New Copper-Catalyzed Reactions of Organoboron and Organosilicon Compounds

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Abstract

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Copper-catalyzed transformations such as allylic substitution, conjugate addition, and electrophilic amination have proven to be indispensable tools for the formation of carbon-carbon and carbon-heteroatom bonds. Nevertheless, the use of highly reactive organometallic reagents limits functional group compatibility of these reactions and can contribute to poor selectivity in certain cases. Presented herein are four reactions that address the above mentioned limitations by catalytically accessing aryl, alkenyl, and alkyl copper intermediates from mild transmetalation partners. Specifically, the use of organoborane and silane transmetalation partners in copper-catalyzed reactions resulted in high levels of chemoselectivity, stereoselectivity, and regioselectivity thus providing products that are unattainable with the traditional approaches.

Chapter 1 will describe the use of arylboronic esters as transmetalation partners in a copper catalyzed allylic substitution reaction. The comparatively low reactivity of the arylboronic esters allowed the preferential formation of monoaryl copper intermediates while avoiding the formation of diaryl cuprates. As a result, high S_N2' selectivity was

observed in the allylic arylation, alkenylation, and alkylation reactions. Finally, the development of an enantioselective variant giving up to 70% ee will be described.

Detailed in chapter 2 is a formal hydroamination of alkenes using copper catalysis. Complete anti-Markovnikov selectivity for the alkene substrates is achieved in one-pot by hydroboration followed by copper-catalyzed electrophilic amination. This methodology was applied to the synthesis of trialkyl amines in the presence of a variety of functional groups, and was used to alkylate heterocycles. Furthermore, while investigating the reaction mechanism, unambiguous evidence of a stable alkyl copper intermediate was provided with the first X-ray crystal structure of such a species.

An extension of the hydroamination methodology will then be described in chapter 3. Copper-catalyzed coupling of arylboronic esters with electrophilic *O*-benzoyl hydroxylamines provided access to 32 different *N,N*-disubstituted anilines and heteroaromatic amines. The products obtained in these reactions have unprecedented levels of steric hindrance, but are nevertheless synthesized under mild conditions and in high yield.

Finally, in chapter 4, I will outline a new approach to catalytic hydrofunctionalization that was used to develop a selective semireduction of alkynes. Simply using a silane and an alcohol, both terminal and internal alkynes were reduced to the alkene with surprising chemoselectivity and complete stereoselectivity. Moreover, as little as 0.5 mol % of a copper catalyst can be used and no over-reduction was observed.

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List of Abbreviations

Δ:	Heat
Ac:	Acetyl
Ad:	Adamantle
Ar:	Aryl
BBN:	Borabicyclononane
BiPh:	Biphenyl
Bn:	Benzyl
Boc:	*tert*-Butyloxycarbonyl
Bz:	Benzyl
C:	Celsius
Cy:	Cyclohexyl
CV:	Column Volumes
d:	Day
DMSO:	Dimethyl sulfoxide
DTBHP:	di-*tert*-butyl hydroperoxide
dr:	Diastereomeric ratio
E^+:	Electrophile
ee:	Enantiomeric excess
eg:	ethylene glycol
eq:	Equation
equiv:	Equivalent

ESI-MS:	Electrospray ionization mass spectrometry
Et:	Ethyl
FTIR:	Fourier transform infrared spectroscopy
h:	Hour
HPLC:	High performance liquid chromatography
HRMS:	High resolution mass spectrometry
Hz:	Hertz
ICy:	1,3-Bis-dicyclohexyl imidazolium
IMes:	1,3-Bis-(2,4,6-trimethylphenyl)imidazolium
*i*Pr:	isopropyl
IPr:	1,3-Bis-(2,6-diisopropylphenyl)imidazolium
MBZ:	Methylbenzoate
Me:	Methyl
Mes:	Mesityl
MHz:	Megahertz
MOC:	Methyloxycarbonyl
mol:	Mole
MOM:	methoxymethyl ether
mp:	Melting point
ND:	Not determined
neop:	neopentylglycol
NHC:	N-heterocyclic carbene

NMR:	Nuclear magnetic resonance

Abbreviations for NMR splitting patterns

s:	singlet
d:	doublet
t:	triplet
q:	quartet
p:	pentet
m:	multiplet
br:	broad

NOESY:	Nuclear Overhauser effect spectroscopy
Ns:	Nitrobenzenesulfonyl
Nu:	Nucleophile
OTf:	Trifluoromethanesulfonate
OTFA	Trifluoroacetate
OTs:	*p*-Toluenesulfonate
PG:	Protecting Group
Ph:	Phenyl
Phth:	Phthalyl
pin:	pinacol
PMHS:	polymethylhydrosiloxane
ppm:	parts per million
rt:	room temperature

*t*Bu:	*tert*-butyl
TBS:	*Tert*-butyldimethylsilyl
TFA:	Trifluoroacetic acid
THF:	Tetrahydrofuran
TIPS:	Triisopropylsilyl
TLC:	Thin layer chromatography
TMDSO:	Tetramethyldisiloxane
TMS:	Trimethylsilyl
tol:	Tolyl
Ts:	*p*-Toluenesulfonyl
Z:	Electron withdrawing group

List of Schemes

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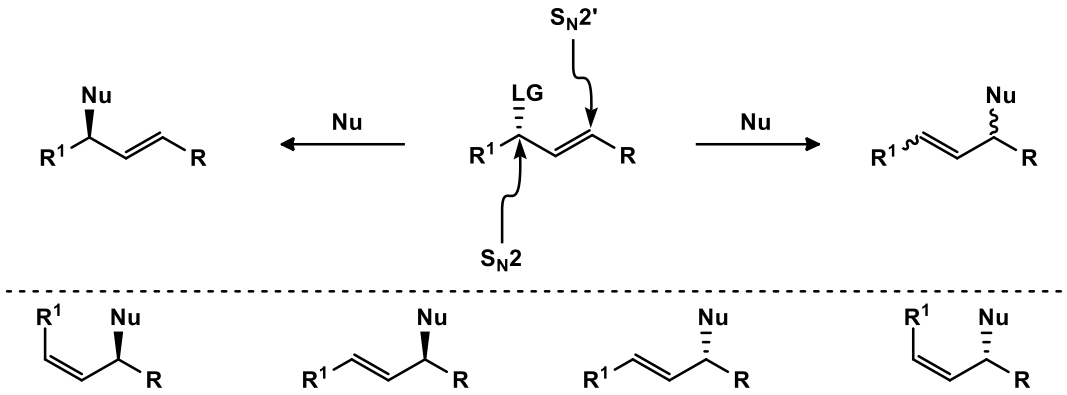
Thank you all.

Chapter 1 – Catalytic S_N2'-Selective Substitution of Allylic Chlorides with Arylboronic Esters

Section 1: Introduction

Nucleophilic substitution of allylic electrophiles has been a topic of great interest for organic chemists for nearly a century.[1] A particularly enticing aspect of this reaction is the ability to access multiple isomeric products from a common allylic electrophile. Two regioisomeric products are the result of the nucleophile's ability to add to either the α (S_N2), or the γ (S_N2') position of the allylic system. The regioisomer arising from γ attack also has four possible stereoisomers. Although special substrates have been used to demonstrate each stereochemical outcome under metal free conditions, control over regioselectivity and stereoselectivity in unbiased systems requires the use of metal catalysts.[2] An example of metal catalyzed allylic substitution is the prolific Tsuji-Trost reaction which utilizes palladium catalysis to enantioselectively deliver soft nucleophiles to a myriad of allylic electrophiles.[3] However, regardless of this successful use of palladium catalysis, copper catalysts must be employed to achieve S_N2' selectivity for hard, carbon based nucleophiles.[4]

Scheme 1.1. Stereochemistry of allylic substitution

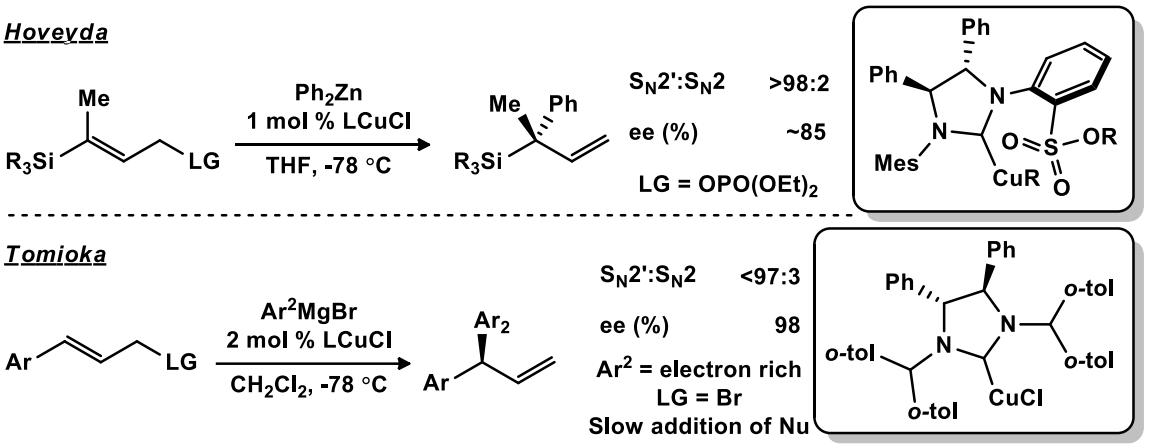


In fact, the copper-catalyzed allylic alkylation reaction has been known since 1969 when it was discovered by Crabbe.[5] After this initial discovery, great interest in the topic resulted in an enantioselective variant being introduced by Backvall and Van Koten in 1995,[6] and today, highly efficient S_N2'-selective asymmetric allylic alkylation can be achieved with a broad range of substrates. Reactions of Grignard, organozinc, organolithium, and organoaluminum nucleophiles have all been successfully applied to the synthesis of many natural products.[7]

In contrast, allylic substitution with sp^2-hybridized carbon nucleophiles remains a formidable challenge. For example, it was not until 2008 that the first allylic alkenylation was reported by Hoveyda et al.[8] Furthermore, by 2010 there were still no general S_N2'-selective allylic arylation reactions, despite the progress made using copper,[9] iridium,[10] and palladium[11] catalysts. In every reported example, the difficulty of obtaining an S_N2' product with aryl nucleophiles was evident by the mixtures of regioisomers obtained with most substrates. A few elegant examples that overcame this challenge are shown in scheme 1.2. Hoveyda and coworkers utilized the long carbon silicon bond in vinyl silanes to achieve high regioselectivity and enantioselectivity,[12] while Tomioka et al.

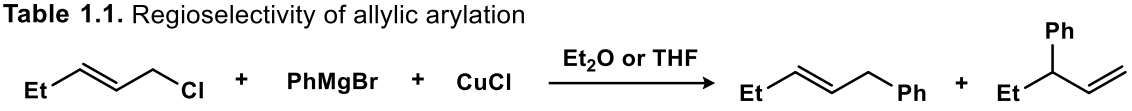
demonstrated improved regioselectivity with a slow addition of Grignard reagent.[13] However, the need for special substrates or special conditions detracts from the generality of either method.

Scheme 1.2. Previous work: S_N2' selective copper-catalyzed allylic arylation



In short, there were no general reactions for the delivery of aryl nucleophiles to the S_N2' position of allylic systems when we began our work in this field.[14] The underlying cause of the poor regioselectivity observed in reactions of primary allylic electrophiles has been studied in great detail. Important empirical evidence was provided by Backvall et al. who observed high S_N2' selectivity in stoichiometric reactions of monoaryl copper complexes, but poor regioselectivity when diaryl Gilman cuprates were employed (table 1.1).[15] To simulate the same effect in a catalytic reaction, a high catalyst loading and slow addition of the nucleophile was required. It was suggested that the slow addition procedure allows the monoaryl copper species to be the predominant reactive species by maintaining a low concentration of Grignard reagent, and therefore a low concentration of Gilman cuprate.

Table 1.1. Regioselectivity of allylic arylation



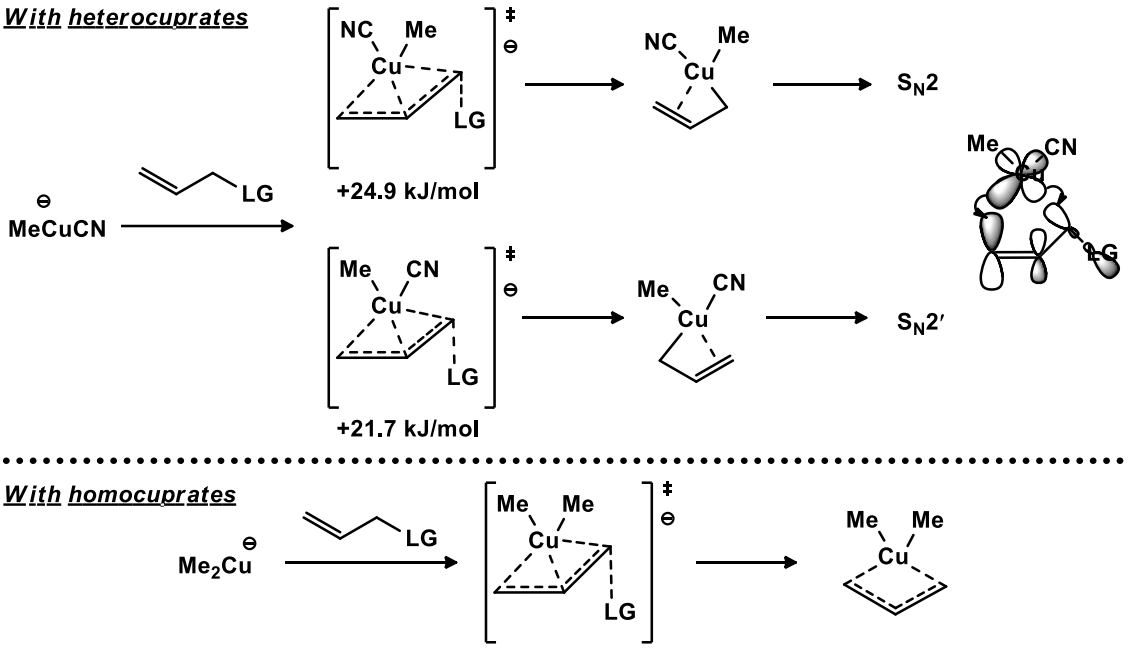
Entry	stoichiometry[a]		$S_N2:S_N2'$
1	1	1	9:91
2	2	1	46:54
3[b]	1	0.5	60:40
4[c]	1	0.5	27:73

a. relative to allylic chloride. b.Grignard added over 1 min. c. Grignard added over 2 h.

Despite the practical knowledge gained from these experiments, the deleterious effects of diaryl cuprates towards S_N2' selectivity were not fully understood until 2008. The most common explanation for the mechanism of S_N2' substitutions, proposed by Backvall, stated that the $S_N2:S_N2'$ selectivity is a reflection of the relative rates of π–allyl isomerization and reductive elimination from copper (III) allyl complexes.[15] Contrary to Backvall's mechanism however, a recent computational study by Nakamura et al. suggested that the regiochemical outcome of the copper-catalyzed allylic substitution is determined during oxidative addition of the cuprate to the allylic system.[16] As shown in scheme 1.3, the asymmetric d-orbitals of a monoaryl cuprate provide the most efficient orbital overlap when the electron rich ligand on copper (the nucleophile) is poised syn to the γ position of the allylic system. From this study it can be concluded that allylic substitution with heterocuprates inherently favors the S_N2' regioisomer. However, the symmetric Gilman cuprates are incapable of electronically differentiating between α and γ attack and therefore poor regioselectivity is observed. A special case where Gilman cuprates can be used to achieve high regioselectivity is when an electronic preference of the substrate towards a selective reductive elimination exists. Barring this scenario, and in accord with both Backvall and Nakamura, the combination of the low reactivity of the

monoaryl copper species paired with the high nucleophilicity of the transmetalation partner results in the formation of Gilman cuprates and ultimately a nonselective reaction.

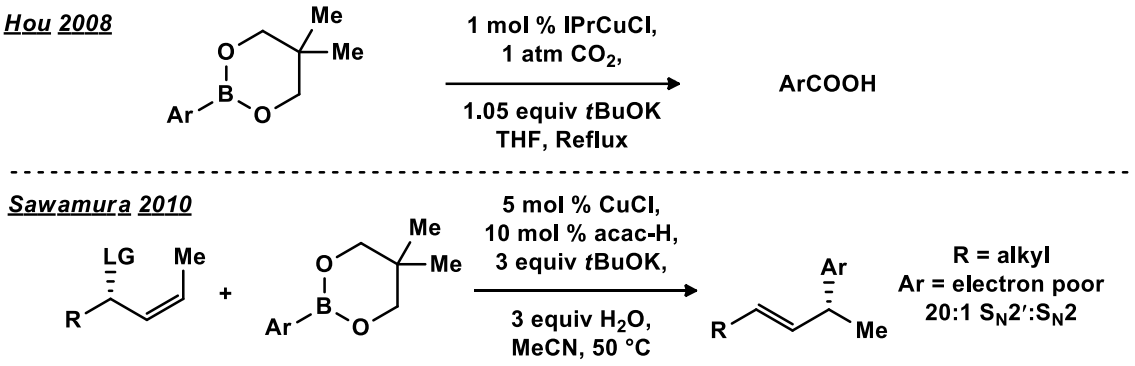
Scheme 1.3. Model for regioselectivity of allylic substitution



We reasoned that the formation of diaryl cuprates could be supressed if less reactive arylboronic esters were used in place of Grignard reagents. This approach is particularly appealing considering the availability, stability, and excellent functional group compatibility of arylboronic esters.[17] Furthermore, at the inception of the project there was only a single unambiguous example of boron-to-copper transmetalation.[18] In 2008, Hou et al. developed a copper-catalyzed synthesis of carboxylic acids by reacting arylboronic esters with carbon dioxide. During the preparation of our manuscript, two additional examples of boron-to-copper transmetalation were published by Sawamura and co-workers.[19] In one of these reports, substitution of secondary allylic electrophiles by arylboronic esters proceeded

with S_N2' selectivity. However, in this report, there were no examples of primary allylic electrophiles which we were particularly interested in because of the ease in synthesizing these substrates in combination with the possible stereochemical consequences of an S_N2'-selective reaction. Despite this progress, there were still no S_N2'-selective methods that deliver hard sp^2 nucleophiles when γ-substitution is sterically less favored than α-substitution. Additionally, achieving high S_N2' selectivity of this substrate class would represent a convenient method to concomitantly generate a stereocenter and a terminal alkene from readily available achiral molecules. Finally, realization of this method would support Nakamura's mechanistic proposal and provide a deeper understanding of the factors controlling the regioselectivity of copper-catalyzed allylic arylation.

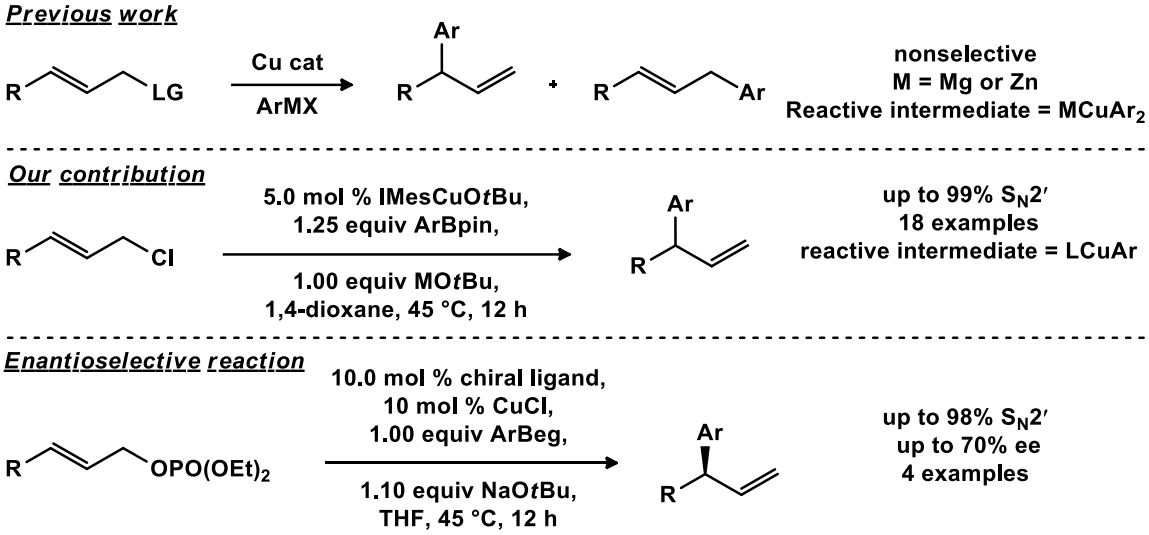
Scheme 1.4. Previous work: Arylboronic esters in copper-catalyzed transformations



In this chapter, the use of organoboron reagents as mild transmetalation partners in the copper-catalyzed allylic substitution reaction is described (Scheme 1.5).[20] These transmetalation partners successfully suppress the formation of Gilman cuprates, thus allowing S_N2'-selective arylation of primary allylic electrophiles for the first time. Additionally, by using commercially available, air-stable arylboronic esters, the reaction

was compatible with sensitive functional groups such as aldehydes and nitroarenes. An investigation into the reaction mechanism and progress towards an enantioselective variation of the allylic arylation reaction are also presented.

Scheme 1.5. Summary: S_N2' selective allylic arylation using aryl boronic esters



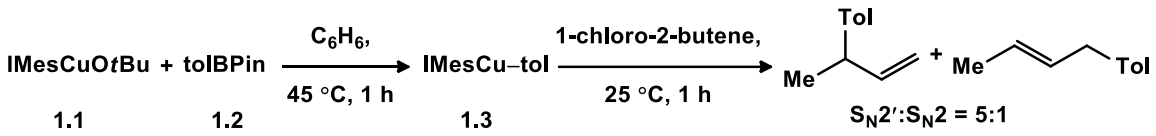
Section 2: Results and Discussion

1.2.a. Optimization

We initiated our investigation with stoichiometric reactions between IMesCuO*t*Bu and the pinacol ester of tolyl boronic acid as shown in scheme **1.6**. Pleasingly, transmetalation from boron to copper was indeed facile, occurring at 45 °C. Monoaryl copper complex **1.2** was successfully isolated, and characterized, representing one of the earliest unambiguous confirmations that arylboronic esters can in fact undergo transmetalation with a copper alkoxide. In agreement with the proposed mechanisms by Backvall and Nakamura, our isolated organocopper complex demonstrated a high

preference for the S_N2' regioisomer when reacted with 1-chloro-2-butene resulting in the branched product in a 5:1 selectivity.

Scheme 1.6. Copper mediated allylic substitution with an aryl boronic ester

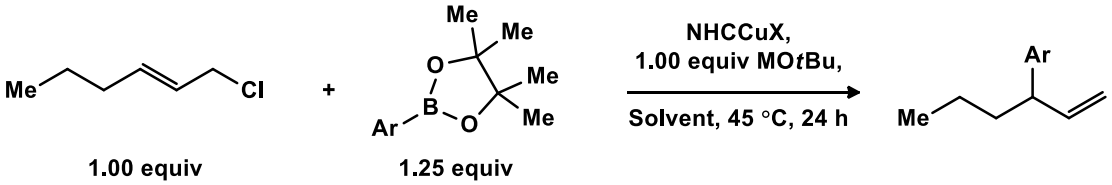


In preliminary screening experiments towards the development of a catalytic reaction, we discovered that with 10 mol % of IMesCuO*t*Bu, only 8% of the product was obtained, and in the absence of catalyst no reaction occurred. Since the stoichiometric reactions described above provided a proof of principal for transmetalation and allylic substitution, we surmised that the problems associated with the catalytic reaction could be addressed with the appropriate reagent to turn over the catalyst. As expected, the addition of a stoichiometric amount of KO*t*Bu successfully regenerated the catalyst and provided 99% yield and 20:1 S_N2':S_N2 if the reaction was performed in THF (Table 1.2). Importantly, allylic arylation of 1-chloro-2-butene with phenyl magnesium bromide and IMesCuCl as a catalyst resulted in exclusive formation of the product of S_N2 reaction, in agreement with previously published results.[21]

In the process of reaction optimization, we discovered that the best S_N2'-selectivity was obtained with catalyst **1.4**, while catalysts **1.5-1.7** provided a higher rate (not shown), albeit with lower selectivity (entries 1-4). Solvent was found to have a dramatic effect on S_N2' selectivity. Although all ethereal solvents gave acceptable S_N2' selectivity, 92% yield, and 42:1 S_N2':S_N2 was achieved with readily available IMesCuO*t*Bu as a catalyst in 1,4-dioxane. Among the alkali *tert*-butoxides, potassium

alkoxide provided the highest yield for electron rich and neutral aryl boronic esters (entries 5-7), with 98% yield obtained with only 5 mol % of the catalyst (entry 8). Alternatively, with electron-poor boronic esters, sodium alkoxides provided slightly better selectivity (entries 9-10). Overall, the best results were obtained using reaction conditions described in entry 8 for electron-rich boronic esters and in entry 10 for electron-poor boronic esters.

