol, 4.0 equiv) was added to a 10-mL pear-shaped flask, flushed with nitrogen, and then dissolved in THF (1 mL). The solution of iodine was added dropwise to the reaction mixture at room temperature via syringe. The resulting mixture was allowed to stir at room temperature for 2 h and then quenched by the addition of saturated aqueous sodium thiosulfate solution (10 mL). The organic layer was collected, extracted with ethyl acetate (3 × 10 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under

reduced pressure. Purification of products was performed by silica column chromatography.

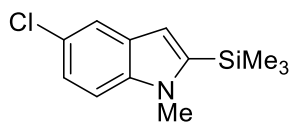
Standard Procedure C: Silylation of Arenes via Deprotonative Zincation. To a vacuum purged and N₂-flushed 8-mL microwave tube containing a solution of arene substrate (0.20 mmol, 1.0 equiv) in THF (to a final concentration of 0.2 M), was added dropwise the solution of [LiNCy₂]_{0.1}·Li[ZnEt₂NCy₂] (0.20 mmol, 1.0 equiv). The mixture was allowed to stir at room temperature for 1 h. Then chlorotrimethylsilane (101 μL, 0.80 mmol, 4.0 equiv) was added dropwise via microsyringe. The resulting reaction mixture was allowed to stir at room temperature for 2 h and then filtered through a plug of silica gel followed by washing with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure. Purification of silylation products was performed by silica column chromatography.

Standard Procedure D: Borylation of Arenes via Deprotonative Zincation. To a vacuum purged and N₂-flushed 8-mL microwave tube containing a solution of arene substrate (0.20 mmol, 1.0 equiv) in THF (to a final concentration of 0.2 M), was added dropwise the solution of [LiNCy₂]_{0.1}·Li[ZnEt₂NCy₂] (0.20 mmol, 1.0 equiv). The mixture was allowed to stir at room temperature for 1 h. Then MeOBpin (131 μL, 0.80 mmol, 4.0 equiv) was added dropwise via microsyringe. The resulting reaction mixture was allowed to stir at room temperature for 2 h, and then filtered through a plug of silica gel followed by washing with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure. Purification of borylated products was performed by silica column chromatography.

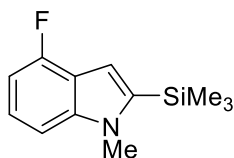
4.3.3 Characterization of compounds



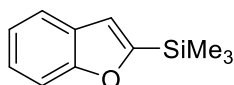
1-Methyl-2-(trimethylsilyl)indole (44). Prepared according to “Standard Procedure C” at a 0.2 mmol scale and a 1.0 mmol scale. Purification by medium pressure chromatography (hexanes) gave **44** as a white solid (39.5 mg, 97% on 0.2 mmol scale and 208.0 mg, 100% on 1.0 mmol scale); $R_f = 0.70$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.64 (d, $J = 7.9$ Hz, 1H), 7.35 (d, $J = 8.3$ Hz, 1H), 7.24 (t, $J = 7.3$ Hz, 1H), 7.10 (t, $J = 7.2$ Hz, 1H), 6.72 (s, 1H), 3.87 (s, 3H), 0.42 (s, 9H). $^1\text{H NMR}$ matched literature spectra.⁸¹



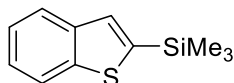
5-Chloro-1-methyl-2-(trimethylsilyl)indole (45). Prepared according to “Standard Procedure C.” Purification by medium pressure chromatography (hexanes to 10% ethyl acetate–hexanes) gave **45** as a white crystalline solid (47.4 mg, 0.199 mmol, 100%); $R_f = 0.63$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.58 (d, $J = 2.0$ Hz, 1H), 7.23 (d, $J = 8.7$ Hz, 1H), 7.18 (dd, $J = 8.7, 1.9$ Hz), 6.64 (s, 1H), 3.84 (s, 3H), 0.42 (s, 9H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 142.8, 138.5, 129.2, 124.8, 122.1, 119.8, 110.7, 109.9, 33.1, -0.6 ; FTIR (thin film): 2955, 1485, 1453, 1353, 1250, 1058, 836, 732 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{12}\text{H}_{17}\text{ClNSi}]^+$ ($[\text{M}+\text{H}]^+$): 238.0813; found: 238.0810.



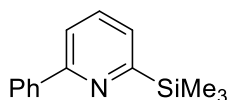
4-Fluoro-1-methyl-2-(trimethylsilyl)indole (46). Prepared according to “Standard Procedure C.” Purification by medium pressure chromatography (hexanes to 10% ethyl acetate–hexanes) gave **46** as a clear oil (39.6 mg, 0.179 mmol, 89%); $R_f = 0.44$ (5% dichloromethane–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.18–7.10 (m, 2H), 6.79 (s, 1H), 6.77–6.74 (m, 1H), 3.87 (s, 3H), 0.43 (s, 9H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 156.2 (d, $J_{\text{C-F}} = 247.3$ Hz), 142.9 (d, $J_{\text{C-F}} = 11.4$ Hz), 141.4, 122.4 (d, $J_{\text{C-F}} = 7.8$ Hz), 117.4 (d, $J_{\text{C-F}} = 22.8$ Hz), 107.0 (d, $J_{\text{C-F}} = 1.1$ Hz), 105.1 (d, $J_{\text{C-F}} = 3.6$ Hz), 103.7 (d, $J_{\text{C-F}} = 19.1$ Hz), 33.3, -0.6 ; $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -122.0 (dd, $J = 10.3$ and 4.9 Hz); FTIR (thin film): 2955, 1501, 1452, 1228, 1071, 997, 753 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{12}\text{H}_{17}\text{FNSi}]^+$ ($[\text{M}+\text{H}]^+$): 222.1109; found: 222.1110.



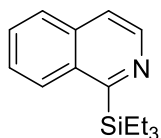
Benzofuran-2-yltrimethylsilane (47). Prepared according to “Standard Procedure C.” Purification by medium pressure chromatography (hexanes) gave **47** as a clear oil (38.1 mg, 0.20 mmol, 100%); $R_f = 0.64$ (5% dichloromethane–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.56 (d, $J = 7.7$ Hz, 1H), 7.50 (d, $J = 8.2$ Hz, 1H), 7.25–7.20 (m, 1H), 7.18 (t, $J = 7.4$ Hz, 1H), 6.95 (t, $J = 1.0$ Hz, 1H), 0.35 (s, 9H). $^1\text{H NMR}$ matched literature spectra.⁸²



Benzo[*b*]thiophen-2-yltrimethylsilane (48). Prepared according to “Standard Procedure C.” Purification by medium pressure chromatography (hexanes) gave **48** as a clear oil (41.5 mg, 0.20 mmol, 100%); $R_f = 0.90$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.90 (d, $J = 8.4$ Hz, 1H), 7.82 (d, $J = 7.7$ Hz, 1H), 7.48 (s, 1H), 7.37–7.30 (m, 2H), 0.40 (s, 9H). $^1\text{H NMR}$ matched literature spectra.⁸²

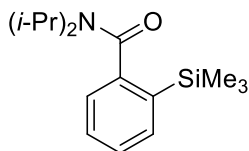


2-Phenyl-6-(trimethylsilyl)pyridine (49). Prepared according to “Standard Procedure C” with 1.3 equiv of base for 2 h for the deprotonation step. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **49** as a yellow oil (23.6 mg, 0.104 mmol, 52%); $R_f = 0.67$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.10–8.08 (m, 2H), 7.65 (d, $J = 4.0$ Hz, 2H), 7.50–7.40 (m, 4H), 0.38 (s, 9H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 168.1, 156.5, 139.9, 134.5, 128.7, 128.6, 127.1, 126.9, 119.2, –1.7; FTIR (thin film): 3062, 2955, 1556, 1453, 1245, 837, 752 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{14}\text{H}_{18}\text{NSi}]^+$ ($[\text{M}+\text{H}]^+$): 228.1203; found: 228.1202.

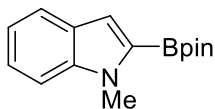


1-(Triethylsilyl)isoquinoline (50). Prepared according to “Standard Procedure C” with chlorotriethylsilane for the silylation step. Purification by flash column chromatography

(hexanes to 20% ethyl acetate–hexanes) gave **50** as a yellow oil (30.0 mg, 0.123 mmol, 62%); $R_f = 0.68$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.70 (d, $J = 5.7$ Hz, 1H), 8.22 (d, $J = 8.3$ Hz, 1H), 7.81 (d, $J = 7.6$ Hz, 1H), 7.67–7.62 (m, 1H), 7.59–7.55 (m, 2H), 1.09–1.05 (m, 6H), 1.02–0.97 (m, 9H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 170.1, 142.9, 134.3, 133.8, 129.2, 127.8, 127.6, 126.5, 119.8, 7.7, 4.7; FTIR (thin film): 3046, 2952, 2873, 1456, 1237, 1004, 825, 733 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{15}\text{H}_{22}\text{NSi}]^+$ ($[\text{M}+\text{H}]^+$): 244.1516; found: 244.1515.

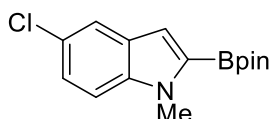


***N,N*-Diisopropyl-2-(trimethylsilyl)benzamide (51)**. Prepared according to “Standard Procedures C.” Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **51** as a white crystalline solid (54.9 mg, 0.20 mmol, 99%); $R_f = 0.50$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.61–7.59 (m, 1H), 7.33–7.30 (m, 2H), 7.16–7.14 (m, 1H), 3.84–3.76 (br m, 1H), 3.54–3.45 (br m, 1H), 1.61–1.51 (m, 6H), 1.20–1.10 (m, 6H), 0.33 (s, 9H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 172.2, 144.0, 138.0, 135.2, 128.1, 127.6, 125.1, 50.8, 45.7, 20.6, –0.1; FTIR (thin film): 3041, 2967, 1619, 1437, 1333, 1242, 833, 749 cm^{-1} ; HRMS-ESI (m/z) Calcd for $(\text{C}_{16}\text{H}_{28}\text{NOSi})$ ($[\text{M}+\text{H}]^+$): 278.1940; found 278.1934.



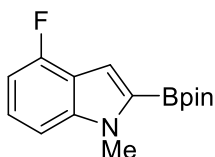
1-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (55). Prepared according to “Standard Procedure D.” Purification by medium pressure chromatography

(hexanes to 10% ethyl acetate–hexanes) gave **55** as a white solid (40.8 mg, 0.159 mmol, 79%); $R_f = 0.60$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.65 (d, $J = 7.6$ Hz, 1H), 7.35 (d, $J = 8.3$ Hz, 1H), 7.29–7.26 (m, 1H), 7.14 (s, 1H), 7.11–7.07 (m, 1H), 3.98 (s, 3H), 1.38 (s, 12H). $^1\text{H NMR}$ matched literature spectra.^{70a}



5-Chloro-1-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (56).

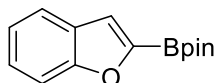
Prepared according to “Standard Procedure D.” Purification by flash column chromatography (hexanes to 20% ethyl acetate–hexanes) gave **56** as a white solid (41.1 mg, 0.141 mmol, 70%); $R_f = 0.36$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.60 (d, $J = 1.9$ Hz, 1H), 7.25 (d, $J = 7.8$ Hz, 1H), 7.19 (dd, $J = 8.8, 1.9$ Hz, 1H), 7.04 (s, 1H), 3.97 (s, 3H), 1.38 (s, 12H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 138.5, 128.7, 125.0, 123.4, 120.7, 113.5, 110.7, 83.9, 32.4, 24.8; FTIR (thin film): 2976, 2937, 1519, 1254, 1133, 1068, 859, 788, 690 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{15}\text{H}_{20}\text{BClNO}_2]^+$ ($[\text{M}+\text{H}]^+$): 292.1270; found: 292.1274.



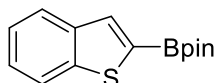
4-Fluoro-1-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (57).

Prepared according to “Standard Procedure D” at 0.2 mmol scale and 3.0 mmol scale. Purification by medium pressure chromatography (hexanes to 10% ethyl acetate–hexanes) gave **57** as a pale yellow solid (39.7 mg, 0.144 mmol, 72% on a 0.2 mmol scale and 567.1

mg, 2.06 mmol, 69% on a 3.0 mmol scale); $R_f = 0.52$ (5% ethyl acetate–hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.22 (s, 1H), 7.16 (dd, $J = 7.7, 5.1$ Hz, 1H), 7.11 (d, $J = 8.2$ Hz, 1H), 6.74 (dd, $J = 10.4, 7.3$ Hz, 1H), 3.97 (s, 3H), 1.38 (s, 12H); ^{13}C NMR (125 MHz, CDCl_3) δ 123.6 (d, $J_{\text{C-F}} = 7.7$ Hz), 110.0, 105.7 (d, $J_{\text{C-F}} = 3.8$ Hz), 103.7 (d, $J_{\text{C-F}} = 19.1$ Hz), 83.8, 32.6, 31.6, 22.6, 24.8, 14.1; ^{19}F NMR (376 MHz, CDCl_3) δ -121.05 (dd, $J = 10.2, 5.0$ Hz); FTIR (thin film): 2976, 1522, 1296, 1232, 1137, 1064, 961, 854, 688 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{15}\text{H}_{20}\text{BFNO}_2]^+$ ($[\text{M}+\text{H}]^+$): 276.1566; found: 276.1569.