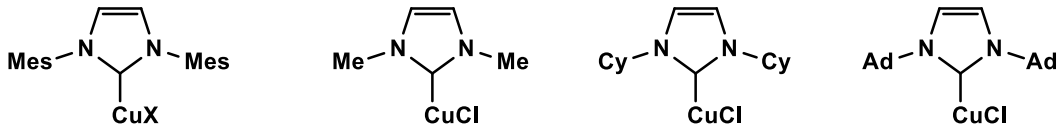
Table 1.2. Reaction optimization



1.00 equiv 1.25 equiv

entry	Ar	catalyst	mol %	M	solvent	$S_N2':S_N2$[a]	yield (%)[a]
1	4-MePh	1.4	10	K	THF	20:1	99
2	4-MePh	1.5	10	K	THF	8:1	99
3	4-MePh	1.6	10	K	THF	8:1	99
4	4-MePh	1.7	10	K	THF	3:1	94
5	4-MePh	1.1	10	K	1,4-dioxane	42:1	92
6	4-MePh	1.1	10	Na	1,4-dioxane	50:1	30
7	4-MePh	1.1	10	Li	1,4-dioxane	35:1	6
8	4-MePh	1.1	5	K	1,4-dioxane	48:1	98
9	4-(CHO)Ph	1.1	5	K	1,4-dioxane	18:1	91
10	4-(CHO)Ph	1.1	5	Na	1,4-dioxane	20:1	95

a. Determined By GC analysis



1.4 X = Cl
1.1 X = O*t*Bu

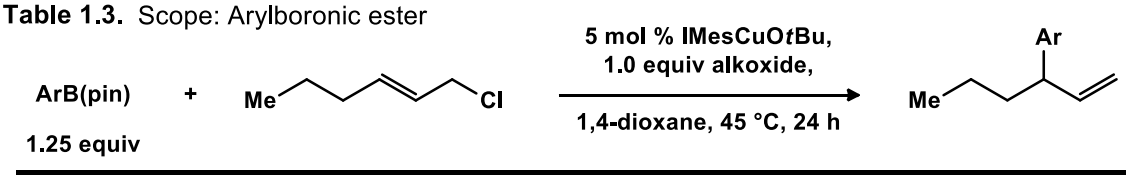
1.5 1.6 1.7

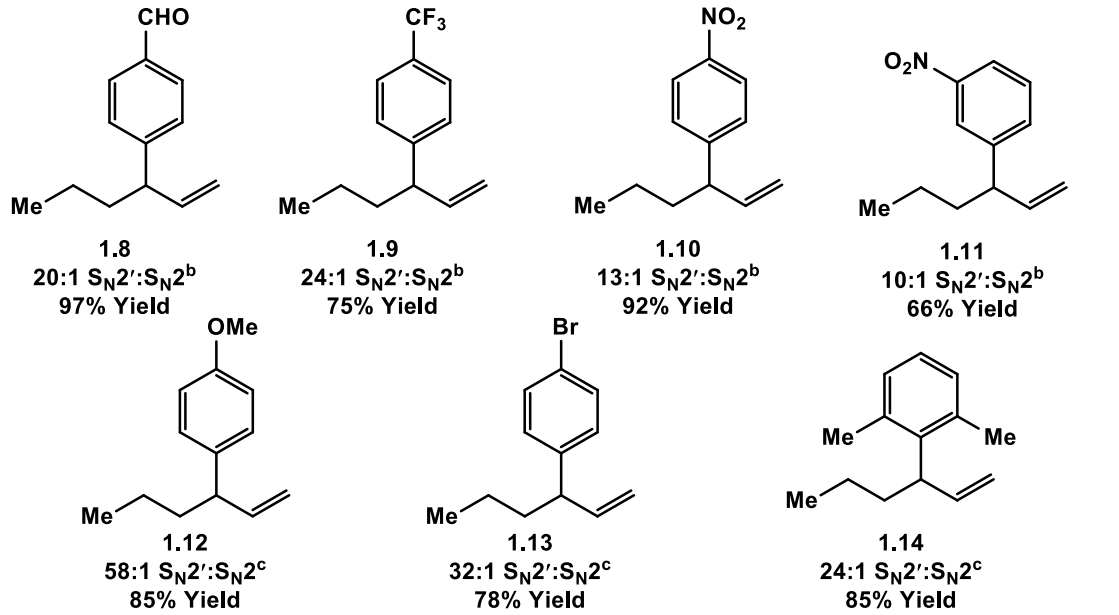
1.2.b. Scope

With the optimized reaction conditions in hand, we explored the reactivity of various arylboronic esters. As expected, the use of boronic esters allowed the reaction to be successfully performed in the presence of a variety of functional groups, including

formyl (**1.8**) and nitro groups (**1.10**), which are not compatible with previously described copper-catalyzed allylic substitution reactions. Furthermore, we observed a direct correlation between the electron-donating ability of the aryl substituents and the regioselectivity of the reaction consistent with Nakamura's proposed mechanism. Regardless of this observation though, even the most poorly performing substrates gave unprecedented levels of the S_N2' isomer (**1.11**). Steric properties of the boronic ester also had little effect on the reaction outcome, as demonstrated by the reaction of the 2,6-disubstituted arylboronic ester (**1.14**).

Table 1.3. Scope: Arylboronic ester



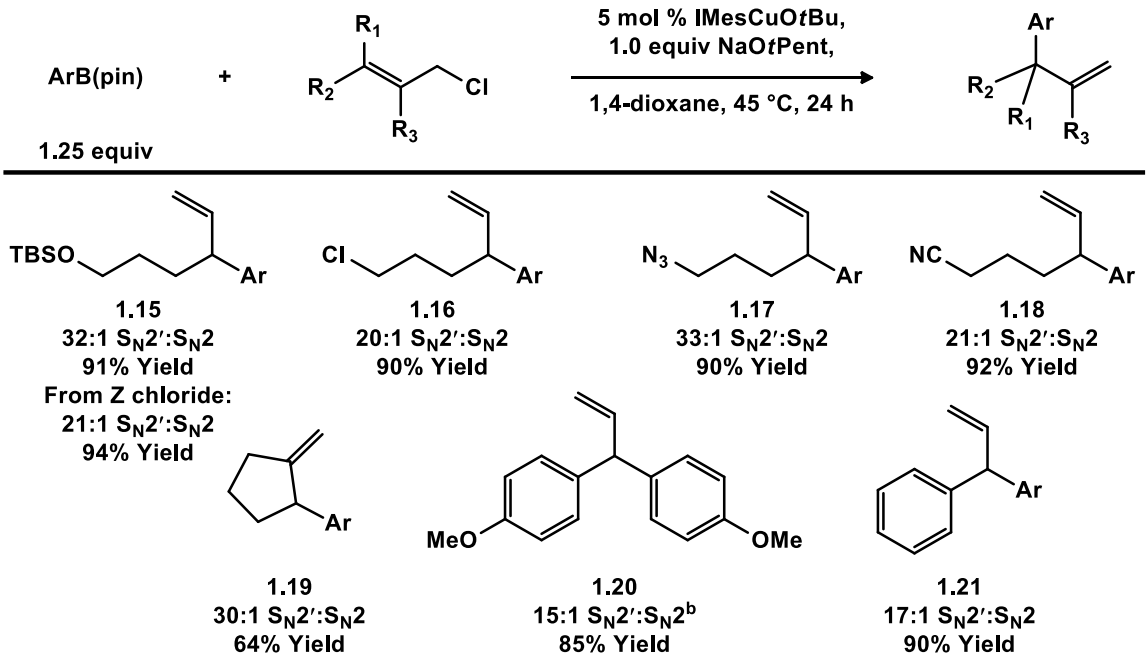


a. All reactions performed on a 0.5 mmol scale. All $S_N2':S_N2$ determined by GC analysis alkoxide. Yields are of isolated products. b. Alkoxide used is NaO*t*Pent. c. Alkoxide used is KO*t*Bu.

The scope of the allylic arylation was further explored in reactions of a variety of allylic chlorides. It was discovered that both *E*- and *Z*-substituted electrophiles can be

used in the reaction with similar success (**1.15**). Alkyl chlorides (**1.16**), azides (**1.17**), nitriles (**1.18**), and TBS-protected alcohols are all compatible with the reaction conditions, further demonstrating the exceptional functional group tolerance of the reaction. Finally, cyclic (**1.19**) and aryl-substituted (**1.20**-**1.21**) allylic chlorides are also suitable substrates for allylic arylation. The success of these substrates demonstrates the generality of the developed method.

Table 1.4. Scope: Allylic chloride

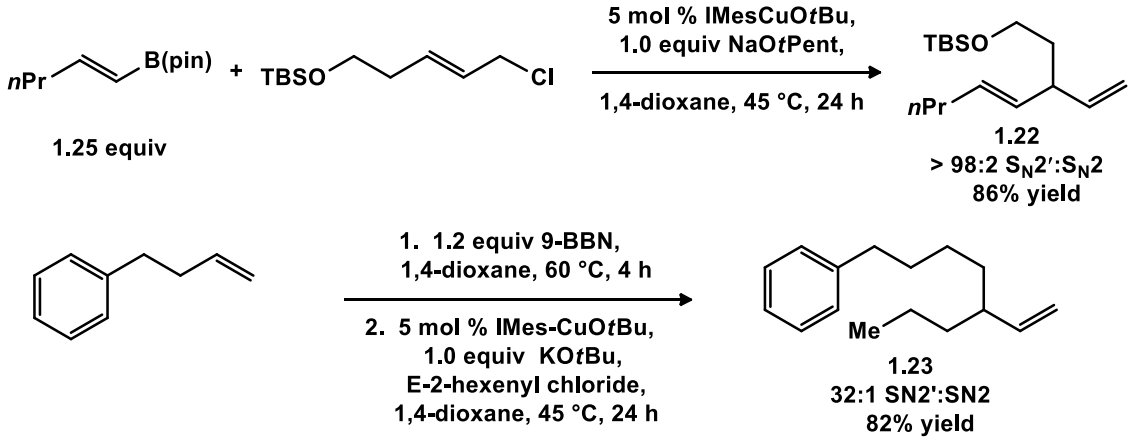


a. All reactions performed on a 0.5 mmol scale. All $S_N2':S_N2$ determined by GC analysis. Yields are of isolated products. b. Alkoxide used is KO*t*Bu. Ar = 4-(COOMe)C_6H_4

In addition to allylic arylation, we discovered that organoboron reagents can also be used as nucleophiles in copper-catalyzed alkenylation and alkylation of primary allylic electrophiles (Scheme **1.7**). With pentenyl boronic ester, the alkenylation product is obtained in good yield and excellent selectivity. In addition, allylic alkylation can be accomplished using trialkylboranes formed in situ from an alkene and 9-BBN. The

hydroboration-allylic alkylation sequence allows highly efficient and selective one-pot coupling of terminal alkenes and allylic chlorides.

Scheme 1.7. Allylic alkenylation and alkylation

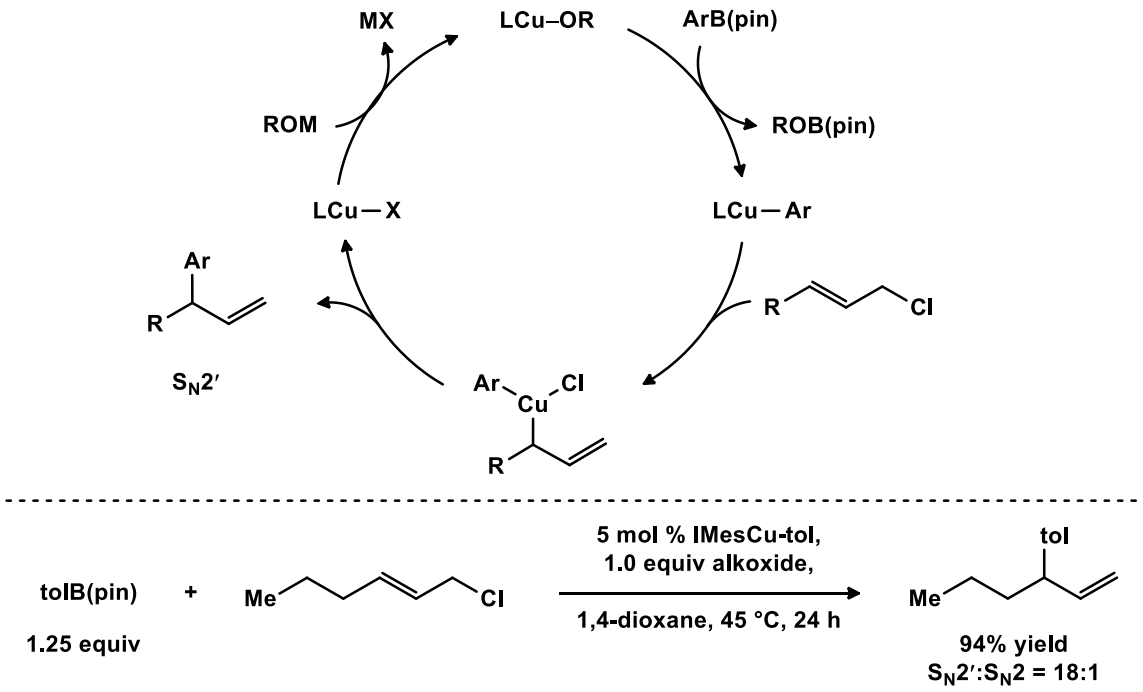


1.2.c. Mechanism

In an attempt to provide a better understanding of the source of the observed S_N2' selectivity, we studied the mechanism of the reaction. Our proposed catalytic cycle is presented in Scheme **1.8**. We propose transmetalation from boron to copper as the first step of the catalytic cycle. Evidence for this elementary step was provided by our ability to isolate the product of transmetalation from a stoichiometric reaction between IMesCuO*t*Bu and tolyl pinacol boronic ester (vide supra). The isolable compound **1.3** also allowed us to investigate the potential role of this complex in the second step of the proposed catalytic cycle as described by the stoichiometric reaction in scheme **1.6**. The formation of the expected product within 1 h, in good yield and with selectivity comparable to the selectivity obtained in a catalytic reaction indicates that the second step of the catalytic cycle occurs by the interaction of aryl copper and allylic chloride. This step has been proposed to proceed through an oxidative addition, reductive elimination,

pathway, without π-allyl isomerization.[22] Further evidence for the intermediacy of **1.3**, is provided by the use of **1.3** as a competent catalyst in the reaction (Scheme **1.8**). Together, these results support the idea that the aryl copper intermediate is the reactive nucleophile responsible for the selectivity observed in catalytic reactions. Finally, in the last step of the catalytic cycle, copper (I) alkoxide is regenerated from copper (I) chloride and KO*t*Bu in a transformation with much precedence.[23]

Scheme 1.8. Proposed mechanism

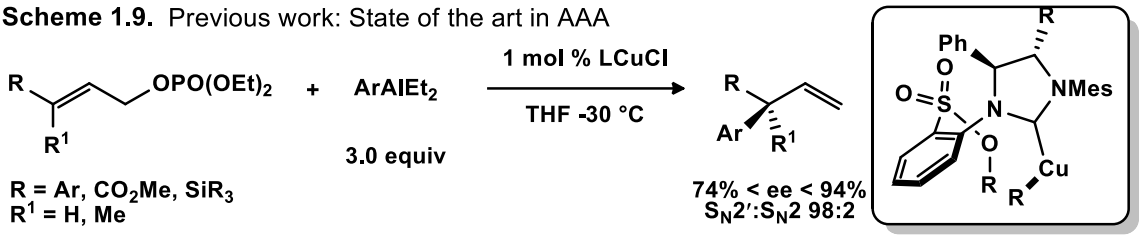


1.2.d. Asymmetric Allylic Arylation

Soon after our publication discussed a priori, an enantioselective allylic arylation representing the state of the art in AAA was published by Hoveyda et al.[24] In this publication the authors describe the use of aluminum reagents to deliver aryl and heteroaryl nucleophiles enantioselectively to alkyl and aryl substituted allylic phosphates forming quaternary carbon stereocenters (Scheme 1.9). Although the S$_N$2′-selectivity of

this reaction is impressive, the reaction requires air sensitive organoaluminum reagents in a large excess to the electrophile. Furthermore, these reagents are prepared from highly reactive organolithium reagents, limiting the functional group compatibility of the reaction. Finally, Hoveyda's method was primarily applied to activated electrophiles and heteroaryl nucleophiles. We envisioned that the use of boronic ester nucleophiles in place of the organoaluminum reagents would address the limitations associated with Hoveyda's method.

Scheme 1.9. Previous work: State of the art in AAA

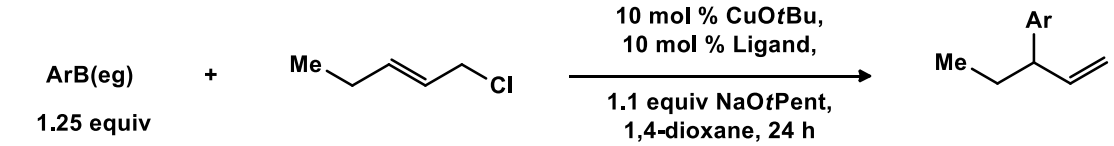


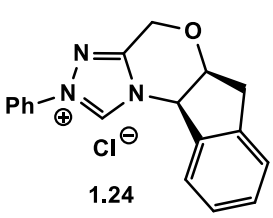
Initial optimization of the enantioselective allylic arylation identified chiral NHCs as the most promising ligands when used in combination with ethylene glycol boronic esters, and allylic phosphates (not shown). It was also quickly determined that the catalysts could be generated in situ by simply adding a copper salt and an NHC ligand. Focusing on these preliminary results, our optimization approach was to test ligands with a great deal of electronic and steric diversity.

Triazole ligand **1.24** was particularly interesting to us considering the ease of synthesis from the corresponding amino alcohol (indanol), thus allowing us to synthesize many analogs from a library of amino acids.[25] Additionally, the Tolman electronic parameters of these ligands revealed that 1,2,4-triazoles are significantly more electron deficient than previously used imidazole based NHC ligands.[26] According to

Nakamura's computational model electron deficient spectator ligands should provide good S_N2' selectivity. As shown in Table 1.5, the ligand did in fact provide high S_N2' selectivity, however, yields were low even at elevated temperatures and enantioselectivity was close to background. Other ligands in this class showed a similar trend (not shown).

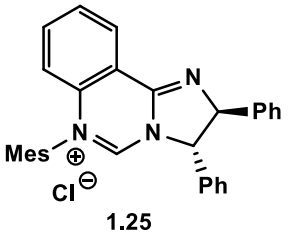
Table 1.5. Ligand Optimization: Monodentate NHC ligands





1.24

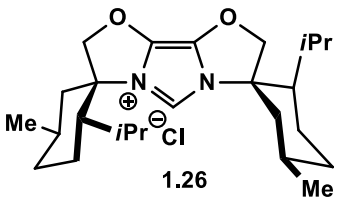
38:1 $S_N2':S_N2$[b]
51% Yield
4% ee



1.25

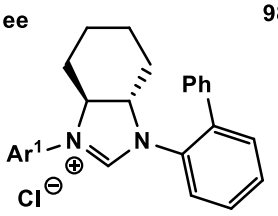
3:1 $S_N2':S_N2$
98% Yield
47% ee

2:1 $S_N2':S_N2$[c]
77% Yield
67% ee



1.26

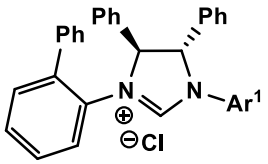
13:1 $S_N2':S_N2$[b]
69% Yield
1% ee



1.27-1.28

Ar^1 = 2,5-Et_2Ph
39:1 $S_N2':S_N2$
44% Yield
1% ee

Ar^1 = 9-Anthracene
38:1 $S_N2':S_N2$
51% Yield
6% ee



1.29-1.30

Ar^1 = 2,5-Et_2Ph
16:1 $S_N2':S_N2$
92% Yield
27% ee

Ar^1 = (o-*t*ol)$_2$CH
1:1 $S_N2':S_N2$
46% Yield
34% ee

a. All reactions performed at 45 °C except when indicated. All $S_N2':S_N2$, e,e and yieds are determined by GC analysis. b. Reaction performed at 60°C. c. Reaction performed at 25 °C. d. Reaction performed in THF. e. Reaction performed in Et_2O.

Ligand **1.25**, first synthesized by McQuade et al. and subsequently used in copper catalyzed borylation reactions of Michael acceptors,[27] and allylic carbonates,[28] was described as a highly electron donating ligand, and therefore piqued our interest as a compliment to the unsuccessful triazoles. In agreement with the findings of McQuade and co-workers, this 6-membered NHC ligand was found to be more reactive than

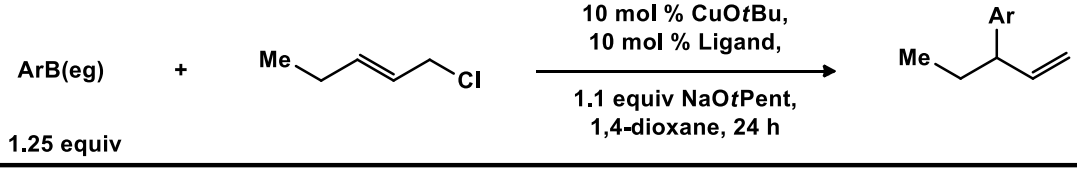
imidazole based NHC ligands, and in our hands provided promising results. At 25 °C, complete conversion occurred with 47% ee of the desired regioisomer. A change in solvent to diethyl ether further improved enantioselectivity to 67% ee, albeit combined with low regioselectivity. Because of this poor regioselectivity and to broaden our ligand options, we decided to investigate the use of the electronically intermediate chiral imidazolinium based NHC ligands.

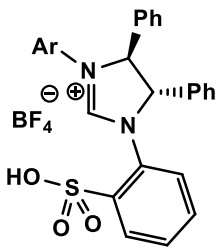
Using this class of ligand we observed that imidazole based NHC ligands derived from diphenyl ethylenediamine rather than cyclohexyldiamine provided increased enantioselectivities while maintaining good S_N2' selectivity. Also, a correlation between enantioselectivity and steric hindrance of the nitrogen substituents was observed (compare ligands **1.27-1.28** and **1.29-1.30**). Unfortunately, no reaction occurred when both nitrogens of the imidazolinium precursors were substituted by the most rigid anthracene substituent (not shown). Additionally, when sp^3-hybridized N-substituents such as benzhydrol were utilized (ligand **1.30**), an enantiomeric excess of 34% was observed, albeit at the expense of diminished regioselectivity.

Finally, imidazolinium **1.26** first synthesized by Glorius et al. takes a different approach to stereochemistry, placing the stereocenters on the N-substituents rather than on the NHC backbone.[29] This ligand represents the most sterically hindered NHC synthesized to date, suggesting that asymmetric induction may be possible provided that the resulting catalyst is not too hindered to react. Surprisingly, the catalyst did provide a moderate yield of 69%, and good regioselectivity of 13:1 $S_N2':S_N2$ at 60 °C. Surprisingly however, no enantioselectivity was obtained from this menthol derived catalyst. Overall,

with all mondentate NHC-derived catalysts, a discouraging trend was apparent. We observed an inverse relationship between enantioselectivity and regioselectivity (compare all ligands in table 1.5).

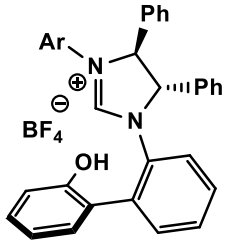
Table 1.6. Ligand Optimization: Bidentate NHC ligands





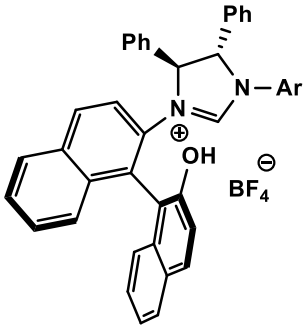
1.31-1.32
Ar = Mes,
17:1 $S_N2':S_N2$
34% Yield
12% ee

Ar = 2-biphenyl
68:1 $S_N2':S_N2$
68% Yield
30% ee

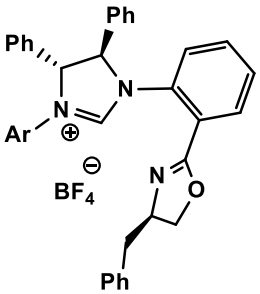


1.33-1.34
Ar = 2,6-Et_2Ph
21:1 $S_N2':S_N2$
44% Yield
48% ee

Ar = 2biphenyl
20:1 $S_N2':S_N2$
71% Yield
60% ee



1.35
Ar = 2-biphenyl
45:1 $S_N2':S_N2$
61% Yield
26% ee



1.36
Ar = 2-iphenyl
6:1 $S_N2':S_N2$
57% Yield
7% ee

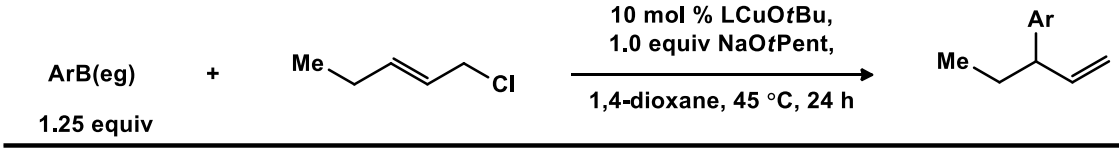
a. all reactions performed at 45 °C except when indicated. All $S_N2':S_N2$, e,e and yielsd are determined by GC analysis. b. Reaction performed at 60°C. c. Reaction performed at 25 °C. d. Reaction performed in THF. e. Reaction performed in Et_2O.

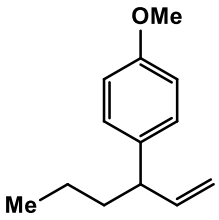
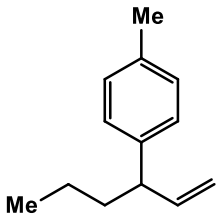
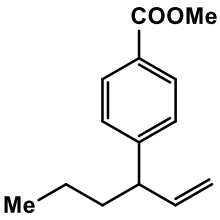
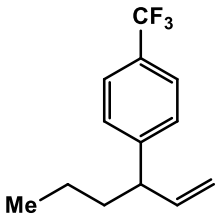
Because of this trend, and the high regioselectivity and enantioselectivity obtained by Hoveyda using bidentate imidazole NHC ligands,[30] we decided to direct our attention to this class of ligand. For the bidentate NHC-derived ligands listed in table 1.6, similar to the monodentate ligands in table 1.5, higher enantioselectivity is obtained with the more sterically hindered N-substituents (compare ligands **1.31-1.32** and **1.33-1.34**). Importantly however, is that the inverse relationship of regioselectivity to enantioselectivity is no longer apparent with bidentate NHC ligands. Of the ligands

tested the highest ee was obtained with phenol substituted ligand **1.34**. An attempt to affect the stereoselectivity with synergistic contributions from chiral imidazole backbones combined with chiral N-substituents was unsuccessful (ligands **1.35-1.36**). Although a match-mismatch effect was indicated by the reversal of the enantiomer obtained in a reaction with catalyst **1.36**, the epimer of either ligand was never successfully synthesized.

A preliminary investigation into reaction scope was conducted using the two most promising ligands **1.25**, and **1.34**. Table 1.7 shows these data. An interesting observation was that the two catalysts investigated gave complimentary reaction profiles. With ligand **1.34** electron poor nucleophiles gave the highest ee (see entries marked b), but with ligand **1.25** electron rich nucleophiles gave the highest ee (see entries marked d). Gratifyingly, the use of electron-poor nucleophiles also resulted in higher S_N2' selectivity with catalyst **1.34**. This regioselectivity was unprecedented for boronic ester nucleophiles with phosphate electrophiles, and is expected to be a result of the bidentate nature of the ligand.[31] Nakamuras mechanistic proposal states that there is a higher preference for the S_N2' regioisomer when aggregates of lithium and copper are present. The bidentate nature of the ligand could have a similar effect, which may also explain the higher enantioselectivity obtained with allylic phosphates as opposed to chlorides (not shown). Consistent with this proposal, is that the use of a more coordinating solvent (THF) results in a lower S_N2' selectivity with ligand **1.34**, but a higher enantioselectivity.