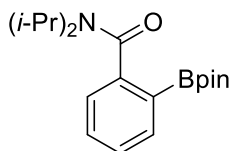


2-(Benzofuran-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (58). Prepared according to “Standard Procedure D.” Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **58** as a clear oil (32.2 mg, 0.132 mmol, 66%); $R_f = 0.28$ (5% ethyl acetate–hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.63 (d, $J = 7.8$ Hz, 1H), 7.57 (d, $J = 8.3$ Hz, 1H), 7.40 (s, 1H), 7.34 (t, $J = 7.8$ Hz, 1H), 7.23 (t, $J = 7.5$ Hz, 1H), 1.39 (s, 12H). ^1H NMR matched literature spectra.⁸³



2-(Benzo[b]thiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (59). Prepared according to “Standard Procedure D.” Purification by medium pressure chromatography (hexanes to 10% ethyl acetate–hexanes) gave **59** as a clear oil (38.4 mg, 0.148 mmol, 74%); $R_f = 0.49$ (5% ethyl acetate–hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.92–7.90 (m, 1H), 7.89

(s, 1H), 7.87–7.84 (m, 1H), 7.38–7.34 (m, 2H), 1.38 (s, 12H). ^1H NMR matched literature spectra.⁸⁴



***N,N*-Diisopropyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (60).**

Prepared according to “Standard Procedure D” with the borylation run at 0 °C for 30 min.

Purification by medium pressure chromatography (hexanes to 30% ethyl acetate–hexanes)

gave **60** as a clear oil (44.3 mg, 0.134 mmol, 67%); R_f = 0.22 (20% ethyl acetate–hexanes); ^1H

NMR (400 MHz, CDCl_3) δ 7.79 (dd, J = 7.5, 1.4 Hz, 1H), 7.39 (td, J = 7.6, 1.5 Hz, 1H), 7.30

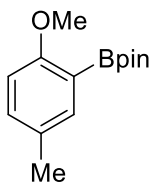
(td, J = 7.6, 1.4 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 3.75–3.68 (m, 1H), 3.53–3.45 (m, 1H), 1.57

(d, J = 6.7 Hz, 6H), 1.30 (s, 12H), 1.11 (d, J = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.2,

144.9, 135.5, 130.5, 127.3, 124.5, 83.7, 65.8, 50.8, 45.7, 24.8, 20.4, 20.1, 15.2; FTIR (thin film):

2976, 2931, 1626, 1432, 1352, 1143, 728 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{19}\text{H}_{31}\text{BNO}_3]^+$

($[\text{M}+\text{H}]^+$): 322.2392; found: 332.2396.

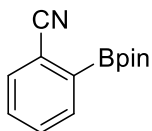


2-(2-Methoxy-5-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (61). Prepared

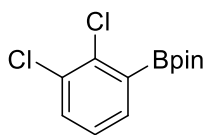
according to “Standard Procedure D” with 1.3 equiv of base for 70 °C for 3 h for the

deprotonation step and the borylation run at 0 °C for 30 min. Purification by medium

pressure chromatography (hexanes to 30% ethyl acetate–hexanes) gave **61** as a clear oil (31.0 mg, 0.125 mmol, 62%); $R_f = 0.19$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.49 (d, $J = 2.5$ Hz, 1H), 7.19 (dd, $J = 8.4, 2.5$ Hz, 1H), 6.76 (d, $J = 8.4$ Hz), 3.80 (s, 3H), 2.28 (s, 3H), 1.36 (s, 12H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 162.2, 137.1, 132.9, 129.1, 110.5, 83.4, 56.0, 24.8, 20.2; FTIR (thin film): 2980, 1607, 1495, 1346, 1265, 1143, 1071, 731 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{14}\text{H}_{22}\text{BO}_3]^+$ ($[\text{M}+\text{H}]^+$): 249.1657; found: 249.1662.

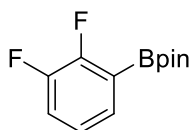


2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (62). Prepared according to “Standard Procedure D” with 0.67 equiv of base for 15 mins for the deprotonation step and with 8.0 equiv of MeOBpin for 24 h for the borylation step. Purification by medium pressure chromatography (hexanes to 30% ethyl acetate–hexanes) gave **62** as a white solid (29.3 mg, 0.128 mmol, 64%); $R_f = 0.26$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.88 (dd, $J = 7.2, 1.6$ Hz, 1H), 7.69 (dd, $J = 7.4, 1.6$ Hz, 1H), 7.56 (td, $J = 7.5, 1.6$ Hz, 1H), 7.52 (td, $J = 7.6, 1.6$ Hz, 1H), 1.38 (s, 12H). $^1\text{H NMR}$ matched literature spectra.⁸⁵



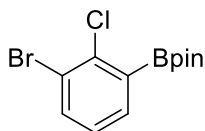
2-(2,3-Dichlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (63). Prepared according to “Standard Procedure D” and with 8.0 equiv of MeOBpin for 24 h for the borylation step. Purification by medium pressure chromatography (hexanes to 10% ethyl acetate–

hexanes) gave **63** as a clear oil (30.6 mg, 0.112 mmol, 56%); $R_f = 0.68$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.56 (d, $J = 7.4$ Hz, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.18, (t, $J = 7.7$ Hz, 1H), 1.37 (s, 12H). $^1\text{H NMR}$ matched literature spectra.⁸⁶



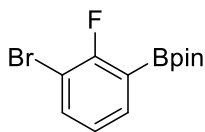
2-(2,3-Difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (64).

Prepared according to “Standard Procedure D” and with 8.0 equiv of MeOBpin for 24 h for the borylation step. Purification by medium pressure chromatography (hexanes to 10% ethyl acetate–hexanes) gave **64** as a clear oil (34.9 mg, 0.145 mmol, 73%); $R_f = 0.61$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.47–7.45 (m, 1H), 7.24–7.20 (m, 1H), 7.09–7.04 (m, 1H), 1.36 (s, 12H). $^1\text{H NMR}$ matched literature spectra.^{70a}

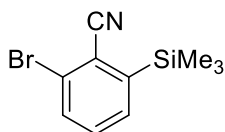


2-(3-Bromo-2-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (65). Prepared according to “Standard Procedure D” and with 8.0 equiv of MeOBpin for 24 h for the borylation step. Purification by medium pressure chromatography (hexanes) gave **65** as clear oil (25.9 mg, 0.082 mmol, 41%); $R_f = 0.48$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.67 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.59 (dd, $J = 7.4, 1.6$ Hz, 1H), 7.10 (t, $J = 7.6$ Hz, 1H), 1.37 (s, 12H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 138.8, 135.8, 134.8, 127.1, 123.6, 84.5, 24.8;

FTIR (thin film): 2980, 2932, 2837, 1620, 1337, 1139, 852; Compound did not ionize by HRMS-ESI; GC-MS (m/z) Calcd for [C₁₂H₁₅BBrClO₂]: 318.0; found: 318.0.

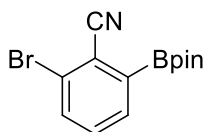


2-(3-Bromo-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (66). Prepared according to “Standard Procedure D” and with 8.0 equiv of MeOBpin for 24 h for the borylation step. Purification by medium pressure chromatography (hexanes to 10% ethyl acetate–hexanes) gave **66** as clear oil (24.6 mg, 0.082 mmol, 41%); $R_f = 0.49$ (5% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.65 (m, 2H), 7.02 (t, $J = 7.6$ Hz, 1H), 1.36 (s, 12H); ¹³C NMR (125 MHz, CDCl₃) δ 162.8 (d, $J_{C-F} = 251.6$ Hz), 136.6, 135.7, 124.8, 109.3 (d, $J_{C-F} = 22.7$ Hz), 84.2, 24.8; ¹⁹F NMR (376 MHz, CDCl₃) δ -96.8 (td, $J = 6.1, 5.7, 2.6$ Hz); FTIR (thin film): 2984, 2931, 2835, 1616, 1490, 1347, 1139, 736 cm⁻¹; Compound did not ionize by HRMS-ESI; GC-MS (m/z) Calcd for [C₁₂H₁₅BBrFO₂]: 300.0; found: 300.0.

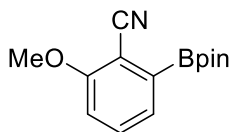


2-Bromo-6-(trimethylsilyl)benzonitrile (67). Prepared according to “Standard Procedure C” with deprotonation step run with chlorotrimethylsilane *in situ* at 0.067M for 18 h. Purification medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **67** as a clear oil (29.6 mg, 0.116 mmol, 58%); $R_f = 0.73$ (20% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, $J = 8.1$ Hz, 1H), 7.53 (d, $J = 7.4$ Hz, 1H), 7.39 (t, $J = 7.6$ Hz,

1H), 0.43 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 134.3, 133.9, 133.2, 132.9, 132.6, 127.6, 127.1, -1.5; FTIR (thin film): 2956, 2226, 1524, 1252, 1081, 840, 730 cm⁻¹; Compound did not ionize by HRMS-ESI; GC-MS (m/z) Calcd for (C₁₀H₁₂BrNSi): 253.0; found: 253.0.

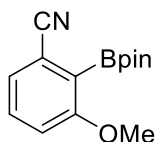


2-Bromo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (68). Prepared according to “Standard Procedure D” with 0.67 equiv of base for 15 min for deprotonation step and with 8.0 equiv of MeOBpin for 24 h for borylation step. Purification by medium pressure chromatography (hexanes to 30% ethyl acetate–hexanes) gave **68** as a clear oil (24.8 mg, 0.081 mmol, 40%); R_f = 0.49 (5% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.81 (dd, J = 7.6, 1.3 Hz, 1H), 7.75 (dd, J = 8.1, 1.3 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 1.38 (s, 12H); ¹³C NMR (125 MHz, CDCl₃) δ 135.1, 134.2, 132.6, 126.9, 116.8, 100.6, 85.1, 24.8; FTIR (thin film): 2979, 2930, 2230, 1586, 1458, 1351, 1137, 962, 857 cm⁻¹; HRMS-ESI (m/z) Calcd for [C₁₃H₁₆BBrNO₂]⁺ ([M+H]⁺): 308.0452; found: 308.0451.

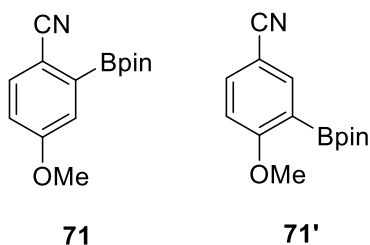


2-Methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (69). Prepared according to “Standard Procedure D” with 0.67 equiv of base for 15 min for the deprotonation step. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **69** as a white solid (32.8 mg, 0.127 mmol, 63%); R_f = 0.48 (20%

ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.50 (dd, $J = 8.4, 7.4$ Hz, 1H), 7.39 (dd, $J = 7.5, 1.1$ Hz, 1H), 7.05 (dd, $J = 8.4, 1.1$ Hz, 1H), 3.91 (s, 3H), 1.36 (s, 12H); $^1\text{H NMR}$ matched literature spectra.⁸⁷

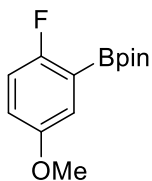


3-Methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (70). Prepared according to “Standard Procedure D” with 0.67 equiv of base for 15 min for the deprotonation step. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **70** as a clear oil (23.1 mg, 0.089 mmol, 45%); $R_f = 0.47$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.42–7.38 (m, 1H), 7.23 (d, $J = 7.6$ Hz, 1H), 7.03 (d, $J = 8.5$ Hz, 1H), 3.82 (s, 3H), 1.41 (s, 12H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.7, 131.5, 124.7, 118.7, 116.8, 114.1, 84.9, 55.9, 24.7; FTIR (thin film): 2978, 2942, 2226, 1591, 1568, 1434, 1261, 1053, 851 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{14}\text{H}_{19}\text{BNO}_3]^+$ ($[\text{M}+\text{H}]^+$): 260.1453; found: 260.1455.



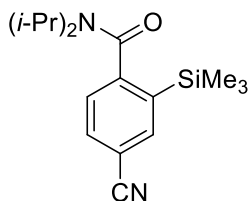
4-Methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (71) and **4-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (71')**. Prepared according to “Standard Procedure D” with 0.67 equiv of base for 15 min for the

deprotonation step. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **71** as a white solid (22.1 mg, 0.085 mmol, 43%) and **71'** as a white solid (4.2 mg, 0.016 mmol, 8%). **71**: $R_f = 0.12$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.62 (d, $J = 8.6$ Hz, 1H), 7.34 (d, $J = 2.8$ Hz, 1H), 7.00 (dd, $J = 8.6, 2.8$ Hz, 1H), 3.87 (s, 3H), 1.38 (s, 12H). $^1\text{H NMR}$ matched literature spectra.⁷⁷ **71'**: $R_f = 0.12$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.96 (d, $J = 2.3$ Hz, 1H), 7.68 (dd, $J = 8.7, 2.3$ Hz, 1H), 6.90 (d, $J = 8.7$ Hz, 1H), 3.89 (s, 3H), 1.36 (s, 12H). $^1\text{H NMR}$ matched literature spectra.⁷⁷

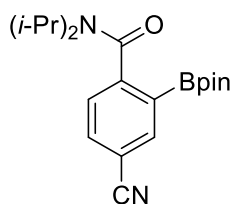


2-(2-Fluoro-5-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (72). Prepared according to “Standard Procedure D” and with 8.0 equiv of MeOBpin for the borylation step. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **72** as a clear oil (26.5 mg, 0.105 mmol, 53%); $R_f = 0.68$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.20–7.18 (m, 1H), 6.95 (d, $J = 2.7$ Hz, 1H), 6.94 (d, $J = 1.8$ Hz, 1H), 3.80 (s, 3H), 1.36 (s, 12H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 161.6 (d, $J_{\text{C-F}} = 243.3$ Hz), 155.2, 119.8 (d, $J_{\text{C-F}} = 8.2$ Hz), 119.3 (d, $J_{\text{C-F}} = 8.6$ Hz), 116.0 (d, $J_{\text{C-F}} = 26.2$ Hz), 83.9, 55.8, 24.8; $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -114.1 (td, $J = 7.3, 6.9$ and 4.9 Hz) FTIR (thin film): 2983,

2952, 2837, 1619, 1585, 1373, 1241, 852 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{13}\text{H}_{19}\text{BFO}_3]^+$ ($[\text{M}+\text{H}]^+$): 253.1406; found: 253.1408.

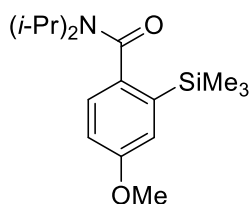


4-Cyano-*N,N*-diisopropyl-2-(trimethylsilyl)benzamide (73). Prepared according to “Standard Procedure C” with 0.67 equiv of base for 15 min for the deprotonation step. Reactions run on both 0.2 and 3.0 mmol scale. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **73** as a white solid (29.5 mg, 0.098 mmol, 49% for 0.2 mmol scale and 349.7, 1.15 mmol, 39% for 3.0 mmol scale); $R_f = 0.57$ (20% ethyl acetate–hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.86 (d, $J = 1.8$ Hz, 1H), 7.61 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.23 (d, $J = 7.9$ Hz, 1H), 3.64 (quin, $J = 6.4$ Hz, 1H), 3.52 (quin, $J = 6.6$ Hz, 1H), 1.55 (d, $J = 6.9$ Hz, 6H), 1.16 (d, $J = 6.6$ Hz, 6H), 0.33 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.4, 147.8, 140.4, 139.1, 131.7, 125.6, 118.8, 111.9, 50.9, 46.1, 20.5, 20.4, – 0.1; FTIR (thin film): 2961, 2230, 1614, 1439, 1371, 868 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{17}\text{H}_{27}\text{N}_2\text{OSi}]^+$ ($[\text{M}+\text{H}]^+$): 303.1887; found: 303.1888.



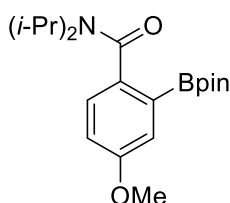
4-Cyano-*N,N*-diisopropyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

(74). Prepared according to “Standard Procedure C” with 0.67 equiv of base for 15 min for the deprotonation step. Purification by medium pressure chromatography (dichloromethane to 5% isopropanol–dichloromethane) gave **74** as a clear oil (35.8 mg, 0.101 mmol, 50%); $R_f = 0.29$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.10 (d, $J = 1.8$ Hz, 1H), 7.68 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.24 (d, $J = 8.3$ Hz, 1H), 3.59–3.48 (m, 2H), 1.56 (d, $J = 6.8$ Hz, 6H), 1.31 (s, 12H), 1.12 (d, $J = 6.7$ Hz, 6H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 169.2, 148.8, 139.6, 134.0, 125.3, 118.4, 111.5, 84.6, 51.1, 45.9, 24.8, 20.2, 20.1; FTIR (thin film): 2974, 2929, 2231, 1625, 1392, 1139 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{20}\text{H}_{30}\text{BN}_2\text{O}_3]^+$ ($[\text{M}+\text{H}]^+$): 357.2344; found: 357.2349.



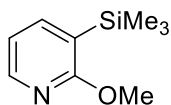
***N,N*-Diisopropyl-4-methoxy-2-(trimethylsilyl)benzamide (75).** Prepared according to “Standard Procedure C” with 1.3 equiv of base for 3 h for the deprotonation step. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **75** as a white solid (61.5 mg, 0.20 mmol, 100%); $R_f = 0.59$ (20% ethyl acetate–hexanes);

^1H NMR (400 MHz, CDCl_3) δ 7.12–7.09 (m, 2H), 6.80 (dd, $J = 8.4, 2.7$ Hz, 1H), 3.91–3.76 (br m, 1H), 3.81 (s, 3H), 3.54–3.41 (br m, 1H), 1.60–1.47 (br m, 6H), 1.20–1.09 (br m, 6H), –0.30 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.2, 158.7, 140.5, 136.6, 126.7, 121.1, 112.4, 55.1, 50.8, 45.7, 20.6, –0.1; FTIR (thin film): 2967, 1619, 1589, 1431, 1332, 872 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{17}\text{H}_{30}\text{NO}_2\text{Si}]^+$ ($[\text{M}+\text{H}]^+$): 308.2040; found: 308.2042.

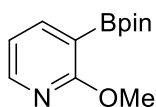


***N,N*-Diisopropyl-4-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide**

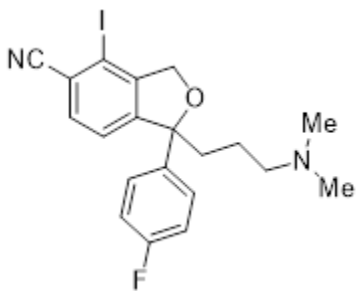
(76). Prepared according to “Standard Procedure D” with 1.3 equiv of base for 3 h for the deprotonation step and the borylation run at 0 °C for 1 h. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **76** as a clear oil (16.6 mg, 0.046 mmol, 23%); $R_f = 0.11$ (20% ethyl acetate–hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.24 (d, $J = 2.7$ Hz, 1H), 7.21 (d, $J = 8.5$ Hz, 1H), 6.86 (dd, $J = 8.5, 2.7$ Hz, 1H), 4.18–4.05 (br m, 1H), 3.84 (s, 3H), 3.62–3.49 (br m, 1H), 1.59–1.51 (br m, 6H), 1.31 (s, 12H), 1.22–1.15 (br m, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.4, 160.0, 134.0, 126.2, 117.8, 115.9, 82.5, 55.3, 50.8, 46.8, 31.5, 25.0, 22.6, 20.5, 20.3; FTIR (thin film): 2974, 1627, 1585, 1337, 1201 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{20}\text{H}_{33}\text{BNO}_4]^+$ ($[\text{M}+\text{H}]^+$): 362.2497; found: 362.2501.



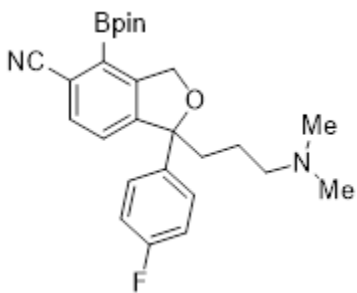
2-Methoxy-3-(trimethylsilyl)pyridine (77). Prepared according to “Standard Procedure C” at 0.2 mmol scale and 3.0 mmol scale. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **77** as a clear oil (20.8 mg, 57% on 0.2 mmol scale and 293.5 mg, 54% on 3.0 mmol scale); $R_f = 0.53$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.14 (dd, $J = 5.1, 2.1$ Hz, 1H), 7.62 (dd, $J = 6.9, 2.1$ Hz, 1H), 6.82 (dd, $J = 6.8, 5.1$ Hz, 1H), 3.92 (s, 3H), 0.25 (s, 9H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 167.6, 147.7, 144.3, 121.6, 116.6, 53.0, -1.6 ; FTIR (thin film): 2950, 2857, 1729, 1569, 1381, 1244, 1021, 836, 783 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_9\text{H}_{16}\text{NOSi}]^+$ ($[\text{M}+\text{H}]^+$): 182.0996; found: 182.1002.



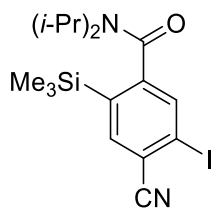
2-Methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (78). Prepared according to “Standard Procedure D” with the borylation step at $0\text{ }^\circ\text{C}$ for 1 h. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **78** as a clear oil (19.5 mg, 0.083 mmol, 42%); $R_f = 0.14$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.22 (dd, $J = 5.0, 2.1$ Hz, 1H), 7.97 (dd, $J = 7.1, 2.1$ Hz, 1H), 6.85 (dd, $J = 7.1, 5.0$ Hz, 1H), 3.96 (s, 3H), 1.35 (s, 12H). $^1\text{H NMR}$ matched literature spectra.⁸⁸



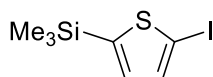
1-(3-(Dimethylamino)propyl)-1-(4-fluorophenyl)-4-iodo-1,3-dihydroisobenzofuran-5-carbonitrile (79). Prepared according to “Standard Procedure B” with 0.67 equiv of base for 15 min for the deprotonation step. Purification by medium pressure chromatography (dichloromethane to 30% isopropanol–dichloromethane) gave **79** as pale yellow solid (76.2 mg, 0.169 mmol, 85%); $R_f = 0.14$ (20% isopropanol–dichloromethane); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.58 (m, 2H), 7.48 (m, 2H), 7.04 (m, 2H), 5.12 (d, $J = 13.5$ Hz, 1H), 5.03 (d, $J = 13.6$ Hz, 1H), 3.37 (m, 2H), 2.17 (s, 6H), 1.83 (m, 2H), 1.24 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 163.3, 148.4, 145.4, 138.3, 134.5, 126.7, 122.4, 120.0, 118.9, 115.9, 115.7, 92.7, 58.1, 54.4, 43.4, 31.0, 28.9, 24.8; $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -114.4 (m); FTIR (thin film): 2933, 2854, 2697, 2229, 1600, 1506, 1449, 1223, 905, 724 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{20}\text{H}_{21}\text{FIN}_2\text{O}]^+$ ($[\text{M}+\text{H}]^+$): 451.0677; found: 451.0684.



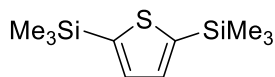
1-(3-(Dimethylamino)propyl)-1-(4-fluorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydroisobenzofuran-5-carbonitrile (80). Prepared according to “Standard Procedure D” with 0.67 equiv of base for 15 min for the deprotonation step. Purification by medium pressure chromatography (dichloromethane to 10% methanol–dichloromethane) gave **80** as a clear oil (61.9 mg, 0.137 mmol, 68%); $R_f = 0.05$ (10% methanol–dichloromethane); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.63 (d, $J = 7.8$ Hz, 1H), 7.41 (m, 3H), 6.99 (t, $J = 8.7$ Hz, 2H), 5.32 (d, $J = 14.2$ Hz, 1H), 5.22 (d, $J = 14.2$ Hz, 1H), 2.23 (t, $J = 7.0$ Hz, 2H), 2.14 (s, 6H), 1.86 (m, 1H), 1.48 (m, 1H), 1.36 (s, 12H), 1.28 (m, 2H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 160.9, 147.9, 147.4, 140.0, 133.1, 126.7, 124.4, 118.8, 116.8, 115.3, 115.1, 90.5, 84.8, 72.9, 59.4, 45.3, 38.9, 24.9, 22.1; $^{19}\text{F NMR}$ (400 MHz, CDCl_3) δ –115.7 Hz; FTIR (thin film): 2943, 2859, 2776, 2229, 1600, 1506, 1136, 1031, 830 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{26}\text{H}_{33}\text{BFN}_2\text{O}_3]^+$ ($[\text{M}+\text{H}]^+$): 451.2563; found: 451.2566.



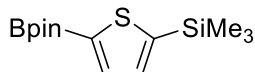
4-Cyano-2-iodo-*N,N*-diisopropyl-6-(trimethylsilyl)benzamide (81). Prepared according to “Standard Procedure B.” Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **81** as a yellow oil (72.3 mg, 0.169 mmol, 84%); R_f = 0.21 (5% ethyl acetate–hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.77 (s, 1H), 7.63 (s, 1H), 3.65–3.57 (m, 1H), 3.54–3.47 (m, 1H), 1.53 (d, J = 6.8 Hz, 6H), 1.17 (d, J = 6.7 Hz, 6H), 0.31 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 168.7, 148.3, 140.9, 139.5, 119.9, 119.3, 98.3, 51.0, 46.2, 20.4, –0.3; FTIR (thin film): 2964, 2230, 1624, 1435, 1338, 838 cm^{-1} ; HRMS-ESI (m/z) Calcd for $[\text{C}_{17}\text{H}_{26}\text{IN}_2\text{OSi}]^+$ ($[\text{M}+\text{H}]^+$): 429.0854; found: 429.0862.