Table 1.6. Scope: AAA



OMe	Me	COOMe	CF_3
			
1.12	1.37	1.38	1.9
32:1 $S_N2':S_N2^b$ 92% Yield 27% ee	20:1 $S_N2':S_N2^{b,c}$ 71% Yield 60% ee	49:1 $S_N2':S_N2^b$ 45% Yield 40% ee	39:1 $S_N2':S_N2^b$ 42% Yield 46% ee
2:1 $S_N2':S_N2^d$ 74% Yield 70% ee	2:1 $S_N2':S_N2^d$ 70% Yield 67% ee	1:2 $S_N2':S_N2^d$ 56% Yield 44% ee	1:6 $S_N2':S_N2^d$ 62% Yield 21% ee

a. All $S_N2':S_N2$, ee, and yields are determined by GC analysis. b. Reaction performed using ligand 1.34. c. Reaction performed in THF. d. Reaction performed using ligand 1.25 in Et_2O.

Section 3: Conclusions

In conclusion, we have developed the first general S_N2'-selective arylation of primary allylic electrophiles using a copper(I) catalyst and arylboronic esters as nucleophiles. The reaction has a broad substrate scope and can be performed in the presence of a variety of functional groups including formyl, carbomethoxy, nitrile, azido, chloro, bromo, and nitro groups. In addition, we demonstrated allylic alkenylation and allylic alkylation using the same approach. The extension of this reactivity towards AAA using boronic ester nucleophiles was also presented herein. In addition to the high S_N2' selectivity, moderate enantioselectivity is possible using bidentate NHCs. This work sets the stage for other AAA reactions using boronic

ester nucleophiles, which may include heteroaryl, alkynyl, alkenyl, or alkyl nucleophiles, in combination with a variety of electrophiles.[32]

Section 4: Experimental

1.4.a. General

All reactions were performed under a nitrogen atmosphere, using flame-dried glassware unless otherwise indicated. Column chromatography was performed on a Biotage Iso-1SV flash purification system using silica gel (Agela Technologies Inc., 60Å, 40-60 μm, 230-400 mesh). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual $CHCl_3$ (7.26 ppm) or C_6D_6 (7.16 ppm). ^{13}C chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$: δ 77.2 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constants in Hertz (Hz). Mass spectra were collected on a JEOL HX-110 Mass spectrometer, a Bruker Esquire 1100 Liquid Chromatograph – Ion Trap Mass Spectrometer or a Hewlett Packard 5971A gas chromatograph – Mass Spectrometer. Melting points were determined on a capillary MEL-TEMP melting point apparatus and are uncorrected. Regioselectivity was determined by GC analysis using Shimadzu GC-2010 with a flame ionization detector

and a SHRXI-5MS column (15 m, 0.25 mm inner diameter, 0.25 μm film thickness). The following temperature program was used: 2 min @ 60 °C, 13 °C/min to 160 °C, 30 °C/min to 250 °C, 5.5 min @ 250 °C.

THF, CH_2Cl_2 and Et_2O and toluene were degassed and dried on columns of neutral alumina. 1,4-dioxane was distilled from purple Na/benzophenone ketyl, and stored over 4Å molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. 1,4-Dioxane-d^8 and THF- d^8 were distilled from purple Na/benzophenone ketyl. All other deuterated solvents degassed, and dried over 4Å molecular sieves. Commercial reagents were purchased from Sigma-Aldrich Co., VWR international, LLC., or STREM Chemicals, Inc., and were used as received. Catalysts **1.1**, **1.4**, **1.5-1.7**,[33] **1.24**,[34] **1.25**,[35] **1.26**,[36] **1.27-1.34**,[37] were prepared according to literature procedures.

1.4.b. Experimental Details

Allylic arylation procedure

In a glove box, a scintillation vial was charged with a stir bar. To the vial was added boronic ester (1.25 equiv, 0.625 mmol), *tert*-butoxide (as specified in tables 2 and 3) (1.00 equiv, 0.500 mmol), and 1,4-dioxane (2.0 mL). After 10 minutes, IMesCuO*t*Bu (0.05 equiv, 0.025 mmol) dissolved in 0.5 mL of 1,4-dioxane was added, and the mixture was stirred for another 10 min at ambient temperature. The allylic chloride was added (1.00 equiv, 0.500 mmol) in one portion and the scintillation vial was heated to 45 °C for 24 h. The vial was removed from the glove box, diluted with Et_2O, filtered through a plug of silica, concentrated in vacuo, and the crude reaction mixture was purified by silica gel

chromatography. For asymmetric reactions the ligand (10 mol %) and copper *tert*-butoxide tetramer (10 mol %) were premixed with base (10 mol %), with no further modifications. It was determined that this method provides identical results to pre-making and isolating the catalyst as long as the appropriate non-coordinating counter ion was chosen.

Allylic alkenylation procedure

In a glove box, a scintillation vial was charged with a stir bar. To the vial was added (E)-4,4,5,5-tetramethyl-2-(pent-1-en-1-yl)-1,3,2-dioxaborolane (1.25 equiv, 139 μL 0.625 mmol), sodium *tert*-pentoxide (1.00 equiv, 55.0 mg, 0.500 mmol), and 1,4-dioxane (2.0 mL). The resulting solution was allowed to stir at 45 °C for 10 minutes. After 10 minutes, IMesCuO*t*Bu (0.05 equiv, 11.0 mg, 0.025 mmol) in 0.5 mL 1,4-dioxane was added and the mixture stirred for another 10 min at ambient temperature. (E) *tert*-butyl((5-chloropent-3-en-1-yl)oxy)dimethylsilane was added (1.00 equiv, 118 mg, 0.500 mmol) in one portion and the scintillation vial was heated to 45 °C for 24 h. The vial was removed from the glove box, and the reaction mixture was diluted with Et_2O, filtered through a plug of silica, concentrated in vacuo and purified by silica gel chromatography. Compound was isolated as a colorless oil (116.2 mg, 86% yield) after purification by silica gel column chromatography.

Allylic alkylation procedure

In a glove box, a scintillation vial was charged with a stir bar. To the vial was added but-3-en-1-ylbenzene (1.25 equiv, 83.0 mg, 0.625 mmol), 9-Borabicyclo[3.3.1]nonane dimer (0.63 equiv, 152 mg, 0.313 mmol), and 1,4-dioxane

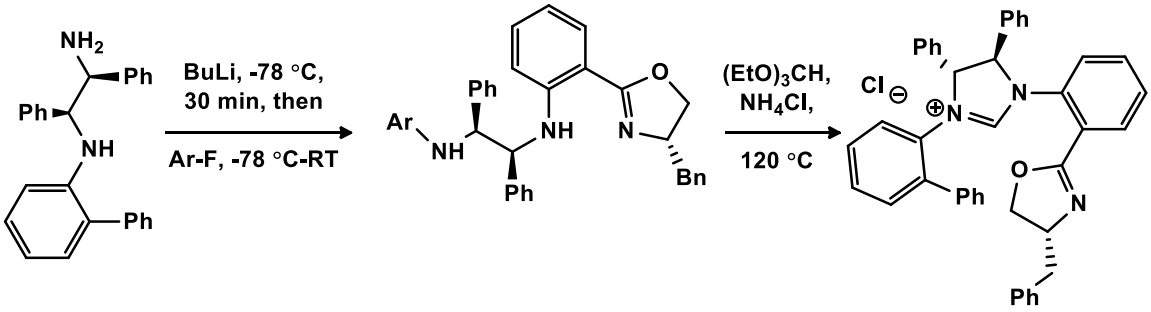
(0.5 mL). The resulting solution was stirred at 60 °C for 4 h. After 4 h, the solution was transferred to a scintillation vial containing IMesCuO*t*Bu (0.05 equiv, 11.0 mg, 0.025 mmol), sodium *tert*-pentoxide (1.00 equiv, 56.0 mg, 0.50 mmol), and 1,4-dioxane (2.0 mL). The resulting solution was allowed to stir at 25 °C for 10 minutes, and then (E)-2-hexenyl-1-chloride (1.00 equiv, 65.9 μL, 0.50 mmol) was added. The resulting solution was allowed to stir at 60 °C for 24 h. The vial was removed from the glove box, the reaction mixture was diluted with Et_2O, filtered through a plug of silica, and concentrated in vacuo. Compound was isolated as a colorless oil (89.0 mg, 82% yield, 32:1 mixture of isomers) after purification by silica gel chromatography.

Synthesis of IMesCu-tol

A 100 mL Schlenk flask was charged with a stir bar and flame-dried under vacuum. The flask was then transferred into a glove box and was charged with IMesCuO*t*Bu (1.1 equiv, 1.00 g, 2.27 mmol) and tolylboronicpinacolate ester (1.0 equiv, 0.45 g, 2.06 mmol). Toluene was added (50 mL, 0.05 M). The resulting solution was heated to 60 °C for 16 h and then filtered over a pad of Celite. The solvent was then removed until cloudy. An equal volume of pentane was added, and the flask was placed into the -20 °C freezer. After 24 h, the filtrate was removed by pipette and the crystals isolated by vacuum filtration. The crystals were then washed with pentane and transferred into a scintillation vial charged with a stir bar. Isooctane was added and the solution was vigorously stirred at room temperature for 0.5 h. The isooctane was then removed in vacuo. This process was repeated twice to yield the desired product as a white solid.

Reaction of IMesCu-tol with (E)-2-hexenyl-1-chloride

In a glove box, a 1 dram vial was charged with a stir bar. To the vial was added (E)-2-hexenyl-1-chloride (1.00 equiv, 6.6 μL, 0.05 mmol) and internal standard 1,3,5-trimethoxybenzene (TMB) in 1,4-dioxane (0.25 mL). Separately, a solution of IMesCu-tol (1.00 equiv, 23.0 mg, 0.05 mmol) in 1,4-dioxane (0.25 mL) was prepared. The solution of IMesCu-tol was added to a 1 dram vial containing (E)-2-hexenyl chloride and the resulting solution was stirred at 45 °C. After 5 minutes, an aliquot of the reaction analyzed by GC indicated complete conversion of (E)-2-hexenyl chloride. The arylation product was obtained in 79% yield (determined by GC analysis) as a mixture of isomers (30:1).

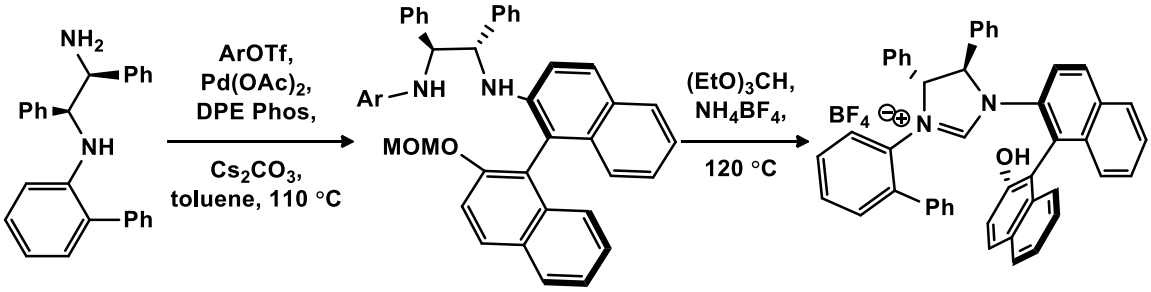


*Synthesis of ligand **1.35***

In a glove box N-biphenyl-1S,2S-diphenyl ethane diamine[38] (550 mg, 1.2 equiv, 1.51 mmol) was added to a reaction flask followed by dry THF (10 mL). The flask was pumped out of the glove box and placed in a dry ice acetone bath. n-BuLi (2.4 M, 0.58 mL, 1.1 equiv, 0.692 mmol) was added dropwise at -78 °C with vigorous stirring over 30 min. At this time 1-(3-benzyl-dihydrooxazole-1-yl)-2-fluoro benzene[39] (180 mg, 1.0 equiv, 1.38 mmol) in dry THF was added at -78 °C and the reaction was allowed to warm to reflux and maintained there for 24 h. Sat. NH_4Cl was slowly added to quench the

reaction, and the aqueous layer was extracted 3 times with ethyl acetate, dried over MgSO4, and concentrated. The crude reaction mixture was then purified by column chromatography 0-40% EA in hex, then again (0-10% EA in HEX) giving the product as a yellow oil (376 mg, 58% yield).

The product was dissolved in triethyl orthoformate (8.0 mL) and added to an oven dried 100 mL reaction flask equipped with a distilling head to remove ethanol. The reaction heated at 120 °C after adding ammonium chloride (2 equiv, 2.76 mmol) for 5 h. The orthoformate was then mostly removed through distillation. The product was purified by column chromatography (0 - 5% EtOH in $CHCl_3$) followed by trituration from CH_2Cl_2/Et_2O, resulting in an orange powder (94 mg, 16% yield).



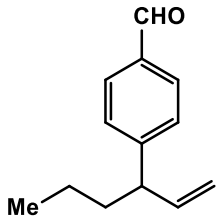
*Synthesis of ligand **1.36***

In a glove box, $Pd(OAc)_2$ (72.8 mg, 0.10 equiv, 0.32 mmol) and DPE-Phos (349.4 mg, 0.20 equiv, 0.65 mmol) were mixed in toluene (10 mL) for 10 min at RT before cesium carbonate (1585.3 mg, 1.5 equiv, 4.87 mmol) was added and mixed for 10 min. N-biphenyl-S1,S2-diphenyl-ethanediamine (1418.7 mg, 1.2 equiv, 3.8924 mmol) was added and the reaction flask was pumped out of the box. 2-methoxymethyl-2`-triflate-S-binol (1500 mg, 1.0 equiv, 3.24 mmol) was added and the reaction was heated to 110 °C for 20 h. The solution cooled to 0 °C and was filtered through a plug of celite, washed

with brine, dried over Na_2SO_4 and concentrated. Compound was isolated as a yellow foam (1519.6 mg, 69% yield) after purification by silica gel column chromatography (0 → 20% EA/hexanes).

The product was then dissolved in triethyl orthoformate (8.0 mL) and added to an oven dry 100 mL reaction flask equipped with a distilling head to remove ethanol. The reaction heated at 120 °C after adding ammonium tetrafluoroborate (2 equiv, 4.46 mmol) for 5 h. The orthoformate was then mostly removed through distillation. Compound was isolated as a tan powder (1251.0 mg, 81% yield) after purification by silica gel column chromatography (0 → 5% MeOH/CH_2Cl_2).

1.4.c. Characterization

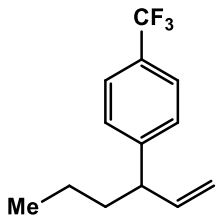


1.8

4-(hex-1-en-3-yl)benzaldehyde

Compound was isolated as a light yellow oil (91.7 mg, 97% yield, 20:1 mixture of isomers) after purification by silica gel column chromatography (5 → 15% EtOAc/hexanes). Major isomer; ^{1}H NMR (300 MHz, C_6D_6) δ 9.71 (s, 1H), 7.56 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 5.71 (ddd, *J* = 17.1, 10.3, 7.6 Hz, 1H), 5.02 – 4.73 (m, 2H), 3.03 (m, 1H), 1.51 – 1.39 (m, 2H), 1.18 – 0.99 (m, 2H), 0.79 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 152.4, 141.6, 135, 130.4, 128.7, 115.3, 50.2, 37.8,

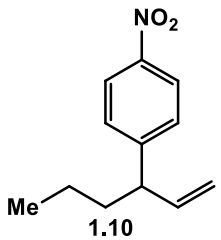
21.0, 14.3. HRMS calculated for $[M+H]^+$ 189.1279, found 189.1281. FTIR (neat, cm^{-1}): 3081 (w), 2930 (m), 2733 (m), 1703 (s), 1576 (m), 1108 (w), 828 (m).



1.9

1-(hex-1-en-3-yl)-4-(trifluoromethyl)benzene

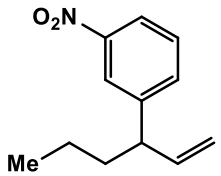
Compound was isolated as a colorless oil (85.5 mg, 75% yield, 24:1 mixture of isomers) after purification by silica gel column chromatography (0 → 15% EtOAc/hexanes). Major isomer; ^{1}H NMR (500 MHz, C_6D_6) δ 7.35 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 5.80 – 5.55 (m, 1H), 5.03 – 4.73 (m, 1H), 3.11 – 2.86 (m, 1H), 1.55 – 1.34 (m, 1H), 1.24 – 0.96 (m, 1H), 0.79 (t, *J* = 7.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9 (d, *J* = 1.0 Hz), 141.6, 128.6 (q, *J* = 32.3 Hz), 128.1, 125.5 (q, *J* = 3.7 Hz), 124.5 (q, *J* = 271.8 Hz), 114.8 (s), 49.6, 37.6, 20.7, 14.1. HRMS calculated for $[M]^+$ 228.1128, found 228.1130. FTIR (thin film, cm^{-1}): 3082 (w), 2931 (m), 1327 (s), 1126 (m), 1609 (m), 917 (m), 839 (m).



1.10

1-(hex-1-en-3-yl)-4-nitrobenzene

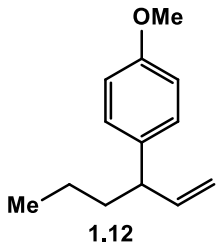
Compound was isolated as a light yellow oil (94.3 mg, 92% yield, 13:1 mixture of isomers) after purification by silica gel column chromatography (5 → 20% EtOAc/hexanes). Major isomer; ^{1}H NMR (500 MHz, C_6D_6) δ 7.84 (d, *J* = 8.7 Hz, 2H), 6.67 (d, *J* = 8.7 Hz, 2H), 5.59 (ddd, *J* = 17.6, 10.2, 7.6 Hz, 1H), 4.87 (m, 2H), 2.92 (m, 1H), 1.43 – 1.27 (m, 2H), 1.13 – 0.93 (m, 2H), 0.78 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 140.7, 128.4, 123.7, 115.4, 49.5, 37.4, 20.5, 13.9. HRMS calculated for $[M+H]^+$ 206.1179, found 206.1183. FTIR (thin film, cm^{-1}): 3080 (w), 2932 (m), 1637 (m), 1519 (s), 1346 (s), 1110 (m), 919 (m), 853 (m).



1.11

1-(hex-1-en-3-yl)-3-nitrobenzene

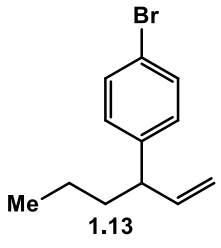
Compound was isolated as a light yellow oil (67.7 mg, 66% yield, 10:1 mixture of isomers) after purification by silica gel column chromatography (10 → 20% EtOAc/hexanes). Major isomer; ^{1}H NMR (500 MHz, C_6D_6) δ 7.95 (s, 1H), 7.79 – 7.66 (d, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.78 (t, *J* = 7.9 Hz, 1H), 5.67 – 5.48 (m, 1H), 4.87 (m, 2H), 2.95 (m, 1H), 1.36 (m, 2H), 1.17 – 0.90 (m, 2H), 0.76 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 148.9, 146.7, 141.1, 133.6, 129.2, 122.6, 121.4, 115.1, 49.4, 37.5, 20.7, 14.0. HRMS calculated for $[M+H]^+$ 206.1179, found 206.1186. FTIR (thin film, cm^{-1}): 3080 (w), 2931 (m), 1638 (m), 1530 (s), 1350 (s), 923 (m), 806 (m).



1.12

1-(hex-1-en-3-yl)-4-methoxybenzene

Compound was isolated as a colorless oil (80.6 mg, 85% yield, 58:1 mixture of isomers) after purification by silica gel column chromatography (5 → 20% EtOAc/hexanes). Major isomer; ^{1}H NMR (500 MHz, C_6D_6) δ 7.03 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.92 (ddd, *J* = 17.4, 10.3, 7.3 Hz, 1H), 5.01 (m, 2H), 3.34 (s, 3H), 3.15 (m, 1H), 1.65 – 1.58 (m, 2H), 1.39 – 1.12 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 143.0, 136.8, 128.6, 113.9, 113.6, 55.3, 48.8, 37.8, 20.7, 14.1. HRMS calculated for $[M+H]^+$ 191.1434, found 191.1437. FTIR (thin film, cm^{-1}): 3077 (w), 2872 (m), 1636 (m), 1512 (s), 1249 (s), 1038 (m), 829 (m).

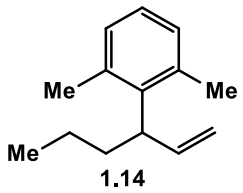


1.13

1-bromo-4-(hex-1-en-3-yl)benzene

Compound was isolated as a colorless oil (92.4 mg, 78% yield, 32:1 mixture of isomers) after purification by silica gel column chromatography using hexanes as an eluent. Major isomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.3 Hz, 2H), 6.69 (d, *J* = 8.3 Hz, 2H), 5.81 – 5.59 (m, 1H), 4.97 – 4.82 (m, 2H), 2.95 (m, 1H), 1.55 – 1.32 (m, 2H),

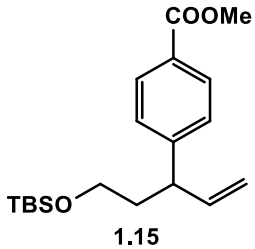
1.21 – 0.91 (m, 2H), 0.78 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 142.1, 131.8, 129.7, 120.2, 114.2, 49.3, 37.7, 20.8, 14.1. HRMS calculated for $[M]^+$ 238.0357, found 238.0362. FTIR (thin film, cm^{-1}): 3079 (w), 2929 (m), 1637 (m), 1488 (m), 1106 (w), 1011 (m), 824 (m).



1.14

2-(hex-1-en-3-yl)-1,3-dimethylbenzene

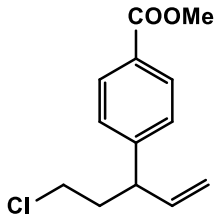
Compound was isolated as a colorless oil (79.9 mg, 85% yield, 24:1 mixture of isomers) after purification by silica gel column chromatography (0 → 20% benzene/hexanes). ^{1}H NMR (500 MHz, C_6D_6) δ 7.02 - 6.92 (m, 3H), 6.01 (ddd, J = 17.3, 10.4, 5.0 Hz, 1H), 4.95 (m, 2H), 3.82 – 3.71 (m, 1H), 2.23 (s, 6H), 1.78 – 1.64 (m, 2H), 1.30 – 1.01 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0, 140.6, 136.8, 126.0, 113.8, 44.0, 35.3, 21.7, 21.5, 14.4. HRMS calculated for $[M]^+$ 188.1567, found 188.1566. FTIR (thin film, cm^{-1}): 3075(w), 2931 (m), 1633 (m), 910 (m), 768 (m).



1.15

Methyl 4-(5-((tert-butyldimethylsilyl)oxy)pent-1-en-3-yl)benzoate

Compound was isolated as a colorless oil (157.5 mg, 94% yield, 32:1 mixture of isomers, from Z alkene) (152.1 mg, 91%, 21:1 mixture of isomers, from E alkene) after purification by silica gel column chromatography (0 → 10% EtOAc in hexanes). Major isomer; ^{1}H NMR (500 MHz, C_6D_6) δ 8.13 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 5.77 (ddd, *J* = 17.5, 10.2, 7.5 Hz, 1H), 5.01 – 4.91 (m, 2H), 3.58 – 3.43 (m, 5H), 3.39 (dt, *J* = 10.0, 6.4 Hz, 1H), 1.80 (m, 2H), 0.96 (s, 9H), -0.01 (d, *J* = 5.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 149.6, 141.2, 129.9, 128.3, 127.9, 115.0, 60.5, 52.1, 45.8, 38.0, 26.0, 18.4, -5.3. HRMS calculated for $[M+H]^+$ 335.2041, found 335.2029. FTIR (neat, cm^{-1}): 3081 (w), 3000 (w), 2953 (s), 1725 (s), 1610 (m), 1278 (s), 1104 (s), 834 (s) 755 (m).

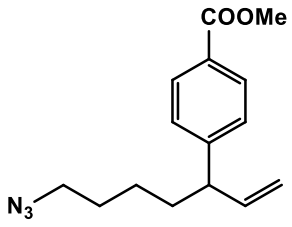


1.16

Methyl 4-(6-chlorohex-1-en-3-yl)benzoate

Compound was isolated as a colorless oil (106.1 mg, 90% yield, 20:1 mixture of isomers) after purification by silica gel column chromatography (30 → 80% benzene in hexanes). Major isomer; ^{1}H NMR (300 MHz, C_6D_6) δ 8.11 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.2 Hz, 2H), 5.64 (ddd, *J* = 17.1, 10.3, 7.6 Hz, 1H), 5.00 – 4.74 (m, 2H), 3.53 (s, 3H) 3.03 (t, *J* = 6.4 Hz, 2H), 2.91 (q, *J* = 7.4 Hz, 1H), 1.62 – 1.17 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 149.3, 140.9, 130.0, 128.5, 127.7, 115.3, 52.1, 49.3, 44.9, 32.4,

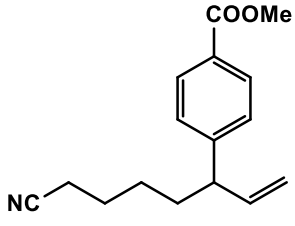
30.6. HRMS calculated for $[M+H]^+$ 253.0996, found 253.1002. FTIR (neat, cm^{-1}):3082 (w), 3000 (w), 2953 (m), 1722 (s), 1609 (m), 1436 (m), 1280 (s), 912 (s), 733 (s).



1.17

Methyl 4-(7-azidohept-1-en-3-yl)benzoate

Compound was isolated as a light yellow oil (123.6 mg, 90% yield, 33:1 mixture of isomers) after purification by silica gel column chromatography (30 → 80% benzene in hexanes). Major isomer; ^{1}H NMR (300 MHz, C_6D_6) δ 8.16 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 2H), 5.83 – 5.55 (m, 1H), 5.00 – 4.82 (m, 2H), 3.52 (s, 3H), 2.95 (m, 1H), 2.59 (t, *J* = 6.8 Hz, 2H), 1.34 (m, 2H), 1.23 – 0.78 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 149.6, 141.2, 130.0, 128.4, 127.7, 115.1, 52.1, 51.3, 49.9, 34.9, 28.8, 24.7. HRMS calculated for $[M+H]^+$ 274.1553, found 274.1557. FTIR (neat, cm^{-1}):3079 (w), 2940 (m), 2095 (s), 1721 (s), 1609 (m), 1435 (m), 1279 (s).