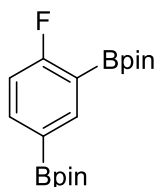
(5-Iodothiophen-2-yl)trimethylsilane (82). Prepared according to “Standard Procedure B” with 0.67 equiv of base for 15 min for the deprotonation step. Purification by medium pressure chromatography (hexanes) gave **82** as a clear oil (46.9 mg, 0.166 mmol, 83%); R_f = 0.69 (hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.27 (d, J = 3.4 Hz, 1H), 6.93 (d, J = 3.4 Hz, 1H), 0.31 (s, 9H). ^1H NMR matched literature spectra.⁸²



2,5-Bis(trimethylsilyl)thiophene (83). Prepared according to “Standard Procedure C” with 0.67 equiv of base for 15 min for the deprotonation step. Purification by medium pressure chromatography (hexanes) gave **83** as a clear oil (32.0 mg, 0.140 mmol, 70%); $R_f = 0.71$ (hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.37 (s, 2H), 0.37 (s, 18H). $^1\text{H NMR}$ matched literature spectra.⁸⁹



Trimethyl(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)silane (84). Prepared according to “Standard Procedure D” with 0.67 equiv of base for 15 min for the deprotonation step. Purification by medium pressure chromatography (hexanes to 10% ethyl acetate–hexanes) gave **84** as a white solid (45.5 mg, 0.161 mmol, 81%); $R_f = 0.35$ (hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.70 (d, $J = 3.4$ Hz, 1H), 7.33 (d, $J = 3.4$ Hz, 1H), 1.35 (s, 12H), 0.33 (s, 9H). $^1\text{H NMR}$ matched literature spectra.⁹⁰



2,2'-(4-Fluoro-1,3-phenylene)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (85). Prepared according to “Standard Procedure D” with 8.0 equiv of MeOBpin for 24 h for the borylation step. Purification by medium pressure chromatography (hexanes to 10% ethyl

acetate–hexanes) gave **85** as a white solid (23.1 mg, 0.066 mmol, 33%); $R_f = 0.31$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.20 (dd, $J = 6.6, 1.9$ Hz, 1H), 7.88 (ddd, $J = 8.1, 6.0, 1.8$ Hz, 1H), 1.35 (s, 12H), 1.33 (s, 12H). $^1\text{H NMR}$ matched literature spectra.⁹¹

5. Lithium zincate mediated α -functionalization of substituted amides

5.1 Significance of α -functionalized amides

Peptides, the building blocks of proteins, contain amide bonds linking amino acids. Therefore, it is unsurprising that a large portion of bioactive molecules contain at least one if not multiple amide motifs. Amides are ubiquitous functional groups in natural products, pharmaceuticals and agrochemicals⁹² and in many cases these valuable amide-containing molecules are highly functionalized and substituted. For example, natural product alkaloids⁹³, fungicides⁹⁴, anticancer⁹⁵, antiviral⁹⁶, antidepressant⁹⁷ and ischemia⁹⁸ drugs contain amides which have α -functionalization (Figure 3).

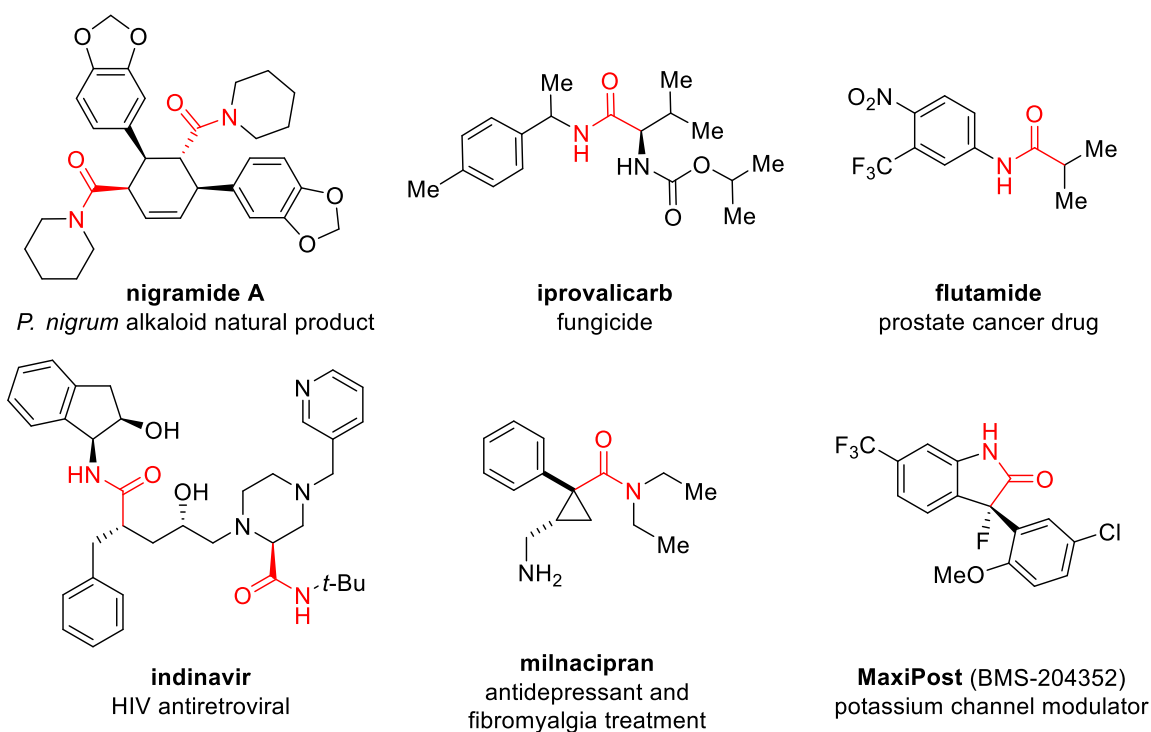


Figure 3: Selected examples of biologically active α -functionalized amides

α -Functionalization of carbonyl derivatives is a common synthetic approach and there are several general methods that have been used for this purpose, often by transition metal catalysis. This introduction will focus on the common and highly useful arylation, alkenylation, and allylation reactions for the α -functionalization of amides. These transformations can occur either through the functionalization of C–halogen or C–H bonds (Scheme 36). When possible, direct C–H functionalization is desirable due to atom economy and the accessibility of precursors, whereas α -halogenated intermediates must be separately synthesized.⁹⁹

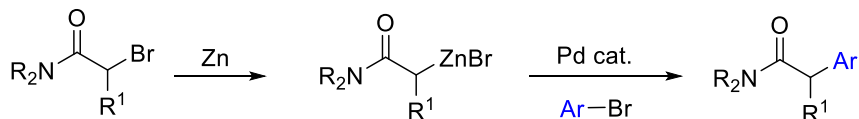
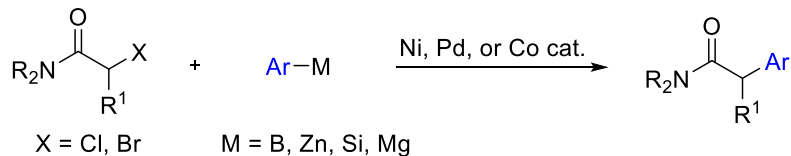
α -Halo amides are known to undergo palladium, nickel or cobalt-catalyzed arylation and alkenylation with organometallic reagents (Scheme 36, I). For palladium-catalyzed arylation, α -chloro acetamides can be coupled with trifluoroborate salts¹⁰⁰ and α -bromo acetamides with boronic acids¹⁰¹, both requiring stoichiometric base, high temperatures and limited to unsubstituted acetamide substrates. Nickel catalysis has enabled arylation of substituted α -halo amides with trifluorosilanes¹⁰², boranes¹⁰³, and organozinc chloride¹⁰⁴ reagents. There are few reports for alkenylation, which include palladium-catalyzed cross-coupling with potassium alkenyltrifluoroborates and α -chloro acetamides,¹⁰⁵ and a nickel-catalyzed Heck type reaction that has been reported with alkenes and substituted α -carbonyl bromides.¹⁰⁶ A general cobalt-catalyzed arylation and alkenylation of α -bromo amides has been demonstrated with Grignard reagents.¹⁰⁷

Additionally α -bromo amides can be converted into zinc amide enolates for palladium-catalyzed arylation with aryl bromides.¹⁰⁸

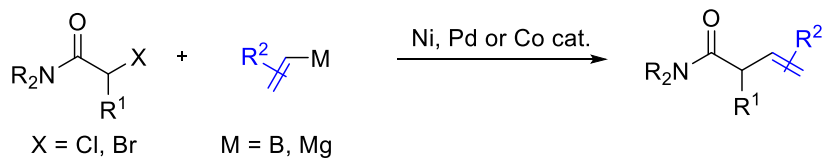
For direct C–H α -functionalization, palladium-catalyzed arylation (Scheme 36, II, a) has been reported with aryl bromides¹⁰⁹ or aryl chlorides¹¹⁰, however the substrate scope is limited to unsubstituted acetamide derivatives or activated 2-aryl substituted acetamides with stoichiometric base and under high temperatures.¹¹¹ Similarly, the arylation of acetamide can be achieved under milder conditions with ZnTMP₂ (**1**) as the base.⁵

(I) Functionalization of α C-X Bonds

(a) Arylation

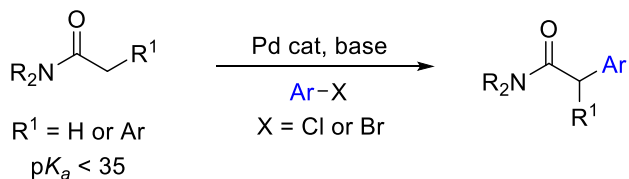


(b) Alkenylation

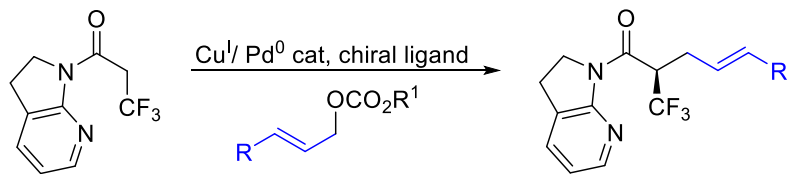
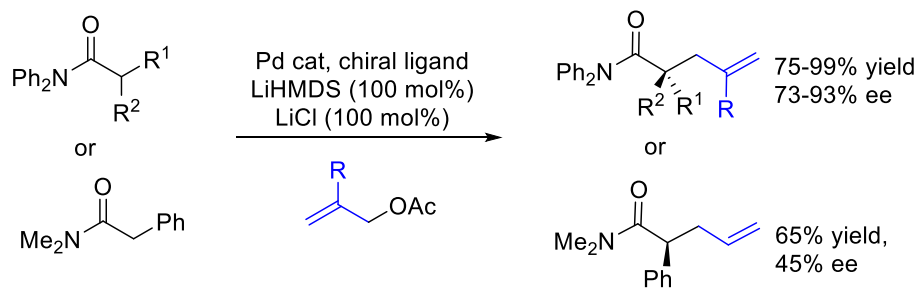


(II) Functionalization of α C-H Bond

(a) Pd-catalyzed arylation



(b) Asymmetric Allylic Alkylation



Scheme 36: Methods for α -functionalization of amides

While asymmetric allylic alkylation (AAA) is a highly useful and well-established palladium-catalyzed transformation, it has not been generally applicable for the allylation of amides, with very specific substrate limitations. Activated methylene nucleophiles such as azlactones¹¹², 3-aryloxindoles¹¹³, pyrazole-5-ones¹¹⁴, and glycine Schiff base derivatives¹¹⁵, which are easily enolized, readily undergo AAA. However, expanding the scope to less activated nucleophiles has been challenging. Synergistic dual catalysis has helped to advance the field, including for the α -functionalization of aldehydes¹¹⁶, α -hydroxyketones¹¹⁷, and pentafluorophenyl esters.¹¹⁸ However, amides are the most difficult to enolize of the carbonyl functionalities (Figure 4) and are underexplored as nucleophiles. For the specific substrate of α -trifluoromethyl-7-azaindoline acetamide, catalytic enolization could be achieved by Cu(I)/Bronsted base cooperative catalysis in conjugation with Pd(0) catalyzed asymmetric allylation (Scheme 36, II, b). In this case the azaindoline coordinated to the copper catalyst to allow for catalytic generation of an amide enolate.¹¹⁹ For a limited scope of acyclic amides, only *N,N*-diphenyl substituted and *N,N*-dimethyl-2-phenylpropionamide palladium-catalyzed AAA can occur with stoichiometric LiHMDS as a base.¹²⁰ Presumably, these substrates can be deprotonated by LiHMDS to form the lithium enolates, and less activated amides may not be able to be deprotonated by that base.

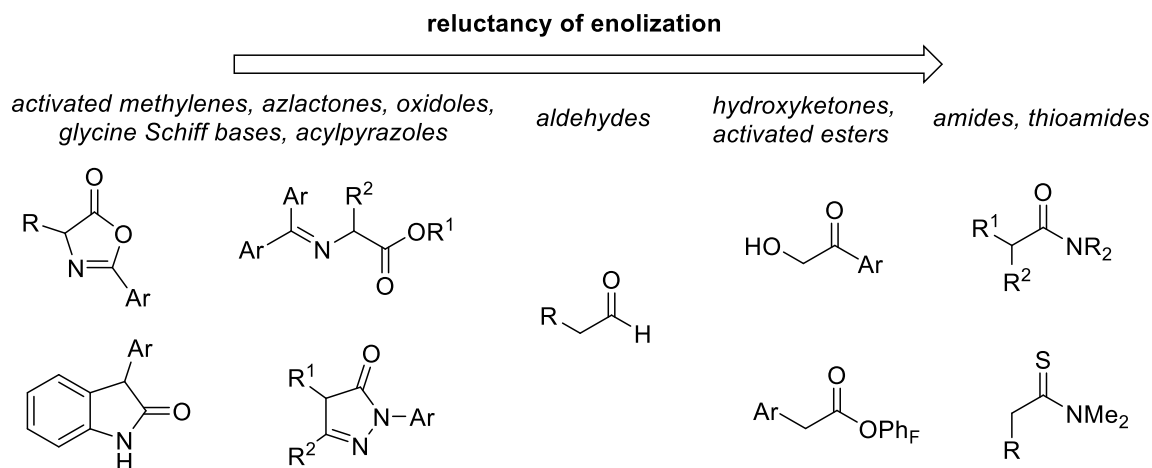


Figure 4: Enolization of carbonyl derivatives

Given current limitations, a generalized approach for the functionalization of unactivated and substituted amides would be highly desirable. Therefore, we proposed the use of lithium zincate bases for the deprotonative zincation of amides to generate zinc amide enolates for subsequent functionalization. Ideally, such zinc enolates could undergo a variety of useful transformations such as electrophilic amination and cross-coupling as a general strategy to access valuable α -functionalized amide products.