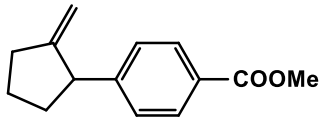


1.18

Methyl 4-(7-cyanohept-1-en-3-yl)benzoate

Compound was isolated as a colorless oil (118.4 mg, 92% yield, 21:1 mixture of isomers) after purification by silica gel column chromatography (10 → 40% EtOAc in

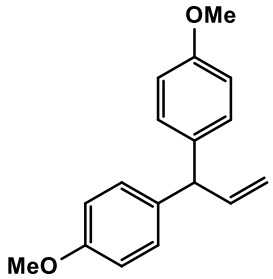
hexanes). Major isomer; ^{1}H NMR (300 MHz, C_6D_6) δ 8.16 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 5.81 – 5.54 (m, 1H), 4.98 – 4.80 (m, 2H), 3.52 (s, 3H), 2.76 – 2.98 (m, 1H), 1.38 – 1.09 (m, 4H), 1.06 – 0.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 149.4, 140.9, 130.0, 128.4, 127.6, 119.6, 115.2, 52.1, 49.7, 34.4, 26.7, 25.3, 17.1. HRMS calculated for $[M+H]^+$ 244.1338, found 244.1333. FTIR (neat, cm^{-1}):3075 (w), 3000 (w), 2947 (m), 2241 (m), 1721 (s), 1609 (m), 1435 (m), 1281 (s), 919 (m).



1.19

Methyl 4-(2-methylenecyclopentyl)benzoate

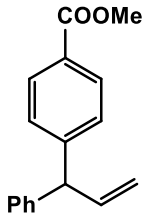
Compound was isolated as a white solid (69.1 mg, 64% yield, 30:1 mixture of isomers) after purification by silica gel column chromatography (0 → 10% EtOAc in benzene). mp 38 °C. Major isomer; ^{1}H NMR (300 MHz, C_6D_6) δ 8.15 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.3 Hz, 2H), 4.97 (d, J = 2.0 Hz, 1H), 4.60 (d, *J* = 2.0 Hz, 1H), 3.52 (s, 3H), 3.32 (t, *J* = 7.4 Hz, 1H), 2.47 – 2.15 (m, 2H), 1.95 – 1.77 (m, 1H), 1.65 – 1.26 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 156.0, 150.8, 129.8, 128.4, 128.1, 107.8, 52.1, 51.3, 36.6, 33.6, 24.9. HRMS calculated for $[M+H]^+$ 217.1227, found 217.1236. FTIR (thin film, cm^{-1}): 3054 (w), 2987 (m), 1717 (s), 1610 (m), 1422 (m), 1265 (s), 896 (s).



1.20

4,4`-(prop-2-ene-1,1-diyl)bis(methoxybenzene)

Compound was isolated as a clear liquid (108.3 mg, 85% yield, 15:1 mixture of isomers) after purification by silica gel column chromatography (0 → 20% benzene in hexanes). Major isomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 – 6.99 (m, 4H), 6.85 – 6.71 (m, 4H), 6.24 (ddd, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.13 (d, *J* = 10.1 Hz, 1H), 4.97 (d, *J* = 17.1 Hz, 1H), 4.58 (d, *J* = 7.0 Hz, 1H), 3.39 – 3.21 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 158.79, 141.93, 136.09, 129.97, 115.70, 114.20, 54.81, 53.83. HRMS calculated for $[M+H]^+$ 254.1306, found 254.1308. FTIR (thin film, cm^{-1}): 3054 (m), 3005 (m), 2958 (m), 1636 (m), 1035 (s), 739 (s).

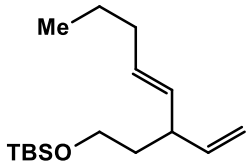


1.21

Methyl 4-(1-phenylallyl)benzoate

Compound was isolated as a clear liquid (114.2 mg, 90% yield, 17:1 mixture of isomers) after purification by silica gel column chromatography (0 → 20% benzene in hexanes).Major isomer; ^{1}H NMR (300 MHz, C_6D_6) δ 8.18 (d, *J* = 8.3 Hz, 2H), 7.35 –

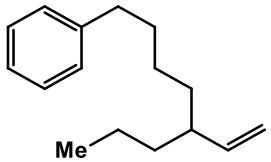
6.95 (m, 7H), 6.18 (ddd, *J* = 17.2, 10.2, 7.2 Hz, 1H), 5.17 (d, *J* = 10.2 Hz, 1H), 4.97 (d, *J* = 17.2 Hz, 1H), 4.61 (d, *J* = 7.2 Hz, 1H), 3.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.06, 148.71, 142.54, 139.89, 129.82, 128.72, 128.62, 128.39, 126.71, 117.06, 54.98, 52.07. HRMS calculated for $[M+H]^+$ 253.1229, found 253.1232. FTIR (thin film, cm^{-1}):3061 (w), 3028 (w), 2952 (m), 1723 (s), 1610 (m), 1436 (m), 1281 (s), 1112.8 (s), 701.7 (m).



1.22

(E)-tert-butyldimethyl((4-vinylnon-5-en-1-yl)oxy)silane

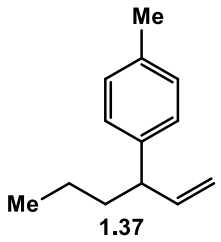
Compound was isolated as a colorless oil (116.2 mg, 86% yield) after purification by silica gel column chromatography (0 → 10% benzene/hexanes). ^{1}H NMR (300 MHz, C_6D_6) δ 5.85 (ddd, *J* = 17.3, 10.2, 7.2 Hz, 1H), 5.68 – 5.33 (m, 2H), 5.27 – 4.93 (m, 2H), 3.72 (t, *J* = 6.4 Hz, 2H), 3.22 – 2.91 (m, 1H), 2.10 – 1.97 (m, 2H), 1.90 – 1.62 (m, 2H), 1.51 – 1.35 (m, 2H), 1.09 (s, 9H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.17 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.2, 133.1, 130.9, 114.0, 61.1, 43.5, 38.2, 35.2, 26.3, 23.1, 18.6, 13.9, -5.0. HRMS calculated for $[M+H]^+$ 269.2295, found 269.2298. FTIR (neat, cm-1): 3080 (w), 2859 (m), 1637 (m), 1102 (m), 969 (m).



1.23

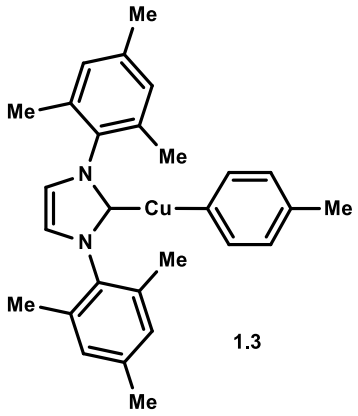
(5-vinyloctyl)benzene

Compound was isolated as a colorless oil (89.0 mg, 82% yield, 32:1 mixture of isomers) after purification by silica gel chromatography (0 → 20% benzene/hexanes). Major isomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.01 (m, 5H), 5.57 (ddd, *J* = 16.9, 10.3, 8.9 Hz, 1H), 5.16 – 4.95 (m, 2H), 2.61 (t, *J* = 7.7 Hz, 2H), 2.13 – 1.91 (m, 1H), 1.80 – 1.55 (m, 2H), 1.52 – 1.14 (m, 8H), 0.99 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 142.9, 128.4, 128.2, 125.6, 113.9, 43.8, 37.3, 36.1, 34.9, 31.7, 27.0, 20.3, 14.2. HRMS calculated for $[M]^+$ 216.1879, found 216.1876. FTIR (neat, cm-1): 3064 (w), 2857 (m), 1639 (m), 956 (m), 745, (m), 698 (s).



1-(hex-1-en-3-yl)-4-methylbenzene

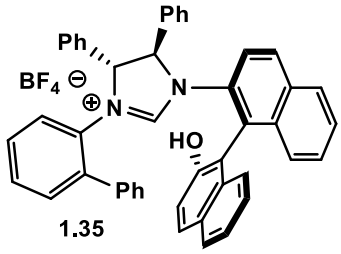
Compound was isolated as a colorless oil (73.8 mg, 85% yield, 60:1 mixture of isomers) after purification by silica gel column using hexanes as an eluent. ^{1}H NMR (300 MHz, C_6D_6) δ 7.11 – 6.92 (m, 4H), 5.93 (ddd, *J* = 17.6, 10.3, 7.4 Hz, 1H), 5.15 – 4.84 (m, 2H), 3.17 (q, *J* = 7.4 Hz, 1H), 2.15 (s, 3H), 1.63 (m, 2H), 1.36 – 1.09 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 141.8, 135.6, 129.2, 127.6, 113.7, 49.3, 37.8, 21.1, 20.8, 14.1. HRMS calculated for $[M]^+$ 174.1409, found 174.1410. FTIR (neat, cm^{-1}): 3079 (w), 2927 (m), 1637 (m), 1513 (m), 1111 (w), 814 (m).



1.3

(4-methylbenzene)[1,3-dihydro-1,3-bis(2,4,6-trimethylphenyl)-2H-imidazol-2-ylidene]-Copper

The product was obtained as a white solid (575.5 mg, 61% yield). ^{1}H NMR (500 MHz, 1,4-dioxane-d^{8}) δ 7.22 (s, 2H), 7.07 (s, 4H), 6.80 (d, J = 7.4 Hz, 2H), 6.54 (d, J = 7.3 Hz, 2H), 2.35 (s, 6H), 2.17 (s, 12H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, THF-d^{8}) δ 184.5, 162.5, 140.8, 139.7, 137.2, 135.8, 131.9, 130.1, 126.8, 123.2, 21.8, 21.4, 18.4.

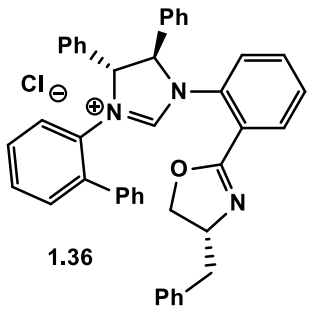


1.35

1-(2-biphenyl)-3-(2'-hydroxy-1R-binapth-2-yl)-4S,5S-diphenyl-4,5-dehydrido-imidazolinium tetrafluoroborate

Compound was isolated as a tan powder (1251.0 mg, 81% yield) after purification by silica gel column chromatography (0 → 5% MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.13 (d, J = 8.8 Hz, 1H), 8.05 (d, J = 8.9 Hz, 1H), 7.93 (d, J = 8.1

Hz, 1H), 7.78 (dd, *J* = 18.5, 8.5 Hz, 2H), 7.61 (t, *J* = 7.2 Hz, 2H), 7.54 – 7.37 (m, 6H), 7.26 (s, 6H), 7.10 – 6.80 (m, 7H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 7.0 Hz, 2H), 5.96 (d, *J* = 7.3 Hz, 2H), 4.44 (d, *J* = 3.6 Hz, 2H).



1.36

1-(2-biphenyl)-3-(2-(3R-benzyloxazole)phenyl)-4S,5S-diphenyl-4,5-dehydrido-imidazolinium tetrafluoroborate

The product was purified by column chromatography (0 - 5% EtOH in $CHCl_3$) followed by tritteration from CH_2Cl_2/Et_2O, resulting in an orange powder (94 mg, 16% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (d, *J* = 6.5 Hz, 1H), 9.14 (s, 1H), 7.69 – 7.59 (m, 1H), 7.50 – 7.00 (m, *J* = 16.4 Hz, 22H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.53 (t, *J* = 7.5 Hz, 1H), 6.40 – 6.21 (m, 2H), 4.95 (d, *J* = 4.3 Hz, 1H), 4.67 (d, *J* = 9.7 Hz, 1H), 4.49 (dd, *J* = 8.7, 5.8 Hz, 1H), 4.24 (dd, *J* = 8.8, 5.2 Hz, 1H), 3.99 (m, 1H), 3.07 (dd, *J* = 13.8, 5.5 Hz, 1H), 2.67 (dd, *J* = 13.8, 8.6 Hz, 1H).

Section 5: References

1. Rappoport, Z.; Marek, I; *The Chemistry of Organocopper Compounds.* **2009,** Wiley, Hoboken, NJ. Krause, N. *Modern organocopper chemistry* **2002,** Wiley, Hoboken, NJ.

2. Magid, R. M. *Tetrahedron* **1980,** *36*, 1901.

3. Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996,** *96,* 395.

4. Streitwieser, A.; Jayasree, E. G.; Hasanayn, F.; Leung, S. S. *J. Org. Chem.* **2008**, *73*, 9426.

5. Ronal, P.; Tokes, J. T.; Crabee, P.J. *Chem. Soc. D.* **1969,** *8,* 43.

6. Van Klaveren, M.; Persson, E. S.; Villar, A. D.; Grove, D. M.; Backvall, J. E.; Van Koten, G. *Tetrahedron Lett.* **1995,** *36,* 3059.

7. Recent reviews of the copper-catalyzed allylic substitution reactions: (a) Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008,** *108,* 2796. (b) Falciola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008,** 3765.

8. Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008,** *130,* 446.

9. (a) Piarulli, U.; Daubos, P.; Claverie, C.; Roux, M.; Gennari, C. *Angew. Chem., Int. Ed.* **2003,** *42,* 234. (b) Demel, P.; Keller, M.; Breit, B. *Chem. Eur. J.* **2006,** *12,* 6669. Also see references 12, 13, and 18

10. Polet, D.; Rathgeb, X.; Falciola, C. A.; Langlois, J. B.; El Hajjaji,S.; Alexakis, A. *Chem. Eur. J.* **2009,** *15,* 1205.

11. Ohmiya, H.; Makida, Y.; Li, D.; Tanabe, M.; Sawamura, M. *J. Am. Chem. Soc.* **2009,** *131,* 17276.

12. Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007,** *46,* 4554.

13. Selim, K. B.; Matsumoto, Y.; Yamada, K.; Tomioka, K. *Angew. Chem. Int. Ed.* **2009,** *48,* 8733.

14. For selected examples that were published after 2011: (a) Gao, F.; Carr, J. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2012,** *51,* 6613. (b) Li, X.; Xing, J.; Zhao, J.; Huynh, P.; Zhang, W.; jiang, P.; Zhang, Y. J. *Org.Lett.* **2012,** 14, 390. Also see references 24 and 32.

15. (a) Backvall, J. E.; Sellen, M.; Grant, B. *J. Am. Chem. Soc.* **1990,** *112,* 6615–6621. (b) Backvall, J. E.; Persson, E. S.; Bombrun, A. *J. Org. Chem.* **1994,** *59,* 4126.

16. Yoshikai, N.; Zhang, S.; Nakamura, E. *J. Am. Chem. Soc.* **2008,** *130,* 12862.

17. Hall, D. G. *Boronic Acids* **2005,** Wiley-VCH, Weinheim, Germany.

18. Ohishi, T.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2008,** *47,* 5792.

19. (a) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010,** *132*, 2895. (b) Ohmiya, H.; Yokokawa, N.; Sawamura, M.*Org. Lett.* **2010,** *12*, 2438.

20. Whittaker, A. M.; Rucker, R. P.; Lalic, G. *Org. Lett.*, **2010**, *12*, 3216.

21. Tominaga, S.; Oi, Y.; Kato, T.; An, D. K.; Okamoto, S. *Tetrahedron Lett.* **2004,** *45*, 5585.

22. Bertz, S. H.; Cope, S.; Dorton, D.; Murphy, M.; Ogle, C. A. *Angew. Chem. Int. Ed.* **2007,** *46*, 7082.

23. Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004,** *23*, 3369.

24. Gao, F.; Lee, Y.; Mandai, K.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2010,** *49*, 8370.

25. Gade, L. H.; Laponnaz, S. B. *Coord. Chem. Rev.* **2007**, *251*, 718.

26. Drege, T. Glorius, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 2.

27. Park, J. K.; Lackey, H. H.; Rexford, M. D.; Kovnir, K.; Shatruk, M.; McQuade, T. *Org. Lett.*, **2010**, *12*, 5008.

28. Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; McQuade, T. *J. Am. Chem. Soc.*, **2011**, *133*, 2410.

29. Wurtz, S.; Lohre, C.; Frohlich, R.; Bergander, K.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 8344.

30. A dinuclear copper complex has been proposed. (a) Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130. (b) Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 1097.

31. Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem. Int. Ed.* **2011**, *37*, 8656.

32. For selected examples that extended this work see: (a) Shido, Y.; Tanabe, M.; Ohima, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012,** *134*, 18573. (b) Tanabe, M.; Ohima, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012,** *134*, 11896.

33. Maj, A. M. Delaude, L.; Demonceau, A.; Noels, A. F. *J. Organomet. Chem.* **2007,** *692*, 3048.

34. See reference 25

35. See reference 27

36. See reference 26

37. Van Veldhuizen, J. J.; Campbell, J. E.; Guidici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877.

38. See reference 37

39. See reference 27

Chapter 2 – Synthesis of Tertiary Alkyl Amines by anti-Markovnikov Hydroamination of Terminal Alkenes

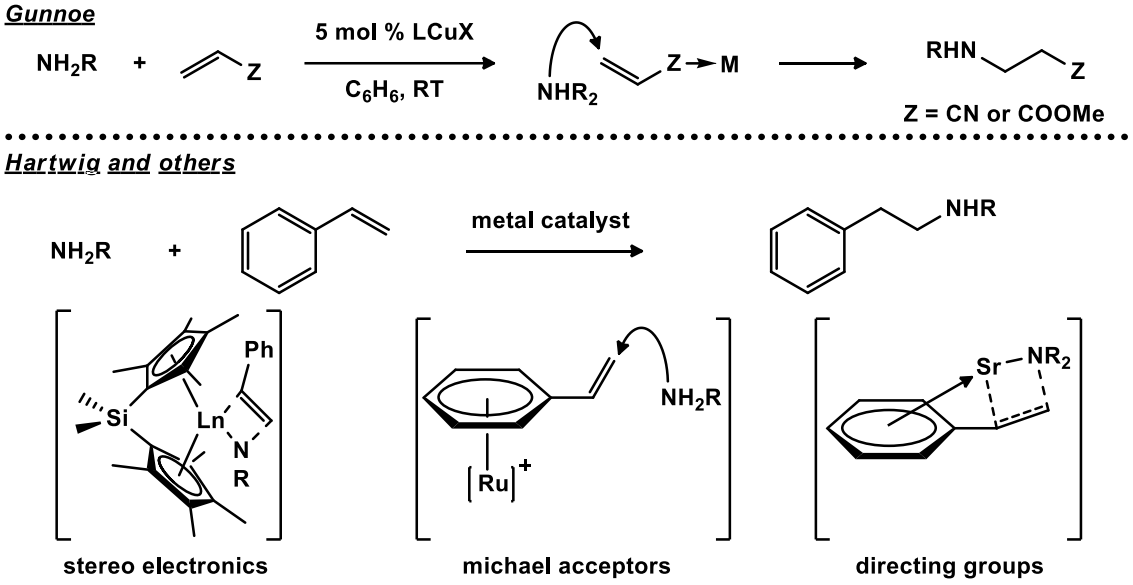
Section 1: Introduction

Amines are ubiquitous among biologically active small molecules, and their synthesis is one of the most investigated and important synthetic tasks.[1] Still, the most commonly employed methods for the introduction of an amino group in the pharmaceutical industry involve transformations of carbonyl compounds or nucleophilic substitution reactions,[2] each of which is met with limitations. Reductive amination is incompatible with highly hindered substrates, and functional groups sensitive to reducing conditions, whereas nucleophilic substitution suffers from over alkylation, necessitating elaborate protection schemes. Because of these limitations, considerable effort has been devoted to broadening the scope of alkyl amine precursors through the development of methods for amination of other common functional groups. In this context, hydroamination of alkenes has received attention as a desirable method to access alkyl amines from readily available alkenes.[3]

The usual approach to the hydroamination of alkenes has been through transition metal-catalysis.[4,5] The most success in this area has been shown with intramolecular hydroamination of amino alkenes, or Markovnikov-selective intermolecular hydroamination[6] including enantioselective methods.[7] Despite the great progress made in developing hydroamination reactions, the control of regioselectivity is still a significant

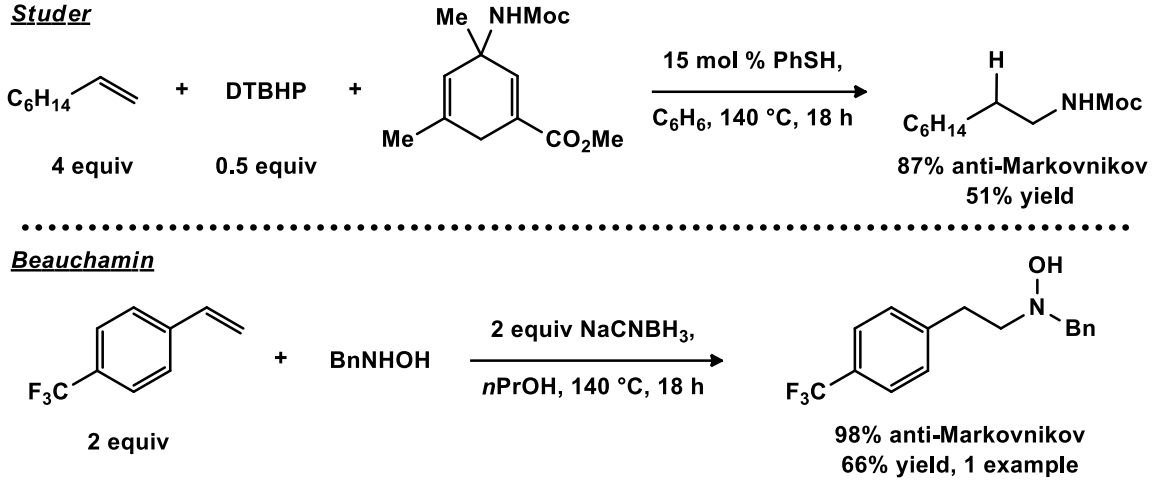
obstacle. Particularly challenging has been the development of a method for anti-Markovnikov hydroamination. All available metal-catalyzed methods giving anti-Markovnikov selectivity rely upon biased substrates, such as activated alkenes[8] and styrenes.[9]

Scheme 2.1. Previous work: Metal-catalyzed anti-Markovnikov hydroamination



Approaches to anti-Markovnikov hydroamination that do not use transition metals have also been explored. Studer has reported a free-radical hydroamination that provides protected primary amines, in moderate yields (~50%),[10] and Beauchemin has pioneered the reverse-Cope elimination as a method for hydroamination of alkenes.[11] However, with both methods moderate to low regioselectivity is usually observed. Additionally, the generality of these transformations is inherently limited. The harsh conditions of radical based methods limit functional group compatibility, while Reverse-Cope reactions require specific motifs to proceed.

Scheme 2.2. Previous work: Metal free anti-Markovnikov hydroamination

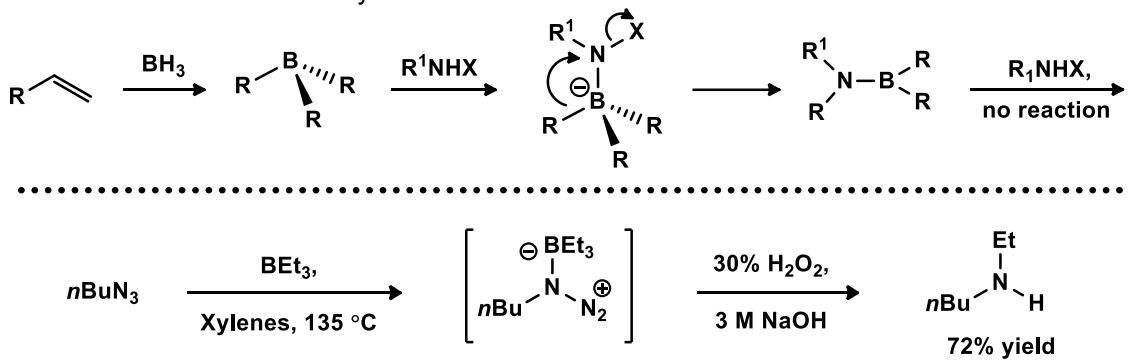


First developed in the 1960s, hydroboration presents an attractive alternative strategy for the anti-Markovnikov hydrofunctionalization of alkenes.[12] The terminal organoboron reagents obtained by this procedure can efficiently be converted to primary alcohols using sodium hydroxide and hydrogen peroxide. The importance of this method has been demonstrated by multiple successful applications of the hydroboration-oxidation sequence in the synthesis of natural products.[13]

However, despite the success of anti-Markovnikov hydration, numerous attempts to extend this sequence to the synthesis of amines by Brown[14] and Kabalka[15] have all provided the amination products in less than 50% yield with respect to the alkene. This limitation is a result of the inefficient transfer of alkyl groups to the aminoboranes. Additionally, the use of the highly regioselective hydroborating reagent 9-BBN is excluded given that secondary alkyl migration occurs preferentially over the corresponding primary alkyl migration.[16] Furthermore, the methods developed mainly focused on the synthesis of primary secondary amines, while the synthesis of secondary

amines requires harsh conditions and multiple steps. To achieve the synthesis of secondary amines using hydroboration, conversion of boronic esters to trifluoroborates, followed by a reaction with excess Lewis acid and alkyl azide is required.[17] Finally, none of the existing procedures for anti-Markovnikov hydroamination allow the preparation of tertiary alkyl amines from alkenes.

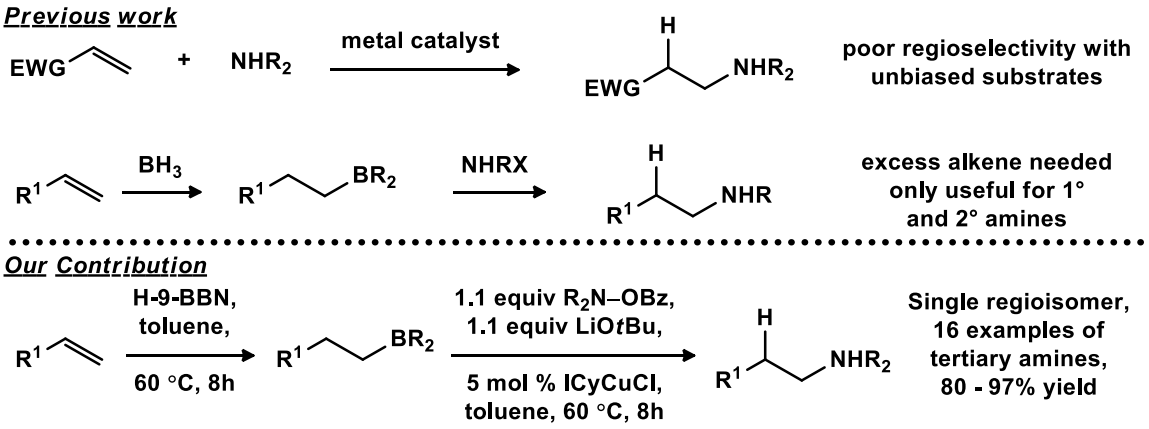
Scheme 2.3. Previous work: Hydroboration-amination



Based on our previously developed transmetalation reaction of carbon nucleophiles from boron to copper,[18] we surmised that the highly regioselective hydroboration reaction could be utilized in combination with copper-catalysis to achieve a formal anti-Markovnikov hydroamination of alkenes. In this chapter, I present a one-pot hydroboration copper-catalyzed electrophilic amination sequence for the synthesis of tertiary alkyl amines as well as protected primary and secondary amines. All reactions proceed with complete anti-Markovnikov selectivity and demonstrate high functional group compatibility.[19] The synthesis and crystal structure of IMesCu-Et along with stoichiometric reactions using this intermediate provide evidence for a catalytic cycle involving an unprecedented stable copper alkyl intermediate. The proposed reaction mechanism is discussed in the context of other anti-Markovnikov hydrofunctionalization

reactions.

Scheme 2.4. Summary: Anti-Markovnikov hydroamination of alkenes



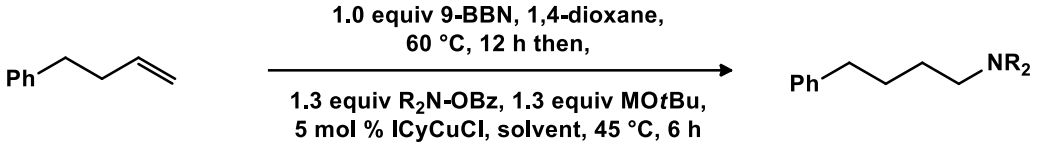
Section 2: Results and Discussion

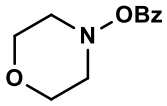
2.2.a. Optimization

The discovery of the one-pot hydroboration, allylic alkylation reaction described in chapter 1 indicated to us that alkenes are suitable substrates for copper-catalyzed nucleophilic substitution reactions. By exchanging electrophilic amines[20] for the previously used allylic chlorides an overall hydroamination reaction was proposed to be feasible. To test this proposal, we decided to explore the hydroamination of 4-phenyl-1-butene using 9-BBN as a hydroboration reagent and *O*-benzoylhydroxylamines as the electrophilic source of nitrogen. Based on our experience with copper-catalyzed transformations of organoboron compounds, we chose ICyCuCl as a catalyst and sodium *tert*-butoxide as a base additive. The hydroboration of the alkene was performed in 1,4-dioxane at 60 °C, after which all components required for electrophilic amination were simply added to the reaction flask. Unfortunately, under these reaction conditions, the

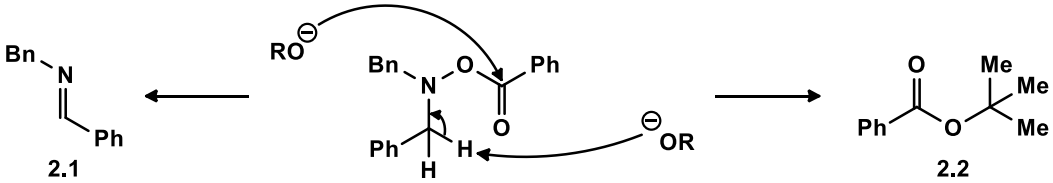
hydroamination product was obtained in a low yield of 16% (Table 2.1, entry 1). Analysis of the reaction mixture showed that the hydroxyl amine was entirely converted and the major product of the reaction was imine **2.1**, along with a small amount of transesterification product **2.2** (reactions below table 2.1). A control experiment confirmed that a fast formation of the imine occurred in a reaction between the electrophile and sodium *tert*-butoxide. After only 30 min, 100% conversion of the hydroxyl amine was observed (not shown). Thus we assumed that by reducing the basicity of the alkoxide, electrophile decomposition should be minimized. As expected, we found that the electrophile decomposition is significantly slower in the presence of lithium *tert*-butoxide in a non-coordinating solvent such as benzene (14% conversion at 30 min). Consistent with this finding, the yield of the hydroamination product obtained in a catalytic reaction significantly increased to 97% when lithium *tert*-butoxide was used together with pentane as a solvent. The conditions in table 2.1, entry 4, are subsequently referred to as conditions A, and were used in the context of the synthesis of protected primary and secondary amines.

Table 2.1. Reaction optimization



entry	R_2N-OBz	M	co-solvent	yield[a]
1	Bn_2N-OBz	Na	1,4-dioxane	16
2		K	1,4-dioxane	11
3		Li	1,4-dioxane	56
4		Li	pentane	97
5		Li	pentane	5
6[b]		Li	pentane	52
7[c]		Li	toluene	86
8[c,d]		Li	toluene	99

a. Yield determined by GC. b. R_2N-OBz added over 6 h. Reaction conducted at 60 °C c. R_2N-OBz added over 3 h at 60 °C. Toluene as solvent in hydroboration reaction. d. 1.1 equiv R_2N-OBz and 1.1 equiv LiO*t*Bu, 0.05 M concentration.



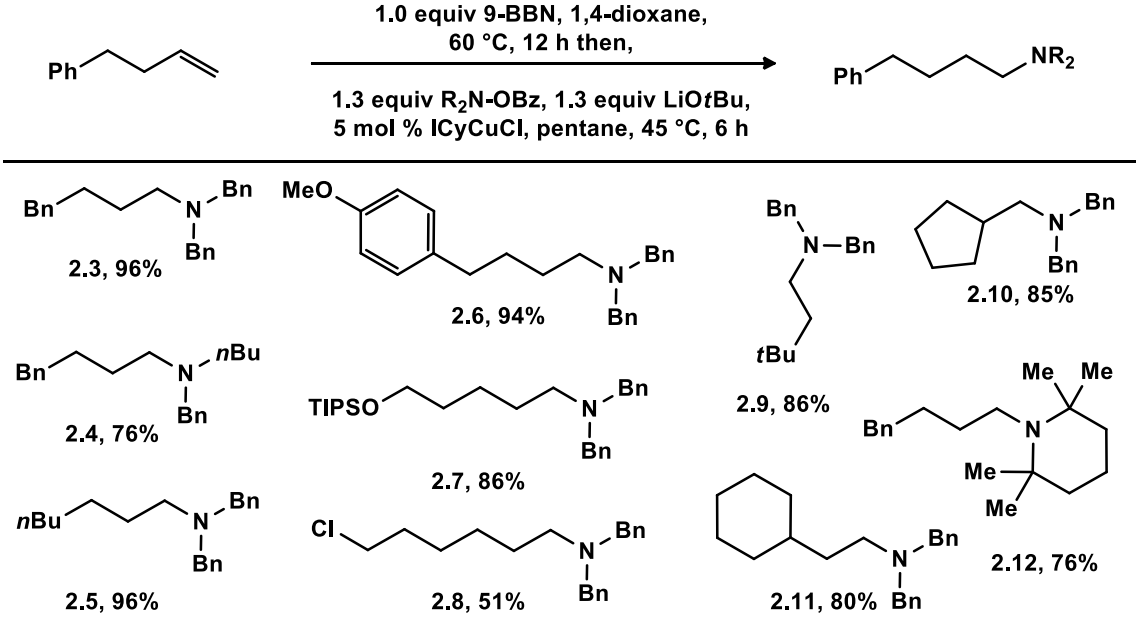
Although the preliminary investigation into the substrate scope revealed that conditions A were in fact useful for the synthesis of protected primary and secondary amines (see section 2.2.b), we discovered that the synthesis of tertiary-alkyl substituted amines was not possible under these conditions. Certain electrophiles, in particular cyclic unhindered electrophiles, quickly decomposed under these reaction conditions (table 2.1, entry 5). For example, the reaction with *O*-benzoyl hydroxy morpholine provided no hydroamination product and instead resulted in almost quantitative formation of *tert*-butylbenzoate as described in the reaction below table 2.1. In order to prevent decomposition of the electrophile during the course of the reaction, we added the electrophile over a 3 h period, and observed the formation of the hydroamination product

in 52% yield (Table 2.1, entry 6). Using toluene led to the further increase in the yield of the desired product. Finally, 99% yield of the hydroamination product was obtained when 1.1 equivalents of electrophile were added to a relatively dilute reaction mixture over 3 hours, at 60 °C. Entry 8 in table 2.1, will be referred to conditions B herein, and is discussed in the context of the synthesis of tertiary amines through hydroamination (see section 2.2.b).

2.2.b. Scope

The set of parameters designated as conditions A in section 2.2.a did prove to be valuable for the synthesis of a variety of benzyl protected primary and secondary amines (table 2.2). The highly selective formal anti-Markovnikov hydroamination reaction could be accomplished in the presence of aryl ethers, and silyl ethers, although alkyl chlorides gave slightly lower yields. Additionally, the reaction proved to be compatible to sterically hindered alkene or hydroxylamine substrates. *Tert*-butyl or cyclohexyl substituted alkenes resulted in yields above 80% (**2.9** and **2.11**), while a 1,1-disubstituted alkene was also successfully used in our hydroamination reaction (**2.10**). Perhaps most impressive was the use of a highly hindered *O*-benzoyl hydroxyl amine derived from tetramethyl piperidine giving alkylated amine **2.12** in 76% yield. However, this substrate was the only successful example of tertiary-alkyl substituted amine synthesis using conditions A.

Table 2.2. Scope: Protected primary and secondary amine synthesis[a]

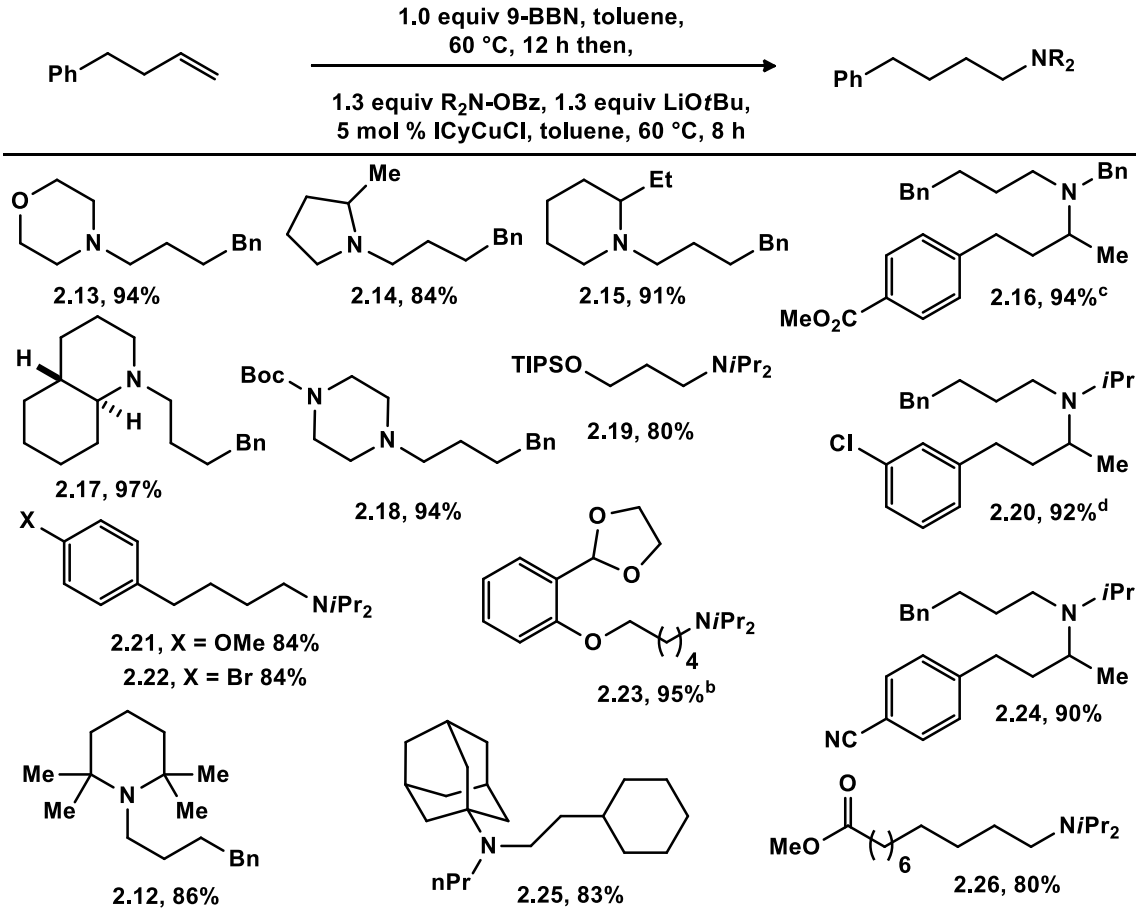


a. Reactions performed on a 0.5 mmol scale in 5 ml of pentane. 1.0 equiv each of R_2N-OBz, and LiO*t*Bu added, the remainder (0.3 equiv) added after 4 h. Yields of isolated product.

The optimized reaction conditions for the synthesis of tertiary alkyl amines (table 2.1, entry 8, conditions B) proved to be even more general than conditions A. The procedure could be used to prepare medicinally relevant heterocycles such as alkylated morpholine, piperidine, pyrrolidine, piperazine and decahydroquinoline derivatives (table 2.3). Equally impressive results were obtained in preparation of acyclic amines, including sterically hindered *N*,*N*-diisopropyl-*N*-alkylamines. Importantly, a myriad of functionalities were tolerated on either the nucleophilic or electrophilic component of the reaction. Esters, Boc-protected amines, nitriles, and aryl chlorides were all tolerated as functional groups on the hydroxyl amines, while silyl and alkyl ethers, acetals, aryl bromides, aryl chlorides, and esters were tolerated as functional groups on the nucleophilic component of the reaction. Even the highly hindered *N*-alkyl-2,2,6,6-tetramethylpiperidine could be formed in 86% yield. The synthesis of such hindered

trialkylamines is not only impossible to achieve using the existing hydroamination methods, but is also difficult to accomplish using the standard reductive amination or alkylation reactions. It is important to note that in all examples only the product of anti-Markovnikov hydroamination is formed with no observable Markovnikov product by GC analysis. Moreover, the lack of side products observed under the optimized conditions allowed pure hydroamination products to be isolated by a simple acid-base extraction in most cases.

Table 2.3. Scope: Tertiary amine synthesis[a]

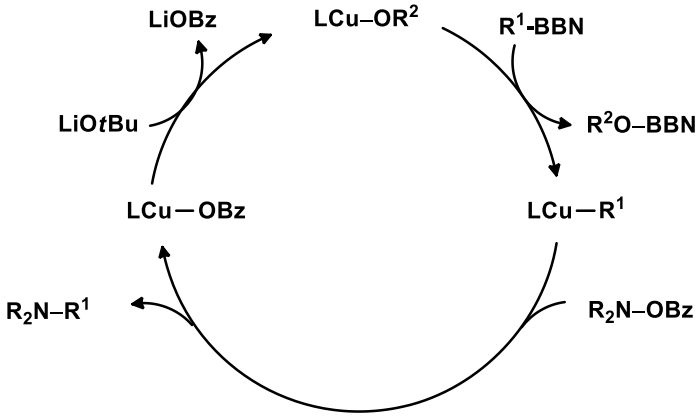


a. Reactions performed on a 0.5 mmol scale in 5 ml of pentane. R_2N-OBz added over 4h. Yields of isolated product. b. GC yield. c. 2.5 mol% of catalyst was used. d. GC yield, isolated is 72%.

2.2.c. Mechanism

We propose that the amination of the alkyl boron compounds proceeds according to the mechanism shown in Scheme 2.5. The reaction involves transmetalation of an alkyl group from boron to copper,[21] followed by electrophilic amination of the alkyl copper intermediate.[22] Finally, copper *tert*-butoxide is regenerated in a reaction with lithium alkoxide.[23] The most intriguing aspect of the proposed mechanism is the presence of a neutral copper(I) alkyl intermediate in a reaction performed at a relatively high temperature. Such molecules have previously been suggested to decompose quickly above -35 °C,[24] and to the best of our knowledge, there are no examples of fully characterized neutral copper(I) alkyl complexes containing beta hydrogen substituents.[25] While similar intermediates have previously been proposed in copper-catalyzed reactions of alkyl boranes, there is little experimental evidence for their involvement.[26]

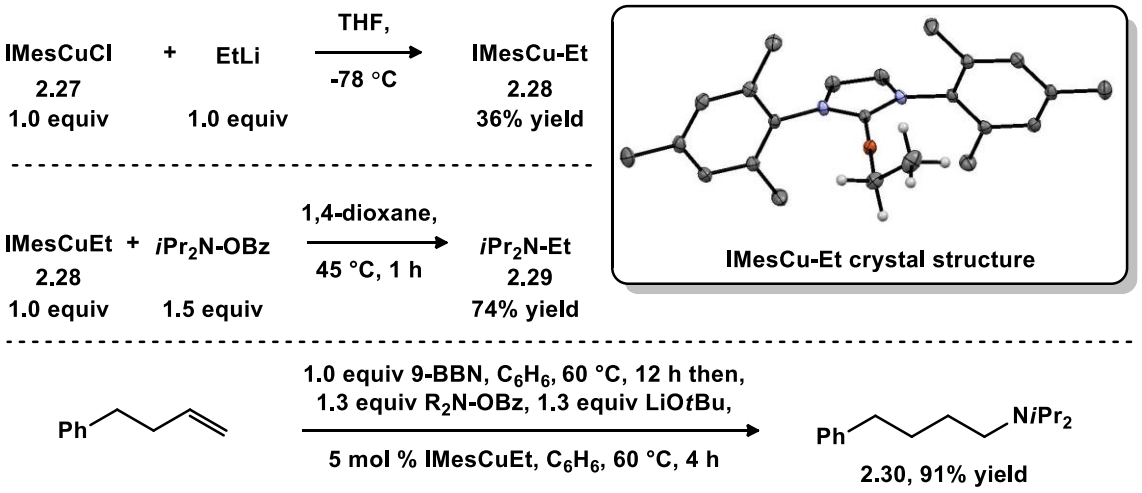
Scheme 2.5. Proposed mechanism



In an effort to explore the role of copper(I) alkyl complexes in the amination reaction, we prepared IMesCu-Et by addition of ethyl lithium to IMesCuCl at low temperature (scheme 2.6). To our surprise, we were able not only to isolate the IMesCu-

Et complex, albeit in low yield (36%), but also to characterize the complex by X-ray diffraction. Using this isolated complex as a representative sample, we set out to investigate the general properties of alkyl copper intermediates. Interestingly we discovered that IMesCu-Et is stable in benzene for at least 4 h at 60 °C, if kept in the dark. However, it decomposes quite readily at room temperature if exposed to light (~50% conversion after 4 h).

Scheme 2.6. Examining the role of alkyl copper



We also showed that IMesCu-Et reacts at 45 °C with *N*,*N*-diisopropyl-*O*-benzoyl hydroxylamine in less than 10 min to produce the expected amination product in 74% yield. Furthermore, when IMesCu-Et was used as a catalyst in a hydroamination reaction of *N*,*N*-diisopropyl-*O*-benzoyl hydroxylamine, under otherwise standard conditions (see table 2.1, entry 8), the desired product was obtained in 91% yield. The results of these experiments provide support for the proposed participation of the neutral copper(I) alkyl complexes in the catalytic amination of alkyl boron compounds. Moreover, these results support the proposed transmetalation of alkyl groups from boron to copper. This finding

suggests that the developed methodology could potentially be applied to other alkene hydrofunctionalization reactions. By simply substituting the electrophilic amine for other electrophiles such as cyanogen bromide or Togni's reagent, novel anti-Markovnikov reactions such as hydrocyanation or hydrotrifluoromethylation can be envisioned.

Section 3: Conclusions

In conclusion, a one-pot hydroamination procedure was presented in this chapter. The method developed in our laboratory allows the direct formation of protected primary, protected secondary, and tertiary alkyl amines from terminal alkenes. The method is compatible with a wide variety of functional groups and can be used to prepare a range of both cyclic and acyclic amines. Furthermore, the procedure can be used to prepare highly sterically hindered amines that can be challenging to prepare even by the well-established methods such as reductive amination and substitution reactions. Finally, we prepared and characterized the first stable copper(I) alkyl complex capable of β-hydride elimination. We also provided experimental evidence supporting the proposed role of the copper(I) alkyl complexes as intermediates in the hydroamination reaction. Considering the overall simplicity of converting alkenes to nucleophilic alkyl groups using this methodology, this sequence may turn out to be of general utility for other hydrofunctionalization reactions.[27]

Section 4: Experimental

2.4.a. General

All reactions were performed under a nitrogen atmosphere with flame-dried glassware, using standard Schlenk techniques, or in a glove box (Nexus II from Vacuum Atmospheres). Column chromatography was performed using a Biotage Iso-1SV flash purification system with silica gel from Agela Technologies Inc. (60Å, 40-60 µm, 230-400 mesh). Ion Exchange Chromatography was performed using analytical grade cation exchange resin from sulfonic acid functionalized styrene (Bio-Rad Laboratories, 200-400 mesh, 5.2 meq/g). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual proteated solvent peak ($CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), or CD_2Cl_2 (5.32 ppm)). ^{13}C chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$: δ 77.2 ppm, C_6D_6: δ 128.1 ppm, CD_2Cl_2: δ 54.0 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constants in Hertz (Hz). Mass spectra were collected on a JEOL HX-110 mass spectrometer. GC analysis was performed on a Shimadzu GC-2010 instrument with a flame ionization detector and a SHRXI-5MS column (15 m, 0.25 mm inner diameter, 0.25 µm film thickness). The

following temperature program was used: 2 min @ 60 °C, 13 °C/min to 160 °C, 30 °C/min to 250 °C, 5.5 min @ 250 °C.

Toluene and benzene were degassed and dried by passing through columns of neutral alumina. 1,4-dioxane was distilled from purple Na/benzophenone ketyl and stored over 4Å molecular sieves. All other solvents were used as received. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. Deuterated solvents were degassed and dried over 4Å molecular sieves before use. Commercial reagents were purchased from Sigma-Aldrich Co., VWR International, LLC., TCI Chemicals USA, or STREM Chemicals, Inc., and were used as received, except for 9-BBN (9-borabicyclo[3.3.1]nonane) dimer, which was recrystallized from dimethoxyethane (glyme).

2.4.b. Experimental Details

Stoichiometeric reactions of hydroxylamines with alkoxides

In a glove box, a 1 dram vial was charged with a stir bar. To the vial was added either LiO*t*Bu or NaO*t*Bu (1.00 equiv, 0.110 mmol), 1,3,5-trimethoxybenzene as an internal standard, and 1,4-dioxane-d^8 (0.35 mL). To the resulting mixture was added *O*-benzoyl-*N*,*N*-dibenzyl hydroxylamine (1.00 equiv, 0.110 mmol) and 1,4-dioxane-d^8 (0.15 mL). The resulting mixture was capped and heated to 45℃ with stirring, and yield was determined by GC analysis using TMB as an internal standard.

Reaction Optimization

Hydroboration of terminal alkenes was performed in a glove box. A 1 dram vial was charged with a stir bar, and to the vial was added 9-BBN dimer (0.50 equiv), alkene (1.00 equiv), and solvent. The vial was capped and heated at 60℃ with stirring for 12 h.

Using *O*-benzoyl-*N*,*N*-dibenzyl hydroxylamine: In a glove box, 4-phenylbut-1-ene (1.00 equiv, 0.017 mL, 0.110 mmol) was subjected to the standard hydroboration conditions described above using 9-BBN dimer (0.50 equiv, 13.4 mg, 0.055 mmol), *n*-dodecane as internal standard, and 1,4-dioxane (0.20 mL, [alkene] = 0.55 M). After 12 h at 60℃, the reaction vial was allowed to reach room temperature, and MO*t*Bu (M = Na, K, Li; 1.00 equiv, 0.110 mmol), copper catalyst (0.05 equiv, 0.006 mmol), *O*-benzoyl-*N*,*N*-dibenzyl hydroxylamine (1.00 equiv, 36.2 mg, 0.110 mmol), 1,4-dioxane (0.075 ml) and the reaction co-solvent (0.275 ml) were added. The vial was capped and stirred at 45 °C for 6 h. Yield of the desired product was determined by gas chromatography using *n*-dodecane as an internal standard.

Using 4-benzoyloxymorpholine: For all optimization reactions, 4-phenylbut-1-ene (1.00 equiv, 0.060 mL, 0.400 mmol) was subjected to the standard hydroboration conditions described above using 9-BBN dimer (0.50 equiv, 48.8 mg, 0.400 mmol) and solvent (1.00 mL, 0.40 M). After 12 h at 60℃, the dram vial was allowed to reach room temperature, and the contents were transferred to a 15 mL Schlenk tube. To the resulting solution was added lithium *tert*-butoxide (1.3 equiv, 41.6 mg, 0.520 mmol), ICyCuCl (0.05 equiv, 6.6 mg, 0.020 mmol), and solvent. Separately, a stock solution of the electrophile was prepared (0.400 mL of reaction co-solvent) and taken up in a gas-tight syringe (500 µL size). The Schenk tube assembly was put on the manifold using

standard air-free techniques. The electrophile was added over the period indicated to the stirred reaction mixture at 60 °C. After addition of the electrophile, the reaction was stopped and allowed to cool to room temperature. The crude product was isolated by diluting the reaction mixture with ether (5 mL) and then washing with aqueous saturated $NaHCO_3$ solution. The aqueous layer was then extracted with diethyl ether (2 x 10 mL), and the combined organic fractions were dried over sodium sulfate. After filtering, 1,3-dinitrobenzene was added as an internal standard to the ether solution, and the yield of the product was determined by GC analysis of an aliquot of this solution.