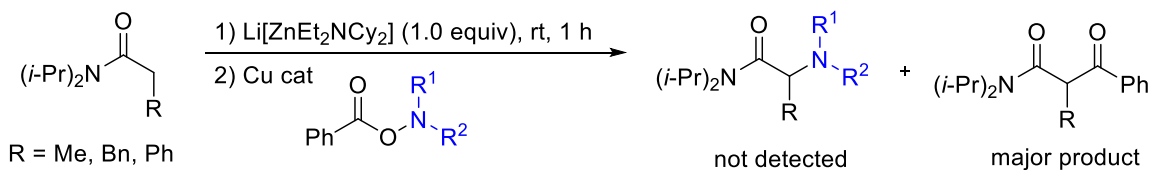
5.2 Results and Discussion

As previously demonstrated, various lithium zincate bases including $\text{Li}[\text{ZnEt}_2\text{NCy}_2]$, $\text{Li}[\text{ZnMe}_2\text{NCy}_2]$, and $\text{Li}[\text{Zn}(\text{NCy}_2)_3] \cdot 2\text{LiCl}$ can give good deprotonation efficiency with unactivated amides and esters, including those which could not be deprotonated by neutral zinc bases (see Chapter 2). It appears that lithium coordination is necessary to facilitate metalation, therefore, lithium zincate bases were examined for their potential utility in functionalization reactions.

5.2.1 Towards electrophilic amination

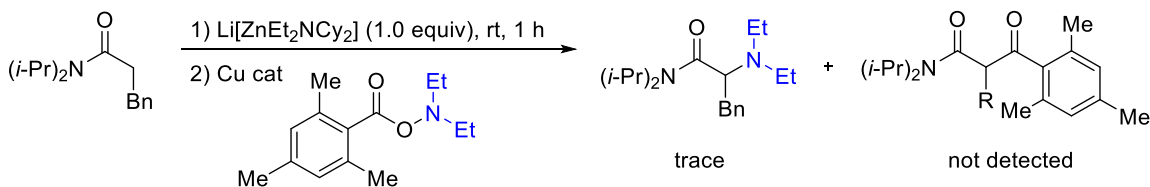
α -Amino carbonyl derivatives are highly valuable products and given our success of using lithium zincate bases for electrophilic amination of arenes and heteroarenes (Chapter 3), we were interested in applying this approach for sp^3 C–H amination. In previous work, ZnTMP₂ (**1**) could only undergo copper-catalyzed electrophilic amination with *O*-benzoyl hydroxylamines for unsubstituted acetamide and acetate substrates (Scheme 6).²¹ Our hope was that the use of a lithium zincate base could expand the scope of substrates to include substituted amides and esters, which would greatly improve the utility of this method.

As the practical lithium zincate base Li[ZnEt₂NCy₂] was shown to have excellent metalation efficiency for various unactivated amide substrates (see Chapter 2), it was examined for electrophilic amination. Initially, *O*-benzoyl hydroxylamines were tested as the electrophile with a copper catalyst; however, only acylation was observed as the major product (Scheme 37). Acylation is a known problem for this type of electrophilic amination because if the organometallic reagent is too nucleophilic it can attack the *O*-benzoyl group before transmetalation to copper. Without copper, acylation is the sole reaction pathway.^{21, 121}



Scheme 37: α -Acylation of amide with *O*-benzoyl hydroxylamine

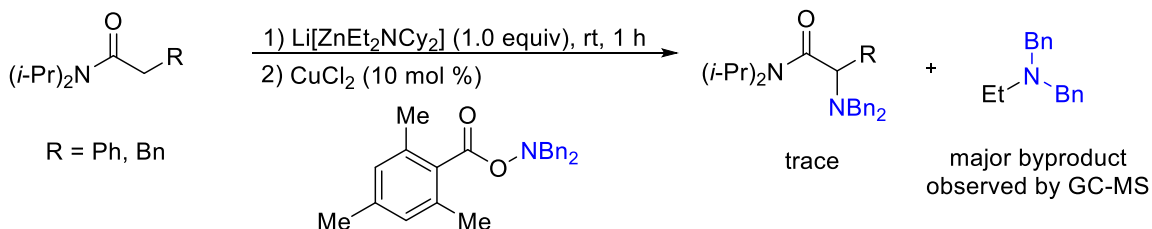
To address this unwanted reactivity, a mesityl *O*-acyl hydroxylamine was synthesized with the hypothesis that the methyl groups would block nucleophilic attack at the carbonyl. Without catalyst, there was no amination or acylation observed and full starting material recovery. In the presence of a copper catalyst, trace amination was obtained without any acylation detected, therefore, this mesityl *O*-acyl hydroxylamine was selected as an electrophile for further studies (Scheme 38). Various copper catalysts, equivalents of reagents and temperatures were screened with *N,N*-diethyl-*O*-mesityl acyl hydroxylamine, however only low conversion was observed for all conditions tested.



Scheme 38: *O*-Mesityl acyl hydroxylamine for electrophilic amination

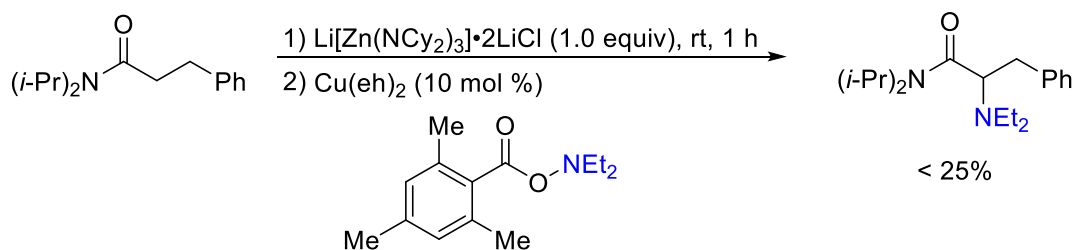
With this approach, one possible problematic side reaction could be ethyl amination instead of α -amide amination. This would occur if the ethyl group transmetallated to copper from the zincate complex instead of the desired amide group. Copper-catalyzed electrophilic amination of diethylzinc has been reported,⁵⁷ and it is conceivable that ethyl transfer may be more rapid than amide transfer, which could be in either the *O*- or *C*-enolate form. To look for this unwanted reactivity, *N,N*-dibenzyl mesityl *O*-acyl hydroxylamine was used to more easily observe any byproduct of this type. A significant amount of ethyl amination with dibenzylamine was observed, suggesting that ethyl transfer is a problem for this reaction (Scheme 39). Additionally, a

dimethyl version of the zincate base, $\text{Li}[\text{ZnMe}_2\text{NCy}_2]$ was tested, but gave no significant improvement in amide α -amination.



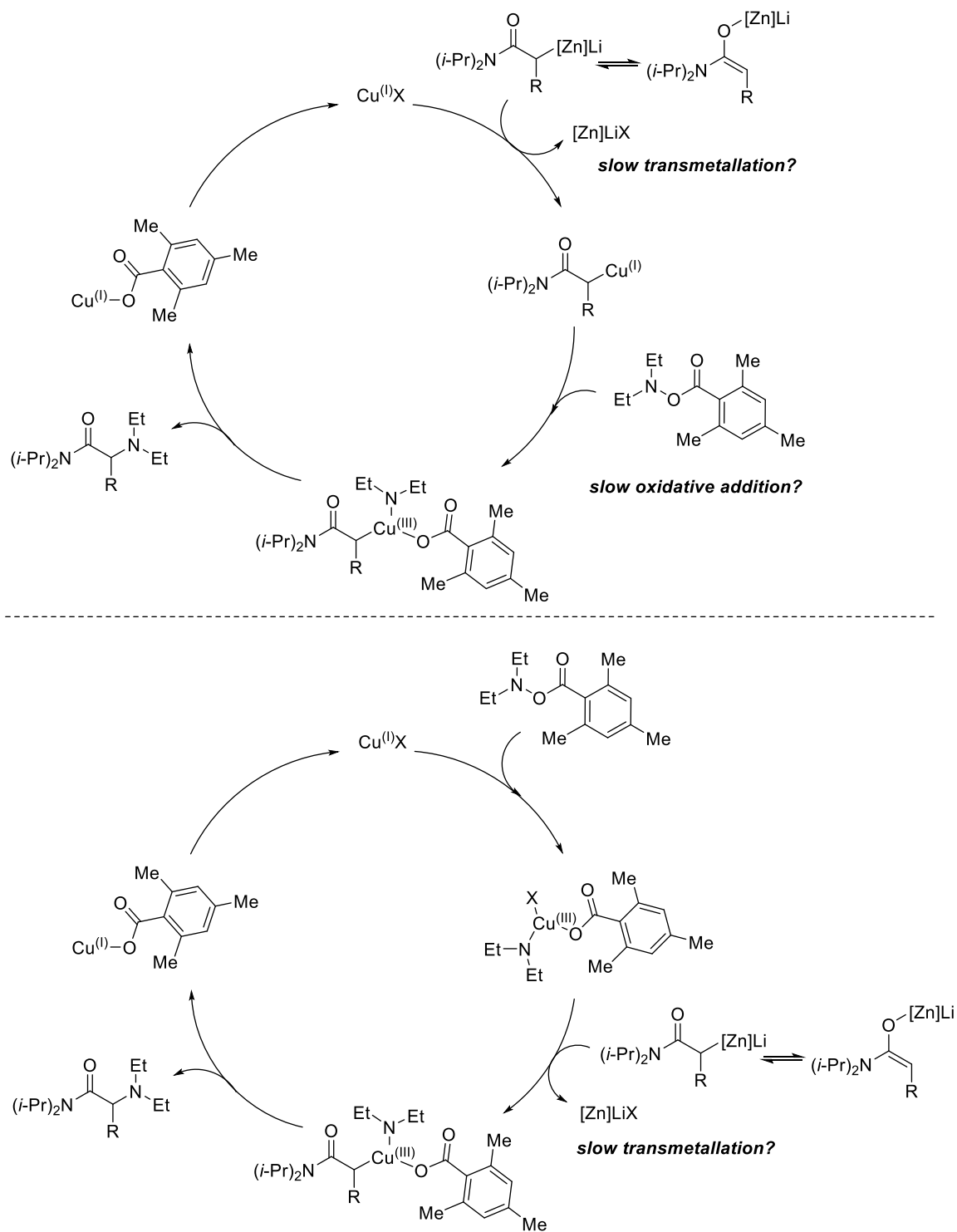
Scheme 39: Ethyl amination observed as a major byproduct with $\text{Li}[\text{ZnEt}_2\text{NCy}_2]$

In an attempt to avoid unwanted alkyl transfer, we considered switching to a different type of zincate base. Previous deprotonation studies indicated that neutral zinc bases could not deprotonate unactivated substituted amides, presumably due to high $\text{p}K_a$, and anionic zincate bases seemed necessary as lithium coordination promotes zincation. The tribasic lithium zincate $\text{Li}[\text{Zn}(\text{NCy}_2)_3] \cdot 2\text{LiCl}$ gave good metalation efficiency without containing alkyl groups, therefore, it was selected to study electrophilic amination. While no significant byproducts were formed and the amide starting material was recovered, unfortunately, low amination conversion was still observed under the conditions tested (Scheme 40).



Scheme 40: Attempted amination of amide lithium zinc enolate generated by $\text{Li}[\text{Zn}(\text{NCy}_2)_3] \cdot 2\text{LiCl}$

The mechanism of the productive amination pathway remains unclear; therefore, it is unknown which step is limiting the reaction. The hydroxylamine is eventually consumed within 24 h in the presence of a copper catalyst, so hydroxylamine consumption is more rapid than the desired reaction pathway. It is possible that transmetallation of the zincate to copper must occur first, followed by the oxidative addition of the hydroxylamine. If this is the case, then either transmetallation of the amide is too slow (potentially hindered by the *O*-enolate form being favored over the *C*-enolate form), or transmetallation occurs, but the oxidative addition of the hydroxylamine to the copper species may be challenging. Alternatively, if the oxidative addition of the hydroxylamine must occur first, then the transmetallation of the amide may be too slow before the degradation pathway occurs (Scheme 41). Further work would be needed to elucidate the mechanism and optimize reaction conditions to successfully achieve α -amination of zincate reagents.