General Hydroamination procedure

In a glove box, a one-dram vial was charged with a stir bar. To the vial was added 9-BBN dimer (0.50 equiv, 48.8 mg 0.200 mmol), toluene (1.00 mL, 0.40 M), and the alkene (1.00 equiv, 0.400 mmol). After 12 h at 60 °C, the reaction mixture was cooled to room temperature and transferred to a 15 mL Schlenk tube. To the resulting solution was added lithium *tert*-butoxide (1.10 equiv, 35.2 mg, 0.440 mmol), ICyCuCl (0.05 equiv, 6.6 mg, 0.020 mmol), and toluene (6.60 mL, 7.60 mL total volume, 0.05 M). Separately, a stock solution of the electrophile was prepared (0.400 mL of reaction co-solvent) and taken up in a gas-tight syringe (500 µL size). The Schenk tube assembly was put on the manifold using standard air-free techniques. The electrophile was added over 4 h to the stirred reaction mixture at 60 °C. After addition of the electrophile, the reaction was allowed to stir at 60 °C and the consumption of electrophile was monitored by tlc. Upon complete consumption of the electrophile, the reaction was cooled to room temperature. The crude product was isolated by diluting the reaction mixture with ether

(5 mL) and then washing with aqueous saturated $NaHCO_3$ solution. The aqueous layer was then extracted with diethyl ether (2 x 10 mL), and the combined organic fractions were dried over sodium sulfate. After filtration and removal of the solvent under reduced pressure, the crude product was obtained as an oil, which was further purified according to one of the following three procedures:

Purification Procedures

A: The crude product was transferred to a 60 mL separatory funnel using 2.5 mL portions of diethyl ether and hexane (5 mL total volume). The organic layer was extracted three times with 5 mL of a 3 M aqueous HCl solution. The organic layer was discarded. The *p*H of the aqueous layer was adjusted by dropwise addition of an aqueous 3 M NaOH solution until *p*H 10 was achieved. The resulting solution was then extracted three times with 10 mL portions of dichloromethane. The organic extracts were washed with 5 mL of saturated brine and then dried over sodium sulfate. Upon filtration and removal of solvent, the purified tertiary amine product was obtained as an oil.

B: Acid-sensitive functional groups, such as the *tert*-butyl carbamate (BOC)-protected amine used in product **8**, and the tris(isopropyl)siloxy (TIPS)-protected alcohol used in product **9**, require the substitution of a weaker acid in place of aqueous HCl. This is readily accomplished by use of an aqueous 3 M sodium acetate and acetic acid solution buffered at *p*H 4. The purification procedure is identical to A except for this substitution.

C: Ion-Exchange Chromatography was used to purify a few products. The crude product was loaded on the cation exchange resin (200 mg resin/mmol product) using

MeOH. The resin was subsequently washed with 4 CV of 2% dichloromethane in MeOH, then with 4 CV of 20% Et_3N in MeOH to elute the product.

Synthesis of IMesCu-Et

The title compound was synthesized according to a modified literature procedure.[28] A 15 mL Schlenk bomb was charged with a stir bar and flame-dried under vacuum. The flask was then transferred into a glove box and IMesCuCl (1.0 equiv, 400 mg, 1.0 mmol) followed by THF (8.0 mL, 0.1 M) were added. Out of the glove box, the flask was cooled to -78 °C at which point ethyl lithium (1.0 equiv, 2.0 mL, 1.0 mmol) was added dropwise over 30 min. The reaction was allowed to stir for 1 h before warming to 0 °C. The reaction was transfered into the glove box, and stirred at 20 °C for 10 min and the mixture was filtered through a pad of celite. The solvent was then removed and toluene (10 mL) was added to the dark brown solid which was stirred for 10 min before 20 mL of pentane was added. The mixture was filtered through a pad celite and concentrated to dryness. The resulting brown solution was taken up in THF (ca. 5 mL) and pentane was added until the solution became cloudy (ca. 20 mL). The mixture was filtered through a pad of celite, resulting in a transparent solution, and a white powder upon concentration Crystals suitable for x-ray analysis were obtained by vapor diffusion of pentane into a saturated solution of THF. Upon exposure of a solution of IMesCu-Et in C_6D_6 to ambient light at 25 °C in a sealed NMR tube, 50% decomposition was observed. The decomposition was indicated by ^{1}HNMR upon the disappearance of the ethyl signals and the appearance of a signal corresponding to ethane. Alternatively, at

60 °C in a sealed NMR tube protected from light, no decomposition of IMesCu-Et was observed after 4 h. However, complete decomposition occurred after 24 h.

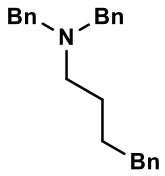
Stoichiometric Reaction of IMesCu-Et

In a glove box, a 1 dram vial was charged with a stir bar. To the vial was added *O*-benzoyl-*N*,*N*-dibenzyl hydroxylamine (1.50 equiv, 11.7 mg, 0.037 mmol) and 1,4-dioxane-d^8 (0.25 mL). Separately, to a shell vial was added IMesCu-Et (1.0 equiv, 9.8 mg, 0.025 mmol) and 1,4-dioxane-d^8 (0.25 mL). The resulting solution was then added dropwise over 10 min to the reaction vial containing *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine with stirring at 45℃. After 1 h 1,3,5-trimethoxybenzene as internal standard was added and the reaction yield was determined by NMR comparison against 1,3,5-trimethoxybenzene.

Hydroamination of phenyl butene using IMesCu-Et as a catalyst

In a glove box, a one-dram vial was charged with a stir bar. To the vial was added 9-BBN dimer (0.50 equiv, 12.2 mg 0.050 mmol), toluene (0.20 mL, 0.40 M), and phenyl butene (1.00 equiv, 13.2 mg, 0.100 mmol). After 12 h at 60 °C, the reaction mixture was cooled to room temperature and lithium *tert*-butoxide (1.10 equiv, 8.8 mg, 0.110 mmol), *O*-benzoyl-*N*,*N*-dibenzyl hydroxylamine (1.10 equiv, 24.3 mg, 0.110 mmol), and toluene (1.3 mL) were added. Finally IMesCu-Et (0.050 equiv, 2.0 mg, 0.005 mmol) in toluene (0.5 mL, 2.0 mL total) was added dropwise over 1 min at 60 °C. The reaction vial was capped and allowed to stir at 60 °C for 4 h before 1,3,5-trimethoxybenzene as internal standard was added and the reaction yield was determined by GC analysis

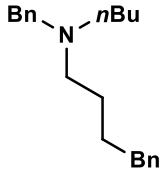
2.4.c. Characterization



2.3

N,N-dibenzyl-4-phenylbutan-1-amine

Compound was isolated as a colorless oil (147.5 mg, 90% yield) after purification by silica gel column chromatography (0 → 30% benzene/hexanes over 3 CV, then 0 → 15% Et_2O/hexanes over 7 CV). ^{1}H NMR (300 MHz, C_6D_6) δ 7.37 (d, *J* = 7.4 Hz, 4H), 7.28 – 6.90 (m, 11H), 3.41 (s, 4H), 2.52 – 2.27 (m, 4H), 1.60 – 1.26 (m, 4H). ^{13}C NMR (125 MHz, C_6D_6) δ 142.8, 140.4, 129.1, 128.8, 128.6, 128.5, 127.2, 126.0, 58.8, 53.3, 35.9, 29.2, 26.9. HRMS calculated for $[M]^+$ 330.2212, found 330.2217. FTIR (neat, cm^{-1}): 3084(w), 2933(m), 1494(m), 1452(m), 1028(w).

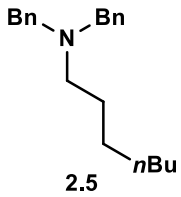


2.4

N-benzyl-N-butyl-4-phenylbutan-1-amine

Compound was isolated as a colorless oil (111.9 mg, 76% yield) after purification by silica gel column chromatography (0 → 5% Et_2O/hexanes over 6 CV). ^{1}H NMR (300 MHz, C_6D_6) δ 7.38 (d, *J* = 7.3 Hz, 2H), 7.25 – 7.06 (m, 8H), 3.42 (s, 2H), 2.46 (t, *J* = 7.5 Hz, 2H), 2.40 – 2.26 (m, 4H), 1.65 – 1.49 (m, 2H), 1.49 – 1.32 (m, 4H), 1.34 – 1.18 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 140.4, 129.0, 128.6,

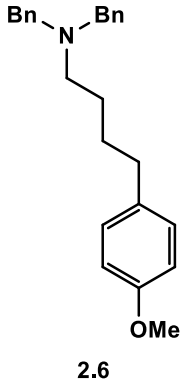
128.4, 128.2, 126.7, 125.7, 58.8, 53.7, 53.6, 35.9, 29.4, 29.3, 26.8, 20.7, 14.2. ESI-MS calculated for $[M+H]^+$ 296.2, found 296.2. FTIR (neat, cm^{-1}): 3025(w), 2930(s), 2795(w), 1494(m), 1453(m).



2.5

N,N-dibenzyloctan-1-amine

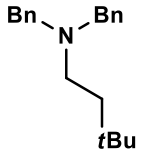
Compound was isolated as a colorless oil (147.8 mg, 96% yield) after purification by silica gel column chromatography (0 → 30% benzene/hexanes over 3 CV, then 0 → 10% Et_2O/hexanes over 6 CV). ^1H NMR (300 MHz, C_6D_6) δ 7.41 (d, *J* = 7.0 Hz, 4H), 7.31 – 7.04 (m, 6H), 3.48 (s, 4H), 2.40 (t, *J* = 7.1 Hz, 2H), 1.45 (m, 2H), 1.35 – 1.09 (m, 10H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 128.9, 128.3, 126.8, 58.4, 53.6, 32.0, 29.6, 29.5, 27.4, 27.1, 22.8, 14.3. ESI-MS calculated for $[M+H]^+$ 310.2, found 310.3. FTIR (neat, cm^{-1}): 3062(w), 3026(w), 2926(s), 1494(w), 1452(m), 1367(w).



2.6

N,N-dibenzyl -4-(4-methoxyphenyl)butan-1-amine

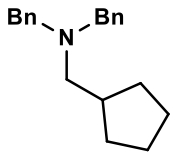
Compound was isolated as a colorless oil (168.8 mg, 94% yield) after purification by silica gel column chromatography (0 → 30% benzene/hexanes over 3 CV, then 0 → 5% Et_2O/hexanes over 6 CV). ^1H NMR (300 MHz, C_6D_6) δ 7.39 (d, *J* = 7.4 Hz, 4H), 7.28 – 7.05 (m, 6H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 3.43 (s, 4H), 3.34 (s, 3H), 2.43 – 2.29 (m, 4H), 1.58 – 1.39 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 140.2, 134.9, 129.4, 128.9, 128.3, 126.9, 113.8, 58.5, 55.4, 53.2, 34.8, 29.2, 26.6. ESI-MS calculated for $[M+H]^+$ 360.5, found 360.4. FTIR (neat, cm^{-1}): 3026(w), 2934(m), 2795(w), 1511(s), 1494(m), 1256(s), 1038(m).



2.9

N,N-dibenzyl-3,3-dimethylbutan-1-amine

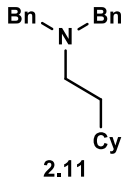
Compound was isolated as a colorless oil (121.7 mg, 86% yield) after purification by silica gel column chromatography (0 → 30% benzene/hexanes over 3 CV, then 0 → 15% Et_2O/hexanes over 6 CV). ^1H NMR (300 MHz, C_6D_6) δ 7.41 (d, *J* = 7.1 Hz, 4H), 7.28 – 7.04 (m, 6H), 3.49 (s, 4H), 2.49 – 2.41 (m, 2H), 1.48 – 1.41 (m, 2H), 0.77 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 128.9, 128.3, 126.9, 58.3, 49.4, 40.4, 30.0, 29.6. ESI-MS calculated for $[M+H]^+$ 282.2, found 282.3. FTIR (neat, cm^{-1}): 3062(w), 3027(w), 2954(s), 1493(w), 1452(m), 1364(m).



2.10

N,N-dibenzyl-1-cyclopentylmethanamine

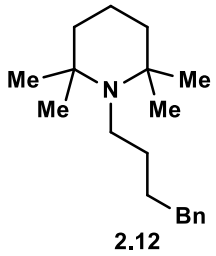
Compound was isolated as a colorless oil (118.9 mg, 85% yield) after purification by silica gel column chromatography (0 → 30% benzene/hexanes over 3 CV, then 0 → 10% Et_2O/hexanes over 6 CV). ^1H NMR (300 MHz, C_6D_6) δ 7.40 (d, *J* = 7.3 Hz, 4H), 7.25 – 7.09 (m, 6H), 3.45 (s, 4H), 2.26 (d, *J* = 7.6 Hz, 2H), 2.09 – 1.94 (m, 1H), 1.74 – 1.61 (m, 2H), 1.46 – 1.37 (m, 4H), 1.22 – 1.02 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 128.9, 128.2, 126.8, 59.5, 58.7, 38.0, 31.1, 25.1. ESI-MS calculated for $[M+H]^+$ 268.2, found 268.2. FTIR (neat, cm^{-1}): 3061(w), 3026(m), 2948(s), 1494(m), 1451(m), 1369(w).



2.11

N,N-dibenzyl-2-cyclohexylethanamine

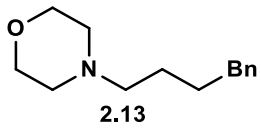
Compound was isolated as a colorless oil (124.8 mg, 81% yield) after purification by silica gel column chromatography (0 → 5% Et_2O/hexanes over 6 CV). ^1H NMR (300 MHz, C_6D_6) δ 7.41 (d, *J* = 7.4 Hz, 4H), 7.26 – 7.07 (m, 6H), 3.48 (s, 4H), 2.42 (t, *J* = 7.4 Hz, 2H), 1.46 – 1.66 (m, 5H), 1.42 – 1.30 (m, 2H), 1.26 – 1.04 (m, 4H), 0.90 – 0.61 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 128.9, 128.2, 126.8, 58.4, 51.1, 35.8, 34.7, 33.6, 26.8, 26.5. ESI-MS calculated for $[M+H]^+$ 308.2, found 308.4. FTIR (neat, cm^{-1}): 3061(w), 3026(m), 2920(s), 2849(s), 1494(m), 1450(m), 1366(w).



2.12

2,2,6,6-tetramethyl-1-(4-phenylbutyl)piperidine

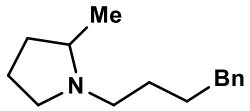
Compound was isolated as a colorless oil (93.7 mg, 86% yield) after purification by acid/base extraction **A**. Reaction time was 4 h. ^{1}H NMR (300 MHz, C_6D_6) δ 7.25 – 7.13 (m, 2H), 7.13 – 7.04 (m, 3H), 2.53 (t, *J* = 7.4 Hz, 2H), 2.45 – 2.25 (m, 2H), 1.69 – 1.28 (m, 10H), 1.01 (s, 12H). ^{13}C NMR (125 MHz, C_6D_6) δ 143.1, 128.7, 128.6, 126.0, 54.5, 45.3, 41.6, 36.4, 36.1, 29.7, 27.7, 18.2. HRMS calculated for $[M]^+$ 274.2535, found 274.2527. FTIR (neat, cm^{-1}): 3082(w), 2928(s), 1377(m), 1262(m), 1129(m)



2.13

4-(4-phenylbutyl)morpholine

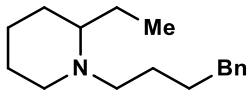
Compounds was isolated as a colorless oil (82.8 mg, 94% yield) after purification by ion exchange chromatography. Reaction time was 4 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.30 (m, 2H), 7.30 – 7.10 (m, 3H), 3.88 – 3.65 (m, 4H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.59 – 2.32 (m, 6H), 1.84 – 1.45 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 128.5, 128.4, 125.8, 67.1, 59.1, 53.9, 35.9, 29.4, 26.3. ESI-MS calculated for $[M+H]^+$ 220.2, found 220.2. FTIR (neat, cm^{-1}): 3083(w), 3024(w), 2935(s), 1603(w), 1453(s), 1118(s).



2.14

2-methyl-1-(4-phenylbutyl)pyrrolidine

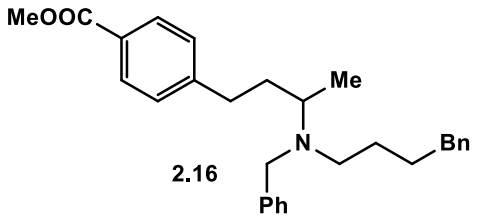
Compound was isolated as a colorless oil (73.1 mg, 84% yield) after purification by ion exchange chromatography. Reaction time was 3 h. ^{1}H NMR (300 MHz, MeOD) δ 7.39 – 7.05 (m, 5H), 3.24 – 3.00 (m, 1H), 2.94 – 2.73 (m, 1H), 2.64 (t, *J* = 6.8 Hz, 2H), 2.49 – 2.25 (m, 1H), 2.25 – 1.85 (m, 3H), 1.87 –3 1.34 (m, 7H), 1.11 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.7, 128.6, 128.4, 125.8, 60.5, 54.2, 54.1, 36.0, 32.8, 29.8, 28.5, 21.7, 19.0. HRMS calculated for $[M+H]^+$ 218.1908, found 218.1915. FTIR (neat, cm^{-1}): 3062(w), 3025(w), 2936(s), 1603(w), 1453(s), 1374(m), 746(s).



2.15

2-ethyl-1-(4-phenylbutyl)piperidine

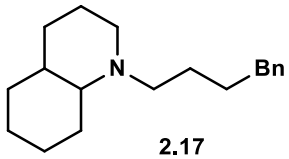
Compound was isolated as a colorless oil (89.6 mg, 91% yield) after acid base extraction **A**. Reaction time was 3 h. ^{1}H NMR (300 MHz, MeOD) δ 7.43 – 7.00 (m, 5H), 2.96 – 2.80 (m, 1H), 2.79 – 2.57 (m, 3H), 2.57 – 2.42 (m, 1H), 2.42 – 2.15 (m, 2H), 1.82 – 1.44 (m, 9H), 1.44 – 1.21 (m, 3H), 0.87 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 142.1, 128.1, 128.0, 125.4, 61.7, 52.8, 51.7, 35.3, 29.2, 28.7, 24.5, 23.8, 23.2, 23.0, 9.2. HRMS calculated for $[M+H]^+$ 246.2221, found 246.2215. FTIR (neat, cm^{-1}): 3054(w), 2933(s), 1734(m), 1437(s), 1265(s), 738(s).



2.16

methyl 4-(3-(benzyl(4-phenylbutyl)amino)butyl)benzoate

Compound was isolated as a colorless oil (161.0 mg, 94% yield) after purification by column chromatography (0-30% ethyl acetate in hexanes over 8 CV). Reaction time was 4 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 7.1 Hz, 2H), 7.27 – 7.19 (m, 4H), 7.16 – 7.07 (m, 4H), 6.95 (d, *J* = 8.3 Hz, 2H), 3.60 – 3.52 (m, 4H), 3.21 (d, *J* = 13.9 Hz, 1H), 2.75 – 2.54 (m, 2H), 2.43 – 2.35 (m, 4H), 2.28 – 2.14 (m, 1H), 1.70 – 1.25 (m, 6H), 0.80 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 148.7, 142.7, 141.3, 129.7, 128.7, 128.5, 128.4, 128.3, 128.1, 127.6, 126.6, 125.6, 54.1, 53.4, 52.0, 49.1, 35.9, 35.8, 33.4, 29.2, 28.3, 13.5. HRMS calculated for $[M+H]^+$ 430.2746, found 430.2735. FTIR (neat, cm^{-1}): 3061(w), 3026(w), 2929(s), 1721(s), 1609(m), 1453(m), 1279(s), 738(m).

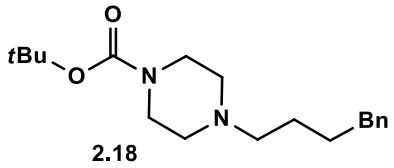


2.17

1-(4-phenylbutyl)decahydroquinoline

Compound was isolated as a colorless oil (105.8 mg, 97% yield) after purification by acid/base extraction **A**. Reaction time was 4 h. ^{1}H NMR (300 MHz, C_6D_6) δ 7.33 – 7.18 (m, 2H), 7.15 – 7.05 (m, 3H), 2.93 – 2.82 (m, 1H), 2.78 – 2.60 (m, 1H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.35 – 2.12 (m, 1H), 2.12 – 1.94 (m, 2H), 1.83 – 1.31 (m, 11H), 1.30 – 1.05

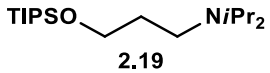
(m, 4H), 1.06 – 0.76 (m, 2H). ^{13}C NMR (125 MHz, C_6D_6) δ 143.0, 128.8, 128.6, 126.0, 66.8, 54.2, 52.9, 42.6, 36.3, 33.6, 33.3, 30.9, 29.9, 26.6, 26.5, 26.2, 26.0. ESI-MS calculated for $[M+H]^+$ 272.2, found 272.3. FTIR (neat, cm^{-1}): 3062(w), 3026(m), 2921(s), 1603(w), 1447(m), 1239(m), 698(s).



2.18

tert-butyl 4-(4-phenylbutyl)piperazine-1-carboxylate

Compound was isolated as a pale yellow oil (119.7 mg, 94% yield) after purification by acid/base extraction **B**. Reaction time was 4 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.13 (m, 2H), 7.07 (t, *J* = 7.1 Hz, 3H), 3.38 – 3.25 (m, 4H), 2.52 (t, *J* = 7.6 Hz, 2H), 2.36 – 2.13 (m, 6H), 1.60 – 1.39 (m, 4H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, C_6D_6) δ 154.7, 142.8, 128.7, 128.7, 126.1, 79.0, 58.5, 53.3, 46.2, 44.6, 43.7, 36.1, 29.4, 28.5, 26.7. ESI-MS calculated for $[M+H]^+$ 319.3, found 319.4. FTIR (neat, cm^{-1}): 3062(w), 3026(m), 2933(s), 1688(s), 1442(m), 1247(m), 1171(m), 1123(m), 1006(m).

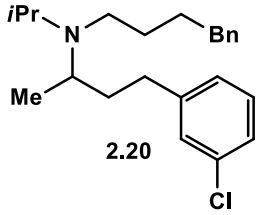


2.19

N,N-diisopropyl-3-((triisopropylsilyl)oxy)propan-1-amine

Compound was isolated as a pale yellow oil (101.0 mg, 80% yield) after purification by acid/base extraction **B**. Reaction time was 6 h. ^{1}H NMR (300 MHz, C_6D_6) δ 3.74 (t, *J* = 6.2 Hz, 2H), 3.07 – 2.85 (m, 2H), 2.68 – 2.47 (m, 2H), 1.80 – 1.65 (m, 2H), 1.21 – 1.10 (m, 21H), 1.00 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR (125 MHz, C_6D_6) δ

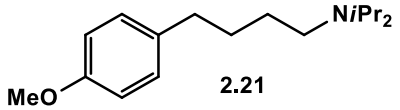
70.7, 62.0, 48.5, 41.6, 34.8, 32.4, 26.7, 22.5, 21.0, 18.4, 12.4. ESI-MS calculated for $[M+H]^+$ 316.3, found 316.5. FTIR (neat, cm^{-1}): 2962(s), 2865(s), 1464(m), 1106(s).



2.20

N-(4-(3-chlorophenyl)butan-2-yl)-N-isopropyl-4-phenylbutan-1-amine

Compound was isolated as a colorless oil (108.6 mg, 76% yield) after purification by column chromatography (0-20% MeOH in CH_2Cl_2 over 8 CV with 0.1% acetic acid as an additive) followed by acid/base extraction **A**. Reaction time was 6 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 2H), 7.21 – 7.10 (m, 5H), 6.96 – 6.90 (m, 2H), 2.92 – 2.86 (m, 1H), 2.78 – 2.54 (m, 4H), 2.48 – 2.24 (m, 3H), 1.86 – 1.24 (m, 6H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 146.6, 143.9, 135.0, 130.8, 129.5, 129.4, 129.3, 127.8, 126.7, 126.6, 53.3, 49.5, 45.8, 38.3, 36.9, 31.0, 30.5, 22.5, 20.1, 17.4. HRMS calculated for $[M+H]^+$ 358.2301, found 358.2296. FTIR (neat, cm^{-1}): 3062(w), 2961(s), 1597(m), 1453(m), 1079(w), 908(s), 733(s).

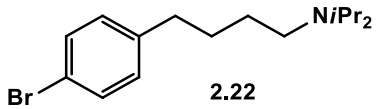


2.21

N,N-diisopropyl-4-(4-methoxylphenyl)butan-1-amine

Compound was isolated as a pale yellow oil (88.7 mg, 84% yield) after purification by acid/base extraction **A**. Reaction time was 4 h. ^{1}H NMR (300 MHz,

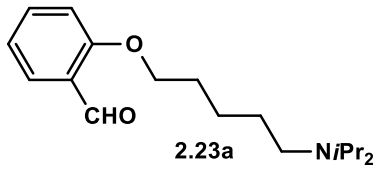
C_6D_6) δ 7.06 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 3.34 (s, 3H), 2.92 (hept, *J* = 6.6 Hz, 2H), 2.55 (t, *J* = 7.6 Hz, 2H), 2.38 (t, *J* = 7.1 Hz, 2H), 1.73 – 1.55 (m, 2H), 1.54 – 1.35 (m, 2H), 0.97 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR (125 MHz, C_6D_6) δ 158.5, 135.1, 129.6, 114.2, 54.8, 48.1, 44.7, 35.5, 30.9, 29.8, 21.0. ESI-MS calculated for $[M+H]^+$ 264.2, found 264.3. FTIR (neat, cm^{-1}): 3033(w), 2962(s), 1751(w), 1465(m), 1245(s), 1039(m).



2.22

4-(4-bromophenyl)-N,N-diisopropylbutan-1-amine

Compound was isolated as a pale yellow oil (104.7 mg, 84% yield) after purification by acid/base extraction **A**. Reaction time was 4 h. ^{1}H NMR (300 MHz, C_6D_6) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 2.99 – 2.76 (m, 2H), 2.39 – 2.21 (m, 4H), 1.53 – 1.26 (m, 4H), 0.95 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR (125 MHz, C_6D_6) δ 142.0, 131.6, 130.5, 119.8, 48.1, 44.6, 35.6, 30.7, 29.2, 21.0. ESI-MS calculated for $[M+H]^+$ 312.1, found 312.5. FTIR (neat, cm^{-1}): 3035(w), 2963(s), 1892(w), 1751(w), 1488(m), 1072(m), 1011(m), 829(m), 677(m).