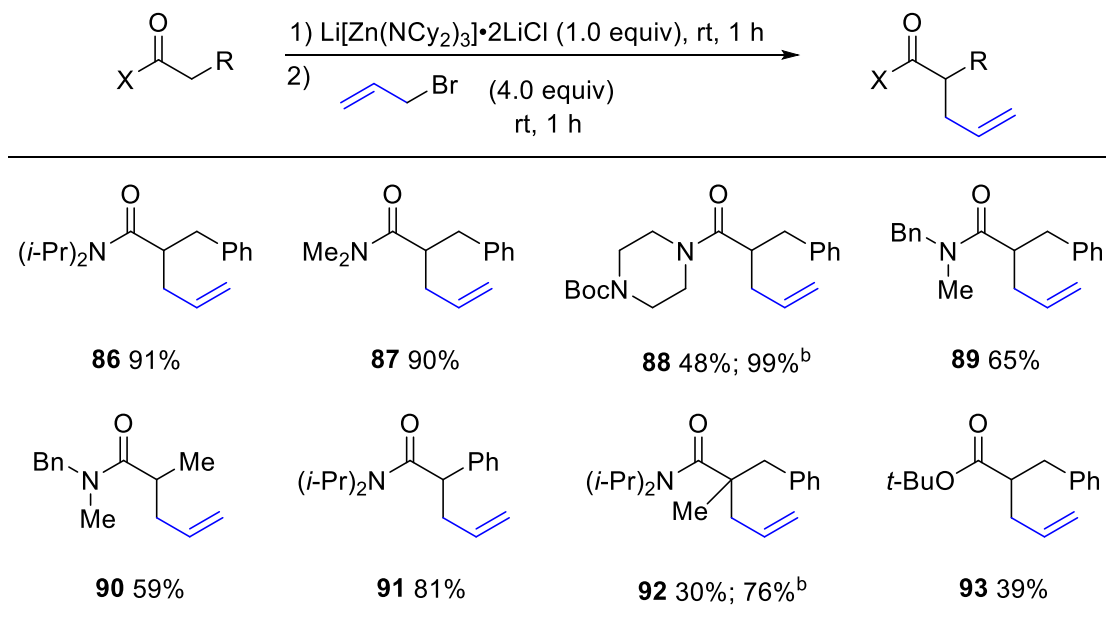
Scheme 41: Possible mechanistic pathways for zincate-mediated α -amination

5.2.2 Direct α -allylation of amides

Given these challenges with electrophilic amination, we were interested in looking at other transformations to learn more about the reactivity of α -amide enolates generated from zincate bases. Copper-catalyzed allylation has been extensively reported with neutral organozinc reagents¹²², including those generated by ZnTMP-derived bases.⁶⁻⁷ The introduction of an allyl group is valuable as the alkene can be further functionalized by a wide variety of well-established alkene functionalization reactions. To the best of our knowledge, α -allylation of amides has not previously been reported other than a few examples with a handful of activated substrates (Scheme 36 II, b).¹¹⁹⁻¹²⁰

Amide substrates deprotonated with lithium zincate bases $\text{Li}[\text{ZnEt}_2\text{NCy}_2]$ and $\text{Li}[\text{Zn}(\text{NCy}_2)_3] \cdot 2\text{LiCl}$ were tested for allylation with allyl bromide. Encouragingly, excellent allylation was observed with both bases and interestingly, no copper catalyst was required. The tribasic zincate $\text{Li}[\text{Zn}(\text{NCy}_2)_3] \cdot 2\text{LiCl}$ was selected to explore the scope of amides for this transformation (Table 18). Various *N,N*-dialkyl substitutions were tolerated on the amide, including benzyl and Boc protecting groups. The amide could have α -substitution in the form of methyl, phenyl, and benzyl substituents, and even hindered α -disubstituted amides worked, generating a new quaternary carbon. (Note that the reactions of **83** and **87** gave good conversion but had lower isolated yields due to difficulty of purification.) Additionally, allylation was also achieved for a *tert*-butyl ester, showing the potentially broad applicability of zincate-mediated functionalization.

Table 18: Scope of α -allylation of amides.^a



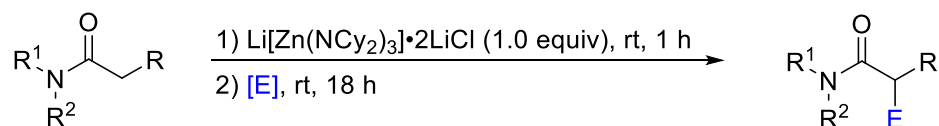
^a Isolated yields given for reactions run on a 0.2 mmol scale in THF. ^b Yield determined by ¹H NMR with CH₂Br₂ as a quantitative internal standard.

5.2.3 Copper-catalyzed arylation and alkenylation

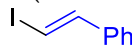
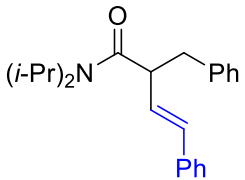
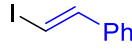
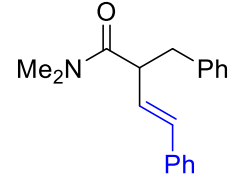
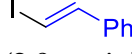
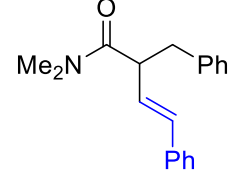
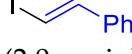
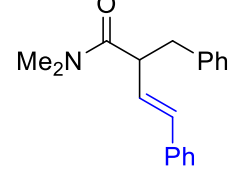
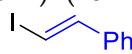
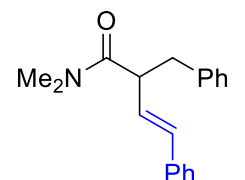
α -Aryl amides are an important motif present in many biologically active compounds and are also precursors of β -aryl amines¹²³ and α -aryl carboxylic acids.¹⁰⁷ α -Vinyl amides (β,γ -unsaturated amides) are also valuable as they can be converted into homoallylic amines.¹²⁴ Given the utility of these products, we were interested in establishing a general method for arylation and alkenylation of unactivated amides utilizing lithium zincate bases for deprotonative zincation. Li[Zn(NCy₂)₃]•2LiCl was chosen as a base for these studies to avoid the issue of unwanted alkyl transfer. Previously, our group has shown that neutral sp² and sp³ organozinc reagents generated by deprotonative zincation with ZnTMPCl•LiCl (**3**) can undergo copper-catalyzed cross-

coupling with aryl and vinyl iodonium salts.^{18,28} Therefore, we began by testing iodonium salts as electrophiles for amide arylation and vinylation. Under the standard reaction conditions previously reported for this transformation, a moderate amount of arylation and a small amount of vinylation was obtained (Table 19, entries 1 and 7). While iodonium salts are air-stable and easily handled, they are not the most atom-economical, and must be synthesized from the corresponding iodide. Since copper-catalyzed cross-coupling of heteroaryl iodides with organozinc reagents has previously been reported,¹²⁵ we were interested to see if aryl iodides or vinyl iodides could directly undergo copper-catalyzed cross-coupling as those starting materials would be more practical and convenient. We were pleased to see that aryl and vinyl iodides could indeed react in the presence of copper iodide as a catalyst (entries 2 and 8) and the amide scope appears to be consistent (entries 3-5). Brief optimization revealed that Cu(eh)₂ gave improved arylation (entry 6) and Cu(OTf)₂ gave improved alkenylation (entry 12). These products were observed by ¹H NMR spectroscopy and GC mass spectroscopy, however their purification was challenging. Only impure products were obtained and therefore no isolated yields could be given. Future work and optimization could demonstrate this method as a valuable approach for the functionalization of unactivated amides.

Table 19: Electrophile screen for arylation and alkenylation of amides.^a



entry	electrophile	product	yield (%) ^b
1	CuOTf (10 mol %) $\text{Ph}-\overset{\oplus}{\text{I}}(\text{Ph})-\text{OTf}^-$ (2.0 equiv)		42
2	CuI (10 mol %) Ph-I (2.0 equiv)		63
3	CuI (10 mol %) Ph-I (2.0 equiv)		60
4	CuI (10 mol %) Ph-I (2.0 equiv)		60
5	CuI (10 mol %) Ph-I (2.0 equiv)		75
6	Cu(eh) ₂ (10 mol %) Ph-I (2.0 equiv)		80
7	Cu(OTf) ₂ (10 mol %) $\text{Ph}-\overset{\oplus}{\text{I}}(\text{CH}=\text{CHPh})-\text{OTf}^-$ (2.0 equiv)		trace

8	CuI (10 mol %)  (2.0 equiv)		46
9	CuI (10 mol %)  (2.0 equiv)		29
10	Cu(eh) ₂ (10 mol %)  (2.0 equiv)		56
11	CuOTf (10 mol %)  (2.0 equiv)		67
12	Cu(OTf) ₂ (10 mol %)  (2.0 equiv)		69

^a Reactions run on a 0.2 mmol scale in THF. ^b Yields determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard.

5.3 Supplemental Information

5.3.1 General Information

General Procedures. Glassware was dried either by propane torch or for at least 12 h in an oven at 140 °C before cooling in a desiccator over Drierite. Optimization and condition screening reactions were performed under N₂ using standard Schlenk techniques in 8-mL microwave tubes sealed with PTFE crimp-top caps. Reactions were stirred magnetically

using Teflon-coated, magnetic stir bars. Thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with 0.25 mm of 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or exposure to vanillin or iodine stain. Organic solutions were concentrated in vacuo using a rotary evaporator. Column chromatography was performed with silica gel (60 Å, standard grade). Medium-pressure chromatography was performed using a Teledyne ISCO Combiflash system using Redisep Gold column cartridges.

Materials. All commercially available reagents were purchased in >98% purity and used as received unless otherwise noted. Anhydrous THF was obtained from an Innovative Technologies solvent purification system. Dicyclohexylamine were dried over CaH₂ and fractionally distilled under reduced pressure and stored under N₂. *n*-Butyl lithium was purchased as a 2.5 M solution in hexanes from Sigma-Aldrich and titrated prior to use with *N*-benzylbenzamide as an indicator.³⁸ The solution of diethylzinc (1.0 M in hexanes) was purchased from Sigma Aldrich and titrated with iodine in THF at 0 °C prior to use.

Instrumentation. Nuclear magnetic resonance spectra were recorded at ambient temperature on 400 MHz or 500 MHz spectrometers. All values for proton chemical shifts are reported in parts per million (δ) and are referenced to the residual protium in CDCl₃ (δ 7.26). All values for carbon chemical shifts are reported in parts per million (δ) and are referenced to the carbon resonances in CDCl₃ (δ 77.0). NMR data are represented as

follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad), coupling constant (Hz), and integration. Infrared spectroscopic data are reported in wavenumbers (cm^{-1}) with selected peaks shown. High-resolution mass spectra were obtained using a liquid chromatography-electrospray ionization and time-of-flight mass spectrometer.

5.3.2 Experimental procedures

Standard Procedure for Lithium Zincate Base $\text{Li}(\text{NR}_2)_{0.1} \cdot \text{Li}[\text{ZnEt}_2(\text{NR}_2)]$ Synthesis. The appropriate amine (3.3 mmol, 1.1 equiv) in a 25-mL round bottom flask with stir bar was cooled to $-78\text{ }^\circ\text{C}$ by dry ice/acetone bath under N_2 and stirred until the amine was frozen. To the flask, was added dropwise *n*-butyl lithium (2.5 M solution in hexanes, 3.3 mmol, 1.1 equiv) at $-78\text{ }^\circ\text{C}$ and the mixture was stirred vigorously for 10 min. Diethylzinc (3.0 mL, 1.0 M solution in hexanes, 3.0 mmol, 1.0 equiv) was added dropwise. The resulting white slurry was allowed to stir at $-78\text{ }^\circ\text{C}$ for 5 min and then warmed up to room temperature followed by the addition of anhydrous THF (3 mL) and titration.

Standard Procedure for Tribasic Lithium Zincate $\text{Li}[\text{Zn}(\text{NCy}_2)_3] \cdot 2\text{LiCl}$ Synthesis. The appropriate amine (6.0 mmol, 3.0 equiv) in a 25-mL round bottom flask with a stir bar was cooled to $-78\text{ }^\circ\text{C}$ by dry ice/acetone bath under N_2 and stirred until the amine was frozen. To the flask, was added dropwise *n*-butyl lithium (2.4 mL, 2.5 M solution in hexanes, 6.0 mmol, 3.0 equiv) at $-78\text{ }^\circ\text{C}$ and the mixture was stirred vigorously for 15 min. In a separate pear flask was added ZnCl_2 (272.6 mg, 2.0 mmol, 1.0 equiv) which was flame dried under

vacuum, cooled under N₂, and dissolved in THF (1.0 mL). The ZnCl₂ solution was added dropwise via syringe to the lithium amide at -78°C. The resulting white slurry was allowed to stir at -78 °C for 5 min and then warmed up to room temperature and titrated before use.

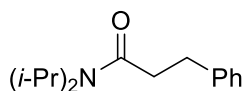
Standard titration. A 15-mL round bottom flask was charged with a stir bar, benzoic acid (approx. 60 mg) and 4-(phenylazo)diphenylamine (approx. 2 mg). The flask was placed under N₂ via sequential vacuum purge/N₂ backfill (3 times) followed by the addition of THF (1.0 mL). The flask was cooled down to 0 °C by ice/water bath and was added dropwise the solution of base until the endpoint of the presumed tribasic zinc complex (i.e., 3.1 equivalents of basic moieties per mole of complex) was observed, as indicated by a persistent dark orange-red color change, providing the concentration of active base.