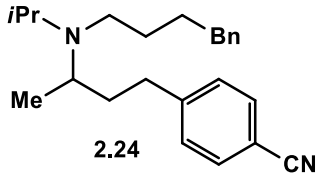


2.23a

2-((5-(diisopropylamino)pentyl)oxy)benzaldehyde

Acetal 2.23 was isolated as the deprotected aldehyde as a colorless oil (123.9 mg, 92% yield) after purification by acid/base extraction **A**. Reaction time was 5 h. ^{1}H NMR

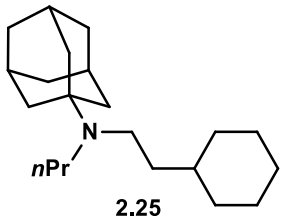
(300 MHz, $CDCl_3$) δ 10.52 (d, *J* = 0.8 Hz, 1H), 7.83 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.53 (ddd, *J* = 8.4, 7.3, 1.9 Hz, 1H), 7.10 – 6.89 (m, 2H), 4.08 (t, *J* = 6.4 Hz, 2H), 3.10 – 2.90 (m, 2H), 2.40 (s, 2H), 2.11 – 1.77 (m, 2H), 1.48 (d, *J* = 7.1 Hz, 4H), 1.00 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1, 161.7, 136.0, 128.3, 125.0, 120.6, 112.6, 68.6, 48.5, 45.2, 31.3, 29.2, 24.0, 20.8. ESI-MS calculated for $[M+H]^+$ 292.2, found 292.2. FTIR (neat, cm^{-1}): 3076(w), 2952(s), 2811(w), 2758(w), 1694(s), 1458(m), 1243(m), 1042(m).



2.24

4-(3-(isopropyl(4-phenylbutyl)amino)butyl)benzonitrile

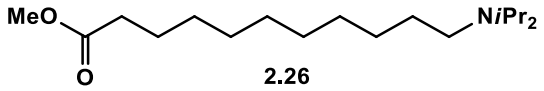
Compound was isolated as a colorless oil (124.8 mg, 90% yield) after acid/base extraction **A**. Reaction time was 8 h. ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.16 (m, 7H), 3.15 – 2.90 (m, 1H), 2.82 – 2.75 (m, 2H), 2.67 – 2.32 (m, 5H), 1.78 – 1.32 (m, 6H), 1.12 – 0.90 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 142.9, 132.2, 129.3, 128.5, 128.4, 125.8, 119.4, 109.4, 51.9, 48.0, 44.4, 37.6, 36.1, 34.0, 30.1, 29.5, 22.7, 19.6, 17.5. HRMS calculated for $[M+H]^+$ 349.2643, found 349.2646. FTIR (neat cm^{-1}): 3086(w), 2961(s), 2226(m), 1606(s), 1453(s), 1152(m), 737(m).



2.25

N-(2-cyclohexylethyl)-N-propyladamantan-1-amine

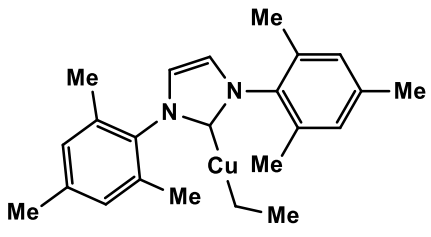
Compound was isolated as a colorless oil which solidified upon standing (101.2 mg, 83% yield) after acid/base extraction **A**. Reaction time was 4 h. ^{1}H NMR (300 MHz, C_6D_6) δ 2.66 – 2.54 (m, 2H), 2.54 – 2.39 (m, 2H), 2.02 (s, 3H), 1.85 – 1.39 (m, 20H), 1.39 – 1.10 (m, 3H), 1.04 – 0.84 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.5, 46.2, 40.0, 37.0, 36.8, 36.5, 33.7, 29.8, 29.7, 26.8, 26.5, 12.1, 12.0. ESI-MS calculated for $[M+H]^+$ 304.3, found 304.3. FTIR (neat, cm^{-1}): 2917(s), 2849(s), 1447(m), 1084(s) 1154(m).



2.26

methyl 11-(diisopropylamino)undecanoate

Compound was isolated as a colorless oil (96.8 mg, 81% yield) after purification by acid/base extraction **A**. Reaction time was 6 h. ^{1}H NMR (300 MHz, C_6D_6) δ 3.46 (s, 3H), 3.15 – 2.97 (m, 2H), 2.60 – 2.41 (m, 2H), 2.30 – 2.15 (m, 2H), 1.79 – 1.54 (m, 4H), 1.47 – 1.18 (m, 12H), 1.10 (d, J = 6.6 Hz, 12H). ^{13}C NMR (125 MHz, C_6D_6) δ 173.3, 50.9, 48.3, 45.1, 34.2, 31.7, 30.2, 30.1, 29.9, 29.7, 29.5, 28.2, 27.8, 25.3, 21.1. ESI-MS calculated for $[M+H]^+$ 300.3, found 300.4. FTIR (neat, cm^{-1}): 2928(s), 2855(m), 1743(s), 1465(m), 1204(m), 1172(m).



2.28

(ethyl)[1,2-dihydro-1,3-bis(2,4,6-trimethylphenyl)-2H-imidazol-2-ylidene]-Copper

The mixture was filtered through a pad of celite, resulting in a transparent solution, and a white powder upon concentration (144 mg, 37% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 6.86 (s, 4H), 6.16 (s, 2H), 2.21 (s, 6H), 2.17 (s, 12H), 1.80 (t, *J* = 8.0 Hz, 3H), 0.70 (q, *J* = 8.0 Hz, 2H). ^{13}C NMR (126 MHz, THF-d^8) δ 183.9, 138.3, 136.2, 134.7, 128.8, 121.5, 20.2, 17.2, 13.4, 0.6.

Section 5: References

1. Henkel, T.; Brunne, R. M.; Muller, H.; Reichel, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 643. (b) Hill, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284.

2. Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

3. For general reviews, see: (a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (b) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (c) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368.

4. Selected examples of intramolecular hydroamination catalyzed by complexes of group IV metals and lanthanides: (a) Manna, K.; Xu, S.; Sadow, A. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 1865. (b) Leitch, D. C.; Payne, P. R.; Dunbar, C. R.; Schafer, L. L. *J. Am. Chem. Soc.* **2009**, *131*, 18246. (c) Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 354. (d) Watson, D. A.; Chiu, M.; Bergman, R. G. *Organometallics* **2006**, *25*, 4731. (e) Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748. (f) Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 1737. (g) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (h) Hong, S.; Tian, S.; Metz, M. V.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 14768.

5. Selected examples of intramolecular hydroamination catalyzed by complexes of late transition metals: (a) Shen, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 564. (b) Julian, L. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 13813. (c) Ohmiya, H.; Moriya, T.; Sawamura, M. *Org. Lett.* **2009**, *11*, 2145. (d) Hesp, K. D.; Tobisch, S.; Stradiotto, M. *J. Am. Chem. Soc.* **2009**, *132*, 413. (e) Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570. (f) Cochran, B. M.; Michael, F. E. *J. Am. Chem. Soc.* **2008**, *130*, 2786. (g) Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246. (h) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747. (i) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070.

6. Selected examples of intermolecular hydroamination: (a) Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220. (b) McBee, J. L.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2008**, *130*, 16562. (c) Brunet, J.-J.; Chu, N.-C.; Rodriguez-Zubiri, M. *Eur. J. Inorg. Chem.* **2007**, *2007*, 4711. (d) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (e) Dorta, R.; Egli, P.; Zürcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857. (f) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738.

7. Recent examples of enantioselective intermolecular hydroamination reactions: (a) Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372. (b) Reznichenko, A. L.; Nguyen, H. N.; Hultzsch, K. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 8984.

8. (a) Munro-Leighton, C.; Blue, E. D.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2006**, *128*, 1446. (b) Fadini, L.; Togni, A. *Chem. Commun.* **2003**, 30. (c) Seligson, A. L.; Trogler, W. C. *Organometallics* **1993**, *12*, 744. (d) Castonguay, A.; Spasyuk, D. M.; Madern, N.; Beauchamp, A. L.; Zargarian, D. *Organometallics* **2009**, *28*, 2134. (e) Kawatsura, M.; Hartwig, J. F. *Organometallics* **2001**, *20*, 1960.

9. (a) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Herwig, J.; Müller, T. E.; Thiel, O. R. *Chem. Eur. J.* **1999**, *5*, 1306. (b) Ryu, J.-S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584. (c) Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 5608. (d) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2702. (e) Takaya, J.; Hartwig, J. F. *J. Am.*

Chem. Soc. **2005**, *127*, 5756. (f) Munro-Leighton, C.; Delp, S. A.; Alsop, N. M.; Blue, E. D.; Gunnoe, T. B. *Chem. Commun.* **2008**, 111.

10. (a) Guin, J.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 779. (b) Guin, J.; Mück-Lichtenfeld, C.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2007**, *129*, 4498.

11. (a) Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M.-E.; Bédard, A.-C.; Séguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893. (b) Loiseau, F.; Clavette, C.; Raymond, M.; Roveda, J.-G.; Burrell, A.; Beauchemin, A. M. *Chem. Commun.* **2011**, *47*, 562.

12. Brown, H. C.; Heydkamp, W. R.; Breuer, E.; Murphy, W. S. *J. Am. Chem. Soc.* **1964**, *86*, 3565.

13. Scott, H. K.; Aggarwal, V. K. *Chem. Eur. J.* **2011**, *17*, 13124.

14. Brown, H. C.; Kim, K.-W.; Srebnik, M.; Bakthan, S. *Tetrahedron* **1987**, *43*, 4071.

15. Kabalka, G. W.; Sastry, K. A. R.; McCollum, G. W.; Yoshioka, H. *J. Org. Chem.* **1981**, *46*, 4296.

16. Brown, H. C.; Cole, T. E.; Srebnik, M.; Kim, K. W. *J. Org. Chem.* **1986**, *51*, 4925. (b) Brown, H. C.; Srebnik, M.; Cole, T. E. *Organometallics* **1986**, *5*, 2300.

17. Matteson, D. S.; Kim, G. Y. *Org. Lett.* **2002**, *4*, 2153. (b) Hupe, E.; Marek, I.; Knochel, P. *Org. Lett.* **2002**, *4*, 2861.

18. (a) Rucker, R. P.; Whittaker, A, M.; Dang, H.; Lalic, G. *Angew. Chem. Int. Ed.* **2012,** *51*, 3953-3957. (b) Uehling, M. R.; Marionni, S. T.; Lalic, G. *Org. Lett.* **2012**, *14*, 362. (c) Whittaker, A. M.; Rucker, R. P.; Lalic, G. *Org. Lett.* **2010**, *12*, 3216.

19. Rucker, R. P.; Whittaker, A, M.; Dang, H.; Lalic, G. *J. Am. Chem. Soc.* **2012,** *134*, 6751.

20. For the most relevant examples of electrophilic amination reactions see: (a) Casarini, A.; Dembech, P.; Lazzari, D.; Marini, E.; Reginato, G.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1993**, *58*, 5620. (b) Zheng, B.; Srebnik, M. *J. Org. Chem.* **1995**, *60*, 1912. (c) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680. (d) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219. (e) Zhang, Z.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 3005. (f) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598. (g). Hatakeyama, T.; Yoshimoto, Y.; Ghorai, S. K.; Nakamura, M. *Org. Lett.* **2010**, *12*, 1516. (h) He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6414.

21. (a) Ohmiya, H.; Yoshida, M.; Sawamura, M. *Org. Lett.* **2011**, *13*, 482. (b) Ohishi, T.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 5792. (d) Dang, L.; Lin, Z.; Marder, T. B. *Organometallics* **2010**, *29*, 917. And references 18, 19, and 26.

22. Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521.

23. Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 3369.

24. Whitesides, G. M.; Stedronsky, E. R.; Casey, C. P.; San Filippo, J. *J. Am. Chem. Soc.* **1970**, *92*, 1426.

25. Goj, L. A.; Blue, E. D.; Delp, S. A.; Gunnoe, T. B.; Cundari, T. R.; Pierpont, A. W.; Petersen, J. L.; Boyle, P. D. *Inorganic Chemistry* **2006**, *45*, 9032.

26. Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 2895. Ohmiya, H.; Tanabe, M.; Sawamura, M. *Org. Lett.* **2011**, *13*, 1086.

27. For selected examples that extendeed this work see: (a) Rossi, S. A.; Shimkin, K. W.; Xu, Q.; Mori-Quiroz, L. M. Watson, D. A. *Org. Lett.* **2013,** *15*, 2314. (b) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2013,** *135*, 4934. (c) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2012,** *51*, 11827.

28. See ref 25.

Chapter 3 – Synthesis of Hindered Anilines: Copper-Catalyzed Electrophilic Amination of Aryl Boronic Esters

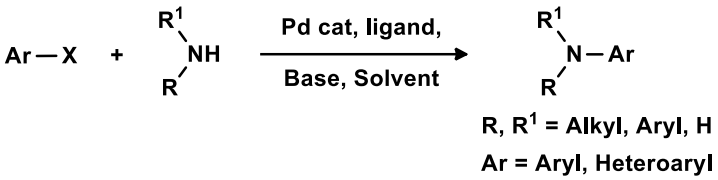
Section 1: Introduction

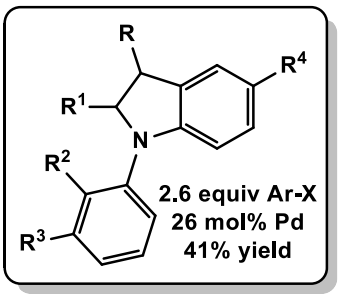
The synthesis of aromatic and heteroaromatic amines has attracted considerable attention in the last two decades as a result of the numerous applications of these compounds in the pharmaceutical industry and medicinal chemistry.[1] In fact, it has been proposed that over 90% of small molecule drugs (MW < 550 da) in the current market contain amines, and of these over 90% contain an aromatic substitution.[2] This high prevalence of aromatic amines in medicine in combination with the development of drug resistant diseases stimulates the continued development of methods for the synthesis of more complex forms of these motifs.

Arguably, the most significant advancement in the field of anilines and heteroaromatic amine synthesis has been the development of several transition metal-catalyzed couplings of aryl halides with amines.[3] These methods have provided a practical means for the preparation of a wide range of products, but, some important challenges remain. For example, the momentous Buchwald-Hartwig reaction, cannot be used for the direct preparation of bromo and iodo substituted anilines.[4] More importantly, the synthesis of hindered anilines is still a major challenge,[5] as illustrated by problems recently encountered by Baran et al. in the total synthesis of (+)-Psychotetramine (Scheme 3.31).[6]

Scheme 3.1. Previous work: Palladium-catalyzed aniline synthesis

Buchwald-Hartwig

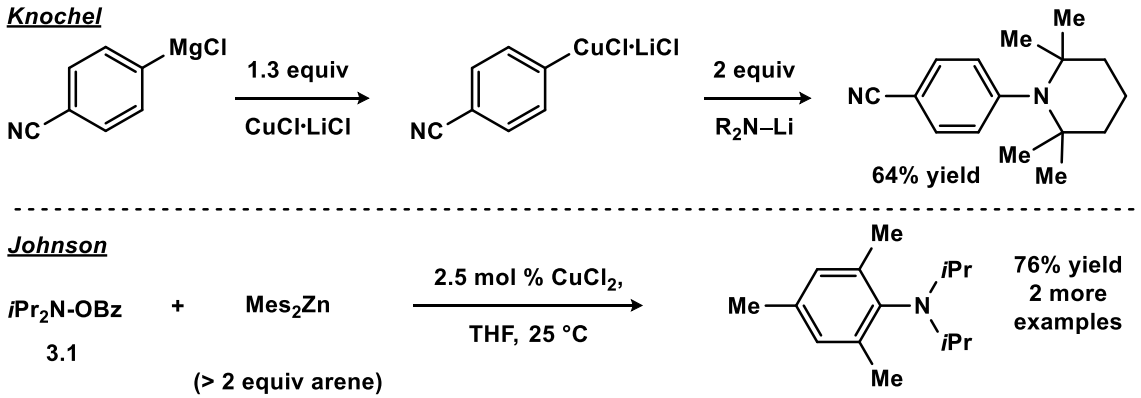




A reactivity umpolung in which the amine is the electrophile would provide a complementary tool for synthesis of complex organic molecules. Methods previously developed for the amination of nonstabilized carbanions using copper(I) catalysts have been indispensable for the synthesis of hindered anilines.[7] This method, pioneered by Johnson, was successfully applied to three examples of electrophilic amination of aryl zinc reagents by hindered electrophiles,[8] but is limited by the need for highly reactive Grignard reagents to prepare the aryl zinc nucleophiles (Scheme 3.32).

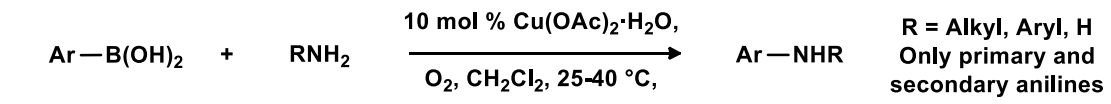
Knochel and co-workers have developed an impressive method for the synthesis of hindered anilines involving the oxidative coupling of organometallic reagents with hindered lithium amides in the presence of stoichiometric amounts of copper.[9] However, in addition to the significant amount of metal waste generated in this reaction, the 3 step synthesis of the reactive intermediates makes the method incompatible with a number of functionalities, and difficult to perform using standard techniques. Furthermore, a common feature of the procedures reported by Johnson and Knochel is that a significant excess (≥ 2 equivalents) of one of the coupling components is necessary.[10] It is therefore desirable to develop a method that does not rely on the use of excess reagents, especially highly reactive aryl lithium or aryl Grignard reagents.

Scheme 3.2. Previous work: Synthesis of hindered anilines



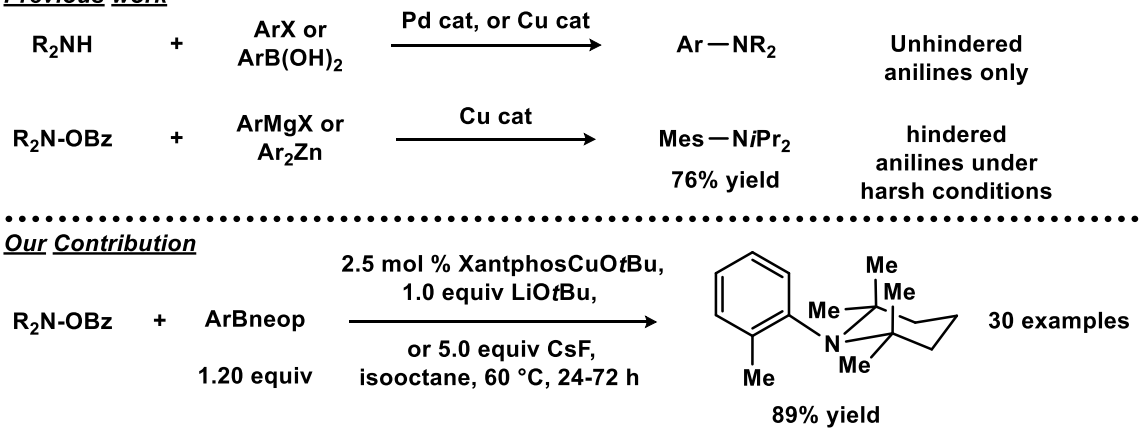
Aryl boronic acids and their derivatives offer significant advantages over the organometallic reagents previously used in the synthesis of hindered anilines. They are stable, readily available, and compatible with a wide range of functional groups,[11] but have not been successfully used in combination with electrophilic amines.[12] A related amination of organoboron reagents developed by Lam,[13] Chan,[14] Evans,[15] and others[16] approaches the problem using amines under oxidative conditions (Scheme 3.3). Unfortunately though, the Chan-Lam-Evans reaction is highly sensitive to the steric properties of amine substrates and can only be used for the synthesis of primary and unhindered secondary anilines.[17] From these studies it is clear that addressing the limitations associated with the methods of Johnson and Knochel by utilizing organoboron reagents an umpolung to the amine reactivity in the Chan-Lam-Evans reaction would be necessary.

Scheme 3.3. Previous work: Organoboranes in copper-catalyzed aniline synthesis



The observed high tolerance to sterically hindered substrates during our reaction of alkyl boranes[18] prompted an exploration of electrophilic amination of arylboronic esters. We hypothesized that by using an electrophilic amination protocol rather than the oxidative coupling of the Chan-Lam-Evans reaction our reaction would be applicable to the synthesis of hindered substrates while enjoying broad functional group compatibility. In this chapter, I describe our success in developing this catalytic method.[19] The synthesis of hindered anilines from aryl and heteroaryl boronic esters was compatible with a wide variety of functional groups, including aryl iodides and bromides. Moreover, the reaction was used to synthesize a myriad of the most sterically hindered anilines known to date in high yield (Scheme 3.34).

Scheme 3.4. Summary: Synthesis of hindered anilines



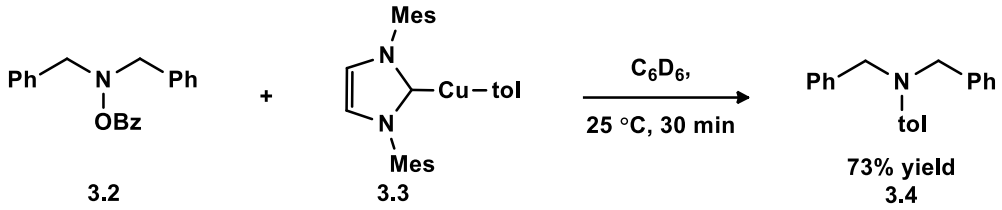
Section 2: Results and Discussion

3.2.a. Optimization

With our experience in using arylboronic esters in copper catalyzed transformations we envisioned that the aryl copper intermediate previously synthesized

by our laboratory (discussed in chapter 1.2.a) and others could be used to test the feasibility of copper-catalyzed aniline synthesis.[20] Thus the monoaryl copper complex IMesCu-tol was synthesized, and to our delight readily gave the corresponding primary protected aniline product in 73% yield when combined with the hydroxylamine *N*,*N*-dibenzyl-*O*-benzoylhydroxylamine (scheme 3.5). However, in an attempt to establish a catalytic protocol using similar conditions to our allylic arylation reaction we were disappointed by a low yield of the desired product.

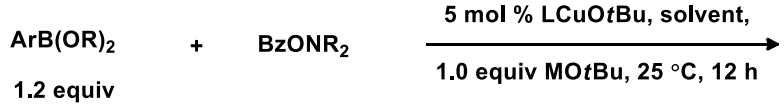
Scheme 3.5. Copper mediated aniline synthesis

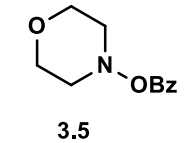
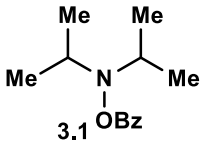


Using tolyl pinacol boronic ester and benzoyloxymorpholine **3.5**, in the presence of sodium *tert*-butoxide and a catalytic amount of IMesCuO*t*Bu, the reaction resulted in less than 5% yield of the desired product upon full conversion of the substrate (table 3.1, entry 1). We speculated that the low yield of the aniline was a consequence of slow transmetalation of the aryl boronic ester allowing decomposition of the hydroxylamine by the alkoxide. As previously discussed (chapter 2.2.a), both the product of transesterification and elimination to the imine were possible.[21] More importantly both side products were observed by NMR analysis of the crude reaction mixture. Although a slow addition of the electrophile has been shown to decrease these side reactions, increasing the reactivity of the transmetalation partner may have a similar effect while avoiding the need for slow addition conditions. Indeed, reactions with ethylene glycol

and neopentyl glycol derived boronic esters, which are known to undergo transmetalation faster than the corresponding pinacol esters,[22] provided the aniline product in 16% and 72% yield, respectively (table 3.1, entries 2 and 3).

Table 3.1. Reaction optimization



entry	$BzONR_2$	$ArB(OR)_2$	L	M	solvent	yield[a] (%)
1		4-MePhB(pin)	IMes	Na	THF	5
2		4-MePhB(eg)	IMes	Na	THF	16
3		4-MePhB(neop)	IMes	Na	THF	72
4[b]		4-MePhB(neop)	Xantphos	Na	1,4-dioxane	99
5		$2,6\text{-Me}_2\text{PhB(neop)}$	Xantphos	Na	1,4-dioxane	8
6		$2,6\text{-Me}_2\text{PhB(neop)}$	Xantphos	Li	1,4-dioxane	56
7	3.5	$2,6\text{-Me}_2\text{PhB(neop)}$	Xantphos	Li	toluene	74
8[c]		$2,6\text{-Me}_2\text{PhB(neop)}$	Xantphos	Li	toluene	81
9[d]		$2,6\text{-Me}_2\text{PhB(neop)}$	Xantphos	Li	isooctane	94
	3.1					

a. Determined by GC analysis. b. Catalyst was formed in situ from Xantphos and $(CuO\textit{t}Bu)_4$.
c. Reaction performed at 45 °C. d. 60 °C, 1.0 M. Toluene used to prepare the catalyst.