Standard Allylation Procedure. To a solution of amide substrate (0.2 mmol) in THF was added freshly prepared and titrated Li[Zn(NCy₂)₃]•2LiCl (0.2 mmol, 1.0 equiv) to a final concentration of 0.2M. The resulting mixture was stirred at room temperature for 1 h before allyl bromide (69 μL, 0.80 mmol, 4.0 equiv) was added dropwise via microsyringe. After stirring at room temperature for 1 h, the reaction was then filtered through a plug of silica (approx. 3 mL) and washed with ethyl acetate (approx. 10 mL). The filtrate was concentrated by rotary evaporation. Crude yields were obtained by ¹H NMR analysis using dibromomethane (7.0 μL, 0.1 mmol) as a quantitative internal standard and purification was performed by medium pressure chromatography.

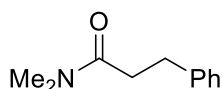
Standard Arylation and Alkenylation Procedure. To a solution of amide substrate (0.2 mmol) in THF was added freshly prepared and titrated $\text{Li}[\text{Zn}(\text{NCy}_2)_3] \cdot 2\text{LiCl}$ (0.2 mmol, 1.0 equiv) to a final concentration of 0.2M. The resulting mixture was stirred at room temperature for 1 h before adding copper catalyst (0.02 mmol, 0.1 equiv) in THF (1 mL), followed by aryl iodide or vinyl iodide (0.4 mmol, 2.0 equiv). After stirring at room temperature for 18, the reaction was then filtered through a plug of silica (approx. 3 mL) and washed with ethyl acetate (approx. 10 mL). The filtrate was concentrated by rotary evaporation. Crude yields were obtained by ^1H NMR analysis using dibromomethane (7.0 μL , 0.1 mmol) as a quantitative internal standard

5.3.3 Preparation of starting materials

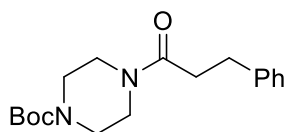
Synthesis of Homobenzyl Amide Precursors. To 3-phenylpropionic acid (3.00 g, 20.0 mmol, 1.0 equiv) in DCM (100 mL) with DMF (4 drops) was added oxalyl chloride (1.86 mL, 22.0 mmol, 1.1 equiv) dropwise via syringe. Upon stirring at room temperature for 3 h, the reaction was cooled to 0 °C, followed by dropwise addition of amine (24.0 mmol, 1.2 mmol) and triethylamine (3.62 mL, 26.0 mmol, 1.3 equiv). The reaction was stirred at 0 °C for 2 h, then room temperature for 15 h and was worked up by filtration through a plug of silica (50 mL) and rinsing with ethyl acetate (100 mL). Following concentration by rotary evaporation, the crude was redissolved in ethyl acetate (75 mL), washed with saturated aqueous sodium bicarbonate (2 x 75mL) and brine (75 mL), dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography.



***N,N*-diisopropyl-3-phenylpropanamide (29).** Precursor for **86** prepared according to homobenzyl amide synthesis procedure with diisopropylamine. Purification by medium pressure chromatography (hexanes to 30% ethyl acetate–hexanes) gave **29** as a pale yellow oil (4.29 g, 18.4 mmol, 92% yield); $R_f = 0.45$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3): 7.31–7.26 (m, 2H), 7.24–7.17 (m, 3H), 3.92 (quint, $J = 6.8$ Hz, 1H), 3.58–3.39 (br s, 1H), 2.98–2.92 (m, 2H), 2.61–2.54 (m, 2H), 1.39 (d, $J = 6.8$ Hz, 6H), 1.13 (d, $J = 6.7$ Hz, 6H). $^1\text{H NMR}$ matched literature spectra.⁴²

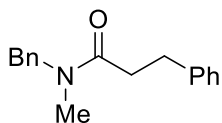


***N,N*-Dimethyl-3-phenylpropanamide.** Precursor for **87** prepared according to homobenzyl amide synthesis procedure with dimethylamine. Purification by medium pressure chromatography (hexanes to 30% ethyl acetate–hexanes) gave clear oil (3.12 g, 17.6 mmol, 88%). $^1\text{H NMR}$ (400 MHz, CDCl_3): 7.31–7.27 (m, 2H), 7.24–7.18 (m, 3H), 2.99–2.96 (m, 2H), 2.95 (s, 3H), 2.93 (s, 3H), 2.64–2.59 (m, 2H). ^1H matched literature spectra.¹²⁶

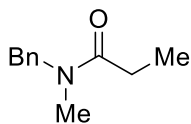


***tert*-Butyl 4-(3-phenylpropanoyl)piperazine-1-carboxylate.** Precursor for **88** prepared according to homobenzyl amide synthesis procedure with *N*-Boc piperazine. Purification by flash column chromatography (20% ethyl acetate–hexanes) gave white solid (5.92 g,

18.6 mmol, 93%). ^1H NMR (400 MHz, CDCl_3): 7.31-7.25 (m, 2H), 7.22-7.18 (m, 3H), 3.60-3.56 (br s, 2H), 3.38-3.26 (m, 6H), 3.00-2.94 (m, 2H), 2.65-2.60 (m, 2H), 1.45 (s, 9H). ^1H matched literature spectra.¹²⁷

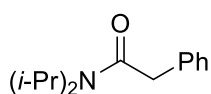


***N*-Benzyl-*N*-methyl-3-phenylpropanamide.** Precursor for **89** prepared according to homobenzyl amide synthesis procedure on a 5.0 mmol scale with *N*-benzylmethylamine. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave clear oil (1.00 g, 3.95 mmol, 79%) as a mixture of conformational isomers. ^1H NMR (400 MHz, CDCl_3): 7.36-7.07 (m, 10H, A+B), 4.60 (s, 2aH, A), 4.47 (s, 2bH, B), 3.06-2.98 (m, 2H, A+B), 2.95 (s, 3bH, B), 2.85 (s, 3aH, A), 2.71-2.65 (m, 2H, A+B). ^1H matched literature spectra.¹²⁸

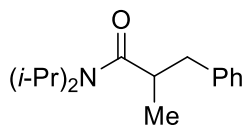


***N*-Benzyl-*N*-methylpropionamide.** Precursor for **90**. To propionyl chloride (0.87 mL, 10 mmol, 1.0 equiv) in DCM (50 mL) at 0 °C was added *N*-benzylmethylamine (1.55 mL, 12.0 mmol, 1.2 equiv) followed by triethylamine (1.81 mL, 13.0 mmol, 1.3 equiv). Upon gradual warming to room temperature and stirring for 18 h, the crude reaction mixture was worked up by filtration through a plug of silica gel (50 mL) followed by rinsing with ethyl acetate (100 mL). Purification by medium pressure chromatography (hexanes to 20%

ethyl acetate–hexanes) gave pale yellow liquid (1.11 g, 6.25 mmol, 63%) as a mixture of conformational isomers. ^1H NMR (400 MHz, CDCl_3): 7.38–7.14 (m, 5H, A+B), 4.60 (s, 2aH, A), 4.53 (s, 2bH, B), 2.95 (s, 3bH, B), 2.91 (s, 3aH, A), 2.40 (q, $J = 7.4$ Hz, 2aH, A), 2.39 (q, $J = 7.3$ Hz, 2bH, B), 1.20 (t, $J = 7.3$ Hz, 3aH, B), 1.16 (t, $J = 7.4$ Hz, 3bH, B). ^1H matched literature spectra.¹²⁹

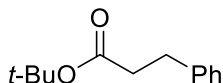


***N,N*-Diisopropyl-2-phenylacetamide (28).** Precursor for **91** prepared following literature procedure.⁴¹



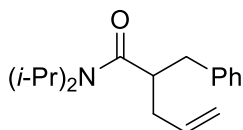
***N,N*-Diisopropyl-2-methyl-3-phenylpropanamide.** Precursor for **92** prepared following standard methylation procedure (see Chapter 2) on a 1.0 mmol scale with 1.0 equiv of $\text{Li}[\text{ZnEt}_2\text{NCy}_2]$. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave a clear oil (175.9 mg, 0.71 mmol, 71%); $R_f = 0.54$ (20% ethyl acetate–hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.26–7.21 (m, 2H), 7.19–7.13 (m, 3H), 3.92–3.78 (br s, 1H), 3.64–3.22 (br s, 1H), 3.02 (dd, $J = 13.0, 8.2$ Hz, 1H), 2.93–2.83 (m, 1H), 2.61 (dd, $J = 13.0, 6.1$ Hz, 1H), 1.32 (d, $J = 6.0$ Hz, 3H), 1.26 (d, $J = 6.7$ Hz, 3H), 1.13 (d, $J = 6.7$ Hz, 3H), 1.09 (d, $J = 6.7$ Hz, 3H), 0.86 (d, $J = 6.7$ Hz, 3H); ^{13}C (125 MHz, CD_3Cl) δ 174.8, 140.4, 129.1, 128.0, 125.9, 45.5, 40.7, 39.7, 39.1, 27.9, 21.3, 20.7, 20.4, 18.3; FTIR (thin film): cm^{-1} 2965, 2930,

1629, 1440, 1149; HRMS-ESI (m/z) Calcd for $[C_{16}H_{26}NO]^+$ ($[M+H]^+$): 248.2009; found 248.2013.

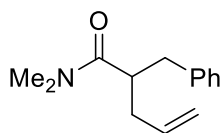


tert-Butyl 3-phenylpropanoate (30). Precursor for 93 prepared following literature procedure.⁴³

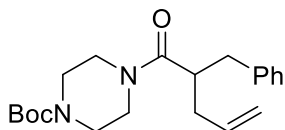
5.3.4 Characterization of compounds



2-Benzyl-N,N-diisopropylpent-4-enamide (86). Prepared according to standard allylation procedure. Purification by medium pressure chromatography (hexanes to 10% ethyl acetate–hexanes) gave **86** as a white solid (49.8 mg, 0.182 mmol, 91%). $R_f = 0.41$ (10% ethyl acetate–hexanes); 1H NMR ($CDCl_3$, 400 MHz): δ 7.23 (d, $J = 7.2$ Hz, 2H), 7.20-7.13 (m, 3H), 5.75 (ddt, $J = 17.3, 10.3, 7.2$ Hz, 1H), 5.08 (dd, $J = 17.0, 1.9$ Hz, 1H), 5.00 (dd, $J = 10.3, 2.0$ Hz, 1H), 3.80-3.73 (m, 1H), 2.97 (dd, $J = 12.2, 10.0$ Hz, 1H), 2.93-2.86 (m, 1H), 2.69 (dd, $J = 12.2, 4.0$ Hz, 1H), 2.50 (m, 1H), 2.21 (m, 1H), 1.33 (d, $J = 6.8$ Hz, 3H), 1.26 (d, $J = 6.8$ Hz, 3H), 1.01 (d, $J = 6.7$ Hz, 3H), 0.61-0.53 (br s, 3H); ^{13}C ($CDCl_3$, 125 MHz): δ 173.2, 140.1, 136.0, 129.2, 128.1, 126.0, 116.5, 48.3, 45.9, 44.7, 39.6, 38.2, 21.0, 20.6, 20.5, 20.2; FTIR (thin film): cm^{-1} 2968, 2856, 1613, 1444, 1310, 1129; HRMS-ESI (m/z) Calcd for $[C_{18}H_{28}NO]^+$ ($[M+H]^+$): 274.2165; found 274.2169.

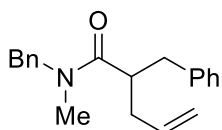


2-Benzyl-*N,N*-dimethylpent-4-enamide (87). Prepared according to standard allylation procedure. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **87** as a clear oil (39.0 mg, 0.179 mmol, 90%). $R_f = 0.21$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.27-7.22 (m, 2H), 7.19-7.13 (m, 3H), 5.75 (ddt, $J = 17.1, 10.2, 7.0$ Hz, 1H), 5.06 (dq, $J = 17.1, 1.5$ Hz, 1H), 5.01 (dd, $J = 10.2, 1.0$ Hz, 1H), 3.01-2.87 (m, 2H), 2.85 (s, 3H), 2.75 (dd, $J = 12.7, 5.0$, 1H), 2.64 (s, 3H), 2.52-2.44 (m, 1H), 2.27-2.19 (m, 1H); ^{13}C (CDCl_3 , 125 MHz): δ 174.5, 139.8, 135.8, 128.9, 128.2, 126.2, 116.6, 43.6, 39.0, 37.0, 35.5; FTIR (thin film): cm^{-1} 3062, 3026, 2924, 1634, 1397, 1139; HRMS-ESI (m/z) Calcd for $[\text{C}_{14}\text{H}_{20}\text{NO}]^+$ ($[\text{M}+\text{H}]^+$): 218.1539; found 218.1543.

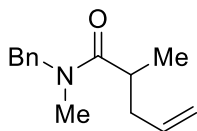


***tert*-Butyl 4-(2-benzylpent-4-enoyl)piperazine-1-carboxylate (88).** Prepared according to standard allylation procedure. Purification by medium pressure chromatography (hexanes to 20% ethyl acetate–hexanes) gave **88** as a clear oil (34.7 mg, 0.097 mmol, 48%). $R_f = 0.10$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.28-7.23 (m, 2H), 7.21-7.14 (m, 3H), 5.74 (ddt, $J = 17.1, 10.2, 7.0$ Hz, 1H), 5.08 (dq, $J = 17.1, 1.5$ Hz, 1H), 5.02 (dd, $J = 10.2, 1.8$ Hz, 1H), 3.70-3.63 (m, 1H), 3.40-3.30 (m, 2H), 3.26-3.20 (m, 1H), 3.17-3.12 (m, 1H), 3.06-2.99 (m, 2H), 2.98-2.94 (m, 1H), 2.94-2.87 (m, 1H), 2.79 (dd, $J = 12.4, 4.3$ Hz,

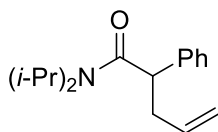
1H), 2.55-2.46 (m, 2H), 2.31-2.23 (m, 1H), 1.42 (s, 9H); ¹³C (CDCl₃, 125 MHz): δ 173.1, 154.3, 139.5, 135.5, 128.9, 128.4, 126.4, 116.9, 80.0, 45.3, 43.3, 41.4, 39.3, 37.3, 28.3; FTIR (thin film): cm⁻¹ 2974, 2858, 1694, 1635, 1413, 1231, 1164; HRMS-ESI (m/z) Calcd for [C₂₁H₃₁N₂O₃]⁺ ([M+H]⁺): 359.2329; found 359.2333.



N,2-Dibenzyl-N-methylpent-4-enamide (89). Prepared according to standard allylation procedure. Purification by medium pressure chromatography (hexanes to 10% ethyl acetate–hexanes) gave **89** as a pale yellow oil as a mixture of conformational isomers A and B (38.2 mg, 0.130 mmol, 65%). *R_f* = 0.41 (20% ethyl acetate–hexanes); ¹H NMR (CDCl₃, 400 MHz): δ 7.25-6.82 (m, 10H, A+B), 5.87-5.68 (m, 1H, A+B), 5.15-5.01 (m, 2H, A+B), 4.62 (d, *J* = 14.7 Hz, 2aH, A), 4.42 (d, *J* = 14.7 Hz, 2aH, A), 4.22 (d, *J* = 16.8 Hz, 2bH, B), 4.16 (d, *J* = 16.8 Hz, 2bH, B), 3.13-2.94 (m, 2H, A+B), 2.85 (s, 3aH, A), 2.78 (ddd, *J* = 21.8, 12.2, 4.4 Hz, 1H, A+B), 2.61 (s, 3bH, B), 2.58-2.44 (m, 1H, A+B), 2.34-2.22 (m, 1H, A+B); ¹³C (CDCl₃, 125 MHz): δ 174.8 (A), 174.5 (B), 139.8 (A) 139.7 (B), 137.1 (B), 136.6 (A), 135.6 (A+B), 129.1 (A), 129.0 (B), 128.6 (A), 128.3 (A+B), 127.8 (B), 127.3 (A), 127.0 (B), 126.3 (A+B), 126.2 (A+B), 117.1 (A), 116.9 (B), 52.8 (A), 50.7 (B), 44.1 (A), 43.7 (B), 39.0 (A+B), 37.4 (A), 37.3 (B), 34.6 (B), 34.0; FTIR (thin film): cm⁻¹ 3062, 3027, 2920, 1634, 1450; HRMS-ESI (m/z) Calcd for [C₂₀H₂₄NO]⁺ ([M+H]⁺): 294.1852; found 294.1858.

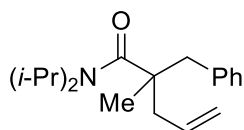


N-Benzyl-N,2-dimethylpent-4-enamide (90). Prepared according to standard allylation procedure. Purification by medium pressure chromatography (hexanes to 10% ethyl acetate–hexanes) gave **90** as a clear oil as a mixture of conformational isomers A and B (25.5 mg, 0.117 mmol, 59%). $R_f = 0.35$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.38-7.14 (m, 5H, A+B), 5.85-5.67 (m, 1H, A+B), 5.10-4.97 (m, 2H, A+B), 4.69-4.51 (m, 2H, A+B), 2.95 (s, 3aH, A), 2.94 (s, 3bH, B), 2.86-2.71 (m, 1H, A+B), 2.53-2.40 (m, 1H, A+B), 2.21-2.09 (m, 1H, A+B), 1.17 (d, $J = 6.8$ Hz, 3bH, B), 1.13 (d, $J = 6.7$ Hz, 3aH, A); ^{13}C (CDCl_3 , 125 MHz): δ 176.4 (A), 175.9 (B), 137.5 (B), 136.8 (A), 136.1 (B), 136.0 (A), 128.8 (A), 128.5 (B), 127.9 (B), 127.5 (A), 127.2 (A), 126.2 (B), 116.6 (A), 116.5 (B), 53.1 (A), 50.8 (B), 38.5 (A), 38.1 (B), 35.7 (A), 35.6 (B), 34.6 (B), 34.1 (A), 17.6 (A), 17.1 (B); FTIR (thin film): cm^{-1} 3064, 2930, 1636, 1451, 1087; HRMS-ESI (m/z) Calcd for $[\text{C}_{14}\text{H}_{20}\text{NO}]^+$ ($[\text{M}+\text{H}]^+$): 218.1539; found 218.1543.

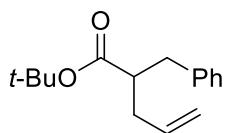


N,N-Diisopropyl-2-phenylpent-4-enamide (91). Prepared according to standard allylation procedure. Purification by medium pressure chromatography (hexanes to 10% ethyl acetate–hexanes) gave **91** as a clear oil (41.8 mg, 0.161 mmol, 81%). $R_f = 0.35$ (20% ethyl acetate–hexanes); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.31-7.27 (m, 2H), 7.25-7.18 (m, 3H),

5.76 (ddt, $J = 17.1, 10.2, 6.9$ Hz, 1H), 4.99 (dq, $J = 17.1, 1.6$ Hz, 1H), 4.94 (dd, $J = 10.2, 1.5$ Hz, 1H), 4.04 (quint, $J = 6.7$ Hz, 1H), 3.67 (t, $J = 7.2$ Hz, 1H), 3.33-3.22 (br s, 1H), 2.84 (dt, $J = 14.1, 7.0$ Hz, 1H), 2.36 (dt, $J = 14.1, 7.0$ Hz, 1H), 1.43 (d, $J = 6.8$ Hz, 3H), 1.35 (d, $J = 6.7$ Hz, 3H), 1.13 (d, $J = 6.7$ Hz, 3H), 0.59 (d, $J = 6.6$ Hz, 3H); ^{13}C (CDCl_3 , 125 MHz): δ 170.8, 140.4, 136.9, 128.5, 127.6, 126.5, 115.8, 50.4, 48.2, 45.8, 39.3, 20.9, 20.7, 20.0, 19.7; FTIR (thin film): cm^{-1} 3065, 2966, 2930, 1634, 1438, 1314, 1133; HRMS-ESI (m/z) Calcd for $[\text{C}_{17}\text{H}_{26}\text{NO}]^+$ ($[\text{M}+\text{H}]^+$): 260.2009; found 260.2013.



2-Benzyl-*N,N*-diisopropyl-2-methylpent-4-enamide (92). Prepared according to standard allylation procedure. Purification by medium pressure chromatography (hexanes to 10% ethyl acetate–hexanes) gave **92** as a clear oil (17.2 mg, 0.06 mmol, 30%). $R_f = 0.70$ (20% ethyl acetate–hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 7.28-7.23 (m, 2H), 7.22-7.16 (m, 3H), 5.78 (dddd, $J = 16.6, 10.6, 7.8, 6.0$ Hz, 1H), 5.08-5.07 (m, 1H), 5.06-5.02 (m, 1H), 4.45 (dt, $J = 11.7, 5.4$ Hz, 1H), 3.33 (dt, $J = 13.7, 7.1$ Hz, 1H), 3.07 (d, $J = 14.0$ Hz, 1H), 2.85 (d, $J = 14.0$ Hz, 1H), 2.64 (dd, $J = 14.5, 6.1$ Hz, 1H), 2.09 (dd, $J = 14.5, 7.9$ Hz, 1H), 1.45-1.41 (m, 6H), 1.22-1.16 (m, 6H), 1.15 (s, 3H); ^{13}C (CDCl_3 , 125 MHz): δ 173.8, 138.2, 135.0, 130.4, 127.9, 126.2, 117.6, 48.2, 47.1, 44.5, 43.9, 31.6, 23.9, 22.6, 20.7, 20.6, 14.1; FTIR (thin film): cm^{-1} 2966, 2930, 1619, 1363, 1032; HRMS-ESI (m/z) Calcd for $[\text{C}_{19}\text{H}_{30}\text{NO}]^+$ ($[\text{M}+\text{H}]^+$): 288.2322; found 288.2328.



tert-Butyl 2-benzylpent-4-enoate (93). Prepared according to standard allylation procedure. Purification by medium pressure chromatography (hexanes) gave **93** as a clear oil (17.0 mg, 0.069 mmol, 35%). $R_f = 0.58$ (5% ethyl acetate–hexanes); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.29-7.25 (m, 2H), 7.21-7.17(m, 3H), 5.78 (ddt, $J = 17.1, 10.2, 6.9$ Hz, 1H), 5.10-5.02 (m, 2H), 2.89 (dd, $J = 13.7, 8.6$ Hz, 1H), 2.74 (dd, $J = 13.7, 6.5$ Hz, 1H), 2.68-2.60 (m, 1H), 2.40-2.31 (m, 1H), 2.24 (dddt, $J = 14.0, 7.0, 5.7, 1.4$ Hz, 1H), 1.33 (s, 9H); FTIR (thin film): cm^{-1} 3029, 2929, 2854, 1723, 1366, 1145; HRMS-ESI (m/z) Calcd for $[\text{C}_{16}\text{H}_{22}\text{NaO}_2]^+$ ($[\text{M}+\text{Na}]^+$): 269.1512; found 269.1513.

6. Conclusions

Many useful zinc bases have been developed to achieve selective zincation of sp^3 , sp^2 and sp C–H bonds. Most of these bases have relied on TMP, which is expensive as a stoichiometric reagent. Neutral zinc bases have been widely explored for their utility in functionalization transformations including iodination, cross-coupling, amination, thiolation and phosphorylation. However, neutral zinc bases are limited to the zincation of fairly acidic C–H bonds and cannot zincate many useful unactivated substrates. Anionic zincate bases, namely lithium dialkyl TMP zincate bases have been found to zincate an expanded scope of useful substrates by directed zincation. However, the most studied zincate base, $Li[Zn(t-Bu)_2TMP]$ (**6**), is practically challenging to synthesize and functionalization transformations have not been fully explored with zincate intermediates. This work extensively studies the design and composition of lithium zincate bases and develops new transformations with zincate intermediates.

Lithium amide diethylzincate bases have been shown to be effective for the zincation of various arenes and heteroarenes by iodination. The previously underexplored $Li[ZnEt_2TMP]$ has been shown to be a practical reagent for efficient zincation with a wide variety of directing groups. Additionally, a novel lithium zincate with dicyclohexylamine as the amide base, $Li[ZnEt_2NCy_2]$, has been synthesized and shown to be an economical alternative to TMP while still provide regioselective zincation. Various lithium zincate bases have been shown capable of C–H α -zincation of substituted

amides and esters by methylation. However, asymmetric zincation with chiral zincate bases does not seem to be viable for enantioselective functionalization.

A highly general copper-catalyzed C–H amination strategy has been developed and provides effective and rapid access to diverse aminoheteroarenes and aminoarenes. Readily available *O*-benzoylhydroxylamines serve as a convenient electrophilic nitrogen sources for amination. Pivotal to this strategy is the use of a lithium amide zincate base that effectively mediates selective *ortho*-zincation with the assistance of an exceptionally diverse range of simple functional groups. The amination is regioselective even for arenes bearing multiple directing groups as well as efficient for scaled-up reactions. The successful amination of complex arenes demonstrate broad applicability of this strategy as a rapid entry to valuable aminoarene derivatives.

A highly modular aryl and heteroaryl functionalization approach has been demonstrated via C–H zincation for silylation, and borylation. A novel lithium amido diethylzincate base $\text{Li}[\text{ZnEt}_2\text{NCy}_2]$ has been developed and shown capable of metallating a wide variety of unactivated arenes and heteroarenes with predictable regioselectivity and excellent functional group compatibility. This C–H zincation/functionalization using lithium amide diethyl zincate bases is a promising strategy for practical and diverse functionalization.

Lithium zincate bases can be used for the deprotonation and functionalization of unactivated and substituted amides. An efficient allylation has been developed with allyl

bromide and no transition metal catalyst, demonstrating a wide scope of unactivated amides substrates. Copper-catalyzed arylation and alkenylation with aryl and vinyl iodides has been observed in preliminary studies, highlighting the potential of lithium zincate bases for use in the cross-coupling of sp^3 C–H bonds. Based on preliminary results, electrophilic amination may be possible, but will require additional optimization.

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Biography

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Publications

Hendrick, C.E., Bitting, K.J., Cho, S., Wang, Q. "Site-Selective Copper-Catalyzed Amination and Azidation of Arenes and Heteroarenes via Deprotonative Zincation." *Journal of the American Chemical Society*, **2017**, 139, 11622-11628.

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Honors and Awards

Pelham Wilder Award for Excellence in Teaching **2016**

Graduate Assistance for Areas of National Need Fellowship (G.A.A.N.N.) **2016-2017**