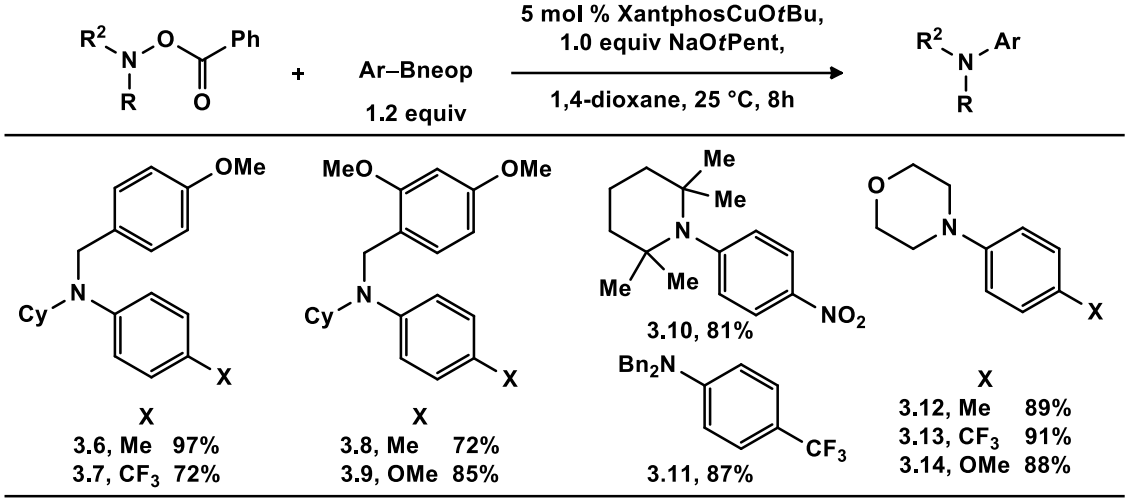
Following the identification of a suitable boronic ester, a catalyst screen performed with a neopentyl glycol derived boronic ester and electrophile **3.5**, identified XantphosCuO*t*Bu, a complex prepared from Xantphos ligand and $(CuO\textit{t}Bu)_4$ in situ, as the best catalyst. The use of 1,4-dioxane as a solvent provided the desired aniline in 99% yield, and will herein be referred to as conditions C. After a preliminary substrate screen using conditions C (vide supra) we discovered that unfortunately, a reaction with more hindered boronic ester (entry 5) resulted in the formation of the desired aniline in only 8% yield, together with 83% yield of *tert*-butyl benzoate. In fact, a control experiment revealed that *tert*-butyl benzoate forms in nearly quantitative yield in a reaction of 4-

benzoyloxymorpholine **3.5** with sodium *tert*-butoxide after only 10 minutes at room temperature. Similar to our developed hydroamination reaction, we found that the decomposition of the electrophile can be suppressed if lithium *tert*-butoxide is used in a non-coordinating solvent (see chapter 2.2.a). Consistent with these findings, a reaction with boronic ester and electrophile performed in toluene in the presence of lithium *tert*-butoxide afforded the desired aniline in 74% yield. Pleasingly, these conditions could also be used to prepare highly hindered *N*,*N*-diisopropyl-2,6-dimethyl aniline. However, for the best result (94% yield) the reaction was performed in a concentrated solution of isooctane. The conditions in table 3.1, entry 9, will herein be referred to as conditions D.

3.2.b. Scope

A preliminary investigation into the substrate scope performed using conditions C revealed that protected primary, secondary, and tertiary amines were all synthesized in high yields. Benzyl, PMB and DMB were all suitable amine protecting groups. The development of a method that is compatible to each protecting group suggests possible applications in natural product synthesis where orthogonal protection schemes are required. Heterocycles, including a variety of *N*-aryl morpholine products and an *N*-aryl 2,2,6,6-tetramethyl piperidine, were synthesized under these conditions. Finally, the electron-donating capacity of the aryl boronic esters had little effect on the reaction yield as evidenced by **3.13**-**3.14**. Unfortunately, as indicated in table 3.1, no hindered aryl boronic esters could be successfully used under conditions C despite the successful application of hindered electrophiles (**3.10**).

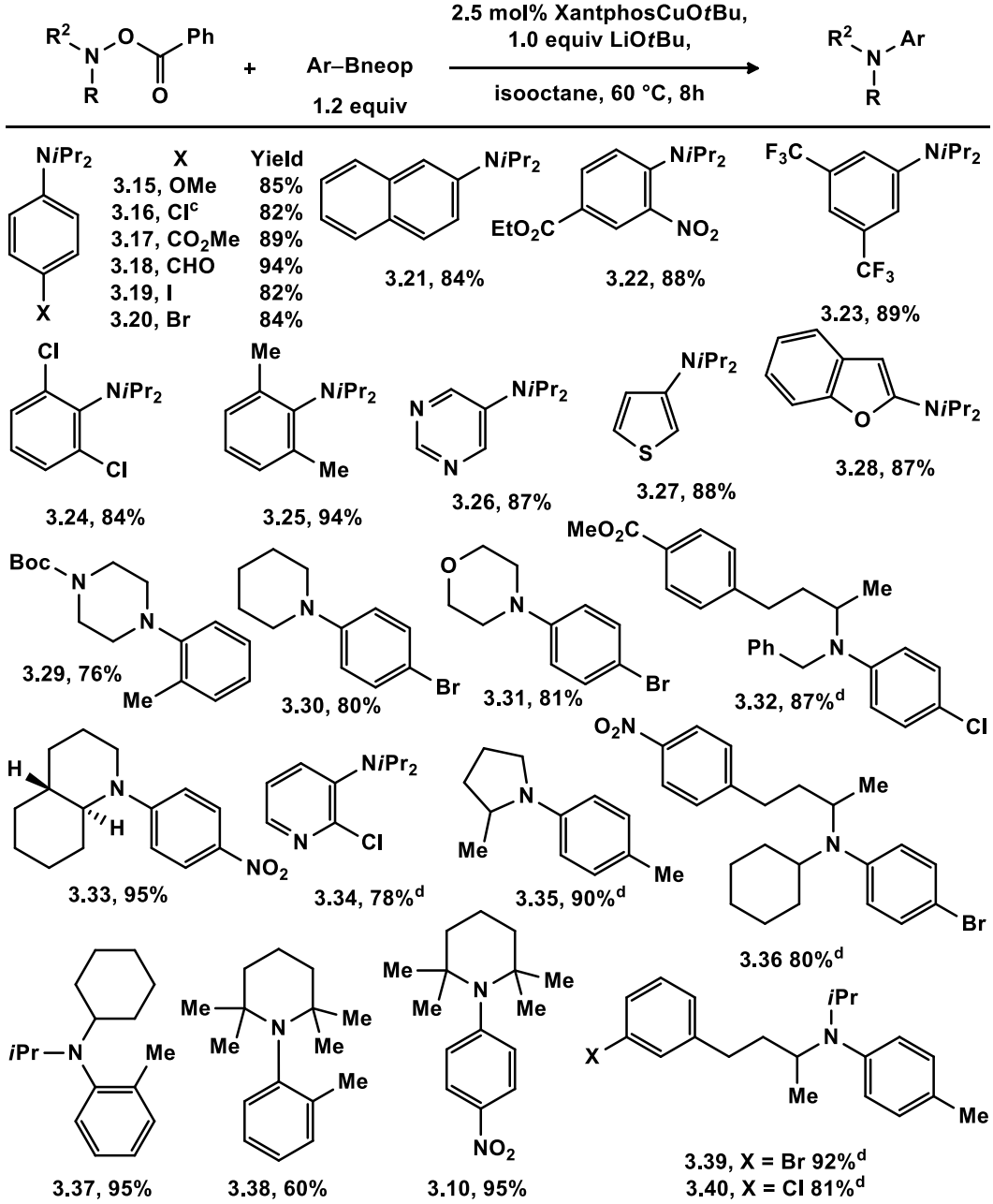
Table 3.2. Scope: Conditions C[a]



a. Reactions performed on 0.5 mmol scale. Yields of isolated products.

On the other hand, the optimized reaction conditions developed for the use of hindered boronic esters (conditions D) proved to be remarkably general in the synthesis of *N,N*-disubstituted anilines, and heteroaromatic amines. We found that reactions with diisopropylamine derived electrophiles could be performed in the presence of a number of functional groups on the arene, including chloro, carbomethoxy, formyl, iodo, bromo, and nitro. It is important to note that highly electron rich arenes such as *p*-methoxy, and highly deactivated arenes such as 3,5-bis(trifluoromethyl)benzene were viable nucleophiles. As the synthesis of anilines **3.24** and **3.25** suggests, hindered boronic esters were successful substrates. In addition, a variety of heteroaromatic boronic esters, including those from pyramidine, thiophene, furan, and 2-chloropyridine can also be used as nucleophiles (**3.26-3.28**, and **3.34**). In most reactions, 2.5 mol % of the catalyst was sufficient to accomplish the full conversion in less than 12 h, while the sterically hindered boronic esters required a higher catalyst loading (5 mol %). Finally, as the synthesis of **3.16** demonstrates, the reaction can be successfully performed on a 5 mmol scale.

Table 3.3. Scope: Conditions D[a,b]



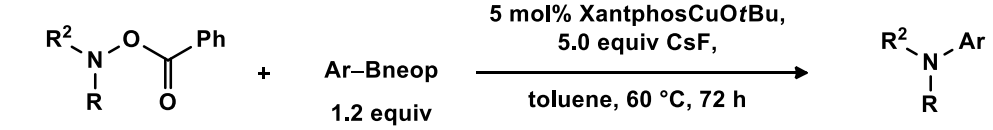
a. Reactions performed on 0.5 mmol scale. Yields of isolated products. Catalyst was added as a 1 M solution in toluene. b. 5 mol% of the catalyst was used. c. The reaction was performed on a 5 mmol scale. d 2.5 mol% of the catalyst were used at 45 °C.

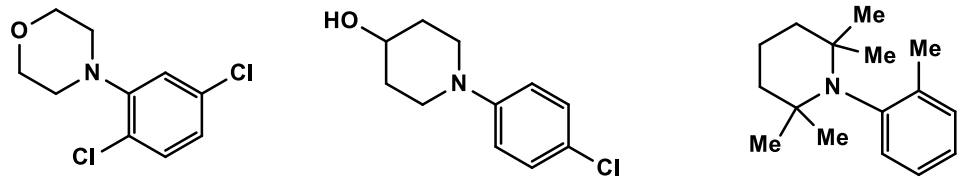
To establish the full scope of the amination reaction under conditions D, we explored the reactivity of various electrophiles. *O*-benzoyl hydroxylamines derived from

common heterocycles such as piperazine, variably substituted piperidines, morpholine, and pyrrole can be used in the reaction. Electrophiles bearing functional groups, such as boc, nitro, carbomethoxy, bromo, and chloro, are also viable substrates and provide the aniline products in excellent yields. The steric properties of an electrophile have no significant effect on the outcome of the reaction. Both 2-methylpyrrole and decahydroquinoline-derived electrophiles provide the expected anilines in high yield. Even a highly hindered electrophile derived from 2,2,6,6-tetramethylpiperidine could be coupled with nitrophenyl boronic ester in 87% yield, while the 2-methylphenyl boronic ester provided the product in 60% yield. This product represents the most hindered aniline synthesized to date.

For a select few substrates, an extension of the substrate scope by avoiding the lithium *tert*-butoxide additive was sought. We discovered that CsF can replace the alkoxide as a catalyst turnover reagent suggesting that aryl boronic esters can in fact transmetalate with copper fluoride. This change was particularly beneficial in coupling *ortho*-substituted boronic esters with less hindered electrophiles (**3.41**). Furthermore, CsF allowed the reaction to be performed in the presence of acidic functional groups, as demonstrated by the reaction of 4-hydroxypiperidine derived electrophile shown in table 3.4. Finally, the extremely hindered aniline **3.38** could be prepared in 89% yield using this procedure.

Table 3.4. Scope: CsF in place of alkoxides[a]





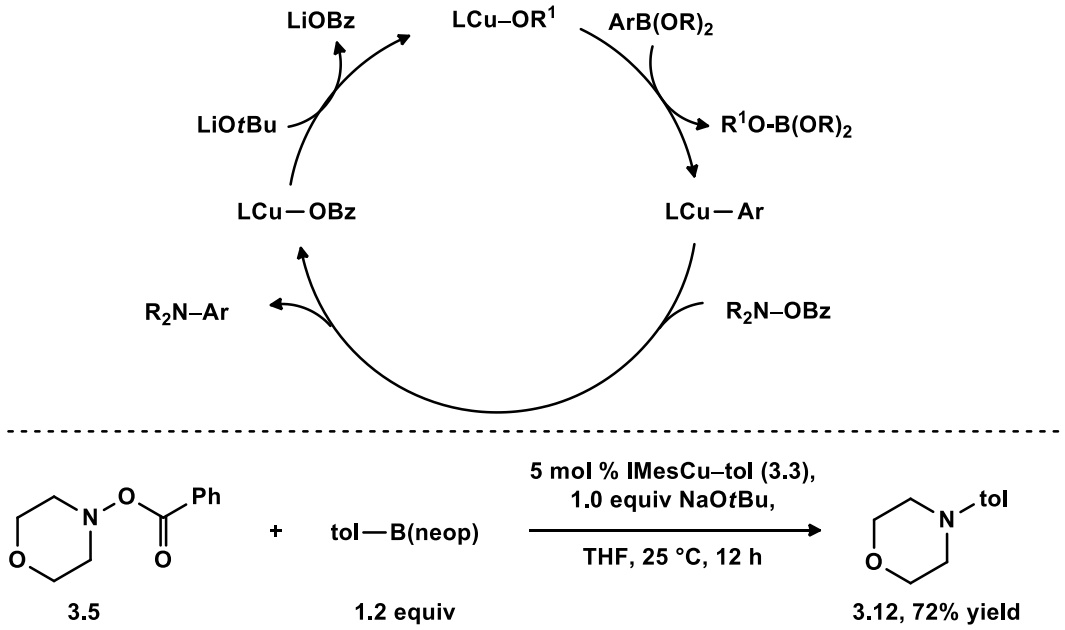
3.41, 91% 3.42, 82% 3.38, 89%

a. Reactions performed on 0.5 mmol scale. Yields of isolated products.

3.2.c. Mechanism

We propose that the amination reaction proceeds according to the mechanism shown in Scheme 2. The reaction involves transmetalation of an aryl group from boron to copper,[23] followed by electrophilic amination of the aryl copper intermediate.[24] Finally, the reactive copper alkoxide is regenerated with lithium alkoxide.[25]

Scheme 3.6. Proposed mechanism



With transmetalation of arenes from boron to copper well documented in the literature at this time by us and others, we focused our attention on the electrophilic amination of the putative aryl copper intermediate. As described in section 3.2.a, the reaction of *N*,*N*-dibenzyl-*O*-benzoyl hydroxylamine with IMes-supported copper aryl complex resulted in a 73% yield of aniline, in less than 30 minutes at room temperature. In addition, when used as a catalyst, IMesCu-tol provided results indistinguishable from those obtained with IMesCuO*t*Bu catalyst (compare scheme 3.6 to table 3.1). The mechanism of this elementary step is proposed to proceed through a nucleophilic substitution of the electrophilic amine, rather than the plausible oxidative addition-reductive elimination sequence. An elegant use of the endocyclic restriction test performed by the Johnson lab in a similar reaction supported the S_N2 type mechanism.[26]

Section 3: Conclusions

In conclusion, we have developed a mild copper-catalyzed reaction for the synthesis of sterically hindered anilines. The method utilizes aryl and heteroaryl boronic esters as mild nucleophiles and therefore is compatible with a wide range of functional groups including carbomethoxy, nitro, hydroxyl, formyl, and methoxy groups. Also, the tolerance of aryl chlorides, bromides, and iodides demonstrates that the method provides a valuable compliment to the established palladium-catalyzed methods. The ability to synthesize highly hindered anilines with unprecedented yields is attributable to the fundamental differences in the mechanism of the developed copper-catalyzed method. Overall, the exceptionally broad scope and reliability of this new procedure, together with

the availability of a wide variety of aryl boronic esters, make it a significant addition to the existing methods for aniline synthesis.[27]

Section 4: Experimental

3.4.a. General

All reactions were performed under a nitrogen atmosphere with flame-dried glassware, using standard Schlenk techniques, or in a glove box (Nexus II from Vacuum Atmospheres). Column chromatography was performed using a Biotage Iso-1SV flash purification system with silica gel from Agela Technologies Inc. (60Å, 40-60 μm, 230-400 mesh). Ion Exchange Chromatography was performed using analytical grade cation exchange resin from sulfonic acid functionalized styrene (Bio-Rad Laboratories, 200-400 mesh, 5.2 meq/g). General method for purification by ion exchange chromatography is as follows: crude product was adsorbed on the cation exchange resin (200 mg resin/mmol product) using MeOH, and the resin was subsequently washed with 10% dichloromethane in MeOH over 4 CV, then 10% Et_3N in MeOH over 4 CV to elute the product. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual proteated solvent peak ($CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), or CD_2Cl_2 (5.32 ppm)). ^{13}C chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon

resonance of the solvent ($CDCl_3$: δ 77.2 ppm, C_6D_6: δ 128.1 ppm, CD_2Cl_2: δ 54.0 ppm, CD_3CN: δ 1.3 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet), integration, and coupling constants in Hertz (Hz). Mass spectra were collected on a JEOL HX-110 mass spectrometer. GC analysis was performed on a Shimadzu GC-2010 instrument with a flame ionization detector and a SHRXI-5MS column (15 m, 0.25 mm inner diameter, 0.25 μm film thickness). The following temperature program was used: 2 min @ 60 °C, 13 °C/min to 160 °C, 30 °C/min to 250 °C, 5.5 min @ 250 °C.

THF, CH_2Cl_2, diethyl ether, and toluene were degassed and dried by passing through columns of neutral alumina. 1,4-dioxane was distilled from purple Na/benzophenone ketyl and stored over 4Å molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. Deuterated solvents were degassed and dried over 4Å molecular sieves before use. Commercial reagents were purchased from Sigma-Aldrich Co., VWR International, LLC., or STREM Chemicals, Inc., and were used as received. *O*-benzoyl hydroxyl amines[28] and aryl boronic esters[29] were prepared according to a literature procedure.

3.4.b. Experimental Details

Reaction Optimization

All optimization reactions were performed in a glove box. A 1-dram vial was charged with a stir bar. To the vial was added alkoxide additive (1.00 equiv), aryl boronic ester (1.20 equiv), copper catalyst (0.05 equiv), *n*-dodecane (0.10 equiv), and solvent (0.1 M). To the resulting mixture was added *O*-benzoyl-*N*,*N*-dialkyl

hydroxylamine (1.00 equiv). The reaction vial was capped and stirred for 24 h with heating at the indicated temperature. Product yield was determined by GC comparison against *n*-dodecane as an internal standard.

Note on Preparation of XantPhosCuOtBu from XantPhos and $(CuOtBu)_4$:

In a glove box, a 1-dram reaction vial was charged with a stir bar. To the vial was added CuO*t*Bu tetramer (0.25 equiv),[30] XantPhos ligand (1.00 equiv) and solvent (0.1 M). The resulting mixture was allowed to stir at 45°C for 0.5 h. The mixture was used as a stock solution of the catalyst.

Amination of Aryl Boronic Esters using alkoxides

In a glove box, a dram vial was charged with a stir bar. To the vial was added CuO*t*Bu tetramer (0.025 equiv, 1.7 mg, 0.0125 mmol), xantphos (0.025 equiv, 7.2 mg, 0.0125 mmol), and toluene (100 µL). After stirring for 30 min at 25 °C, the mixture was transferred to a dram vial containing the boronic ester (1.20 equiv, 0.600 mmol), LiO*t*Bu (1.00 equiv, 40.0 mg, 0.500 mmol), *O*-benzoyl-*N*,*N*-dialkyl hydroxylamine (1.00 equiv, 0.500 mmol), and isooctane (300 µL). An additional 100 µL of isooctane was used to rinse the dram vial containing the catalyst into the reaction vial. The mixture was allowed to stir at the specified temperature until complete conversion of the hydroxylamine by TLC. The mixture was then diluted in dichloromethane (2 mL), and filtered through a silica plug using successively dichloromethane (5 mL) and then diethyl ether (5 mL) as an eluent. The solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography or ion exchange chromatography.

Amination of Aryl Boronic Esters using CsF

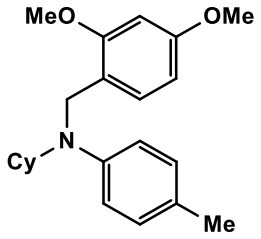
In a glove box, a dram vial was charged with a stir bar. To the vial was added CuO*t*Bu tetramer (0.025 equiv, 1.7 mg, 0.0125 mmol), xantphos (0.025 equiv, 7.2 mg, 0.0125 mmol), and toluene (100 µL). After stirring for 30 min at 25 °C, the mixture was transferred to a dram vial containing the boronic ester (1.20 equiv, 0.600 mmol), CsF (5.00 equiv, 379.7 mg, 2.500 mmol), *O*-benzoyl-*N*,*N*-dialkyl hydroxylamine (1.00 equiv, 0.500 mmol), and toluene (400 µL). The mixture was allowed to stir at 60 °C for 72 h. The mixture was then diluted in dichloromethane (2 mL), and filtered through a silica plug using successively dichloromethane (5 mL) and then diethyl ether (5 mL) as an eluent. The solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography.

Stoichiometric Reactions of Organocopper Complexes

All reactions were performed in a glove box. A 1-dram vial was charged with a stir bar. To the vial was added *O*-benzoyl-*N*,*N*-diisopropylhydroxylamine (1.00 equiv, 0.100 mmol, 22.1 mg), 1,3,5-trimethoxybenzene, and toluene (0.2 mL). To a shell vial was added IMesCu-tol[31] (1.00 equiv, 0.100 mmol, 45.9 mg) and toluene (0.2 mL). This solution was then added over 1 min to the stirred solution of *O*-benzoyl-*N*,*N*-diisopropylhydroxylamine and the shell vial rinsed with toluene (0.1 mL). The reaction vial was capped and stirred at 25 °C. Yield of *N*,*N*-diisopropyl-4-methylaniline was determined by GC using 1,3,5-trimethoxybenzene as an internal standard. The reaction was completed within 1 h. This complex was also substituted for IMesCuO*t*Bu as a catalyst in a reaction using *O*-benzoyl-*N*,*N*-diisopropyl hydroxylamine and tolyl boronic ester under the conditions described

(Table S1, Entry 15). After 24 h reaction time, an 82% yield of product was obtaine

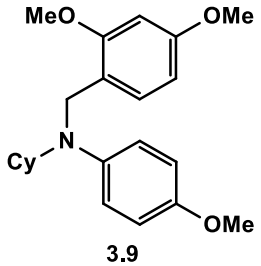
3.4.c. Characterization



3.8

4-methyl-N-cyclohexyl-N-(1-(2,4-dimethoxyphenyl)methan-1-yl)aniline

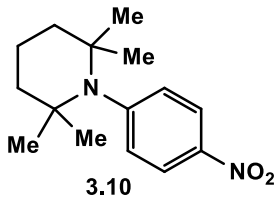
Compound was isolated as a white powder (150.0 mg, 97% yield) after purification by silica gel column chromatography (0 → 15% Et_2O/hexanes). ^1H NMR (500 MHz, C_6D_6) δ 7.20 (s, 1H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.80 (t, *J* = 8.2 Hz, 4H), 4.24 (s, 3H), 3.72 – 3.56 (m, 1H), 3.32 (s, 3H), 2.20 (s, 3H), 1.88 – 1.81 (m, 2H), 1.64 – 1.55 (m, 2H), 1.48 (d, *J* = 12.5 Hz, 1H), 1.17 (dt, *J* = 17.9, 9.6 Hz, 4H), 0.96 – 0.83 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.26 (s), 147.23 (s), 133.17 (s), 129.73 (s), 127.44 (s), 125.44 (s), 113.85 (s), 113.37 (s), 77.41 (s), 57.60 (s), 55.36 (s), 48.96 (s), 30.56 (s), 26.33 (s), 26.08 (s), 20.28 (s). HRMS calculated for $[M]^+$ 309.2089, found 309.2084. FTIR (neat, cm^{-1}): 3005(m), 2928(w), 1421(m), 1363(s), 1223(s).



3.9

4-methoxy-N-cyclohexyl-N-(1-(2,4-dimethoxyphenyl)methan-1-yl)aniline

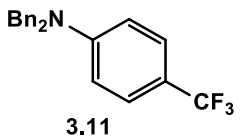
Compound was isolated as a colorless oil (151.5 mg, 85% yield) after purification by silica gel column chromatography (0 → 20% EA in hexanes). ^{1}H NMR (300 MHz, C_6D_6) δ 7.40 (d, *J* = 8.6 Hz, 1H), 6.90 – 6.77 (m, 4H), 6.53 (d, *J* = 2.3 Hz, 1H), 6.37 (dd, *J* = 8.3, 2.3 Hz, 1H), 4.54 (s, 2H), 3.68 – 3.55 (m, 1H), 3.40 (s, 3H), 3.38 (s, 3H), 3.37 (s, 3H), 1.93 – 1.87 (m, 2H), 1.64 – 1.55 (m, 2H), 1.46 (d, *J* = 12.5 Hz, 1H), 1.21 (dt, *J* = 17.9, 9.6 Hz, 4H), 0.95 – 0.80 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 157.4, 151.0, 144.1, 128.3, 121.1, 114.8, 114.2, 103.6, 98.2, 57.8, 55.9, 55.4, 55.3, 44.8, 30.3, 26.3, 26.1. HRMS calculated for $[M]^+$ 355.2151, found 355.2142. FTIR (neat, cm^{-1}): 2932(m), 2853(m), 1510(s), 1242(m), 1041(m).



3.10

2,2,6,6-tetramethyl-1-(4-nitrophenyl)piperidine

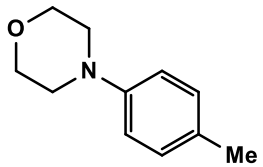
Compound was isolated as a yellow oil (114.3 mg, 87% yield) after purification by silica gel column chromatography (100% hexanes over 2CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 9.0 Hz, 2H), 1.74 (m, 2H), 1.67 – 1.46 (m, 4H), 1.03 (s, 12H).^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 145.7, 134.8, 123.2, 54.7, 42.1, 29.8, 18.3. HRMS calculated for $[M+H]^+$ 263.1761, found 263.1759. FTIR (neat, cm^{-1}): 3085(w), 2968(s), 2869(m), 1586(s), 1345(s), 1277(s), 1174(m), 1130(s), 1036(m),



3.11

N,N-dibenzyl-4-trifluoromethylaniline

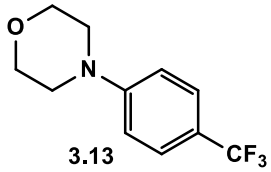
Compound was isolated as a white powder (148.9 mg, 87% yield) after purification by silica gel column chromatography (0 → 5% Et_2O/hexanes). ^1H NMR (500 MHz, C_6D_6) δ 7.28 (d, *J* = 8.6 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 4H), 7.08 (d, *J* = 7.1 Hz, 2H), 6.92 (d, *J* = 7.4 Hz, 4H), 6.40 (d, *J* = 8.7 Hz, 2H), 4.15 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 137.6, 129.0, 127.4, 125.1, (q, J = 270.3 Hz), 126.7, 126.2(q, J = 3.9 Hz), 118.4 (q, J = 32.7 Hz), 111.68 (s), 54.31 (s). ESI-MS calculated for $[M-H]^-$ 340.1, found 340.2.



3.12

4-(4-methylphenyl)morpholine

Compound was isolated as a white powder (78.9 mg, 89% yield) after purification by silica gel column chromatography (0 → 20% Et_2O/hexanes). ^1H NMR (300 MHz, C_6D_6) δ 7.13 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2H), 3.76 – 3.63 (m, 4H), 2.92 – 2.78 (m, 4H), 2.29 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 129.8, 129.7, 116.2, 67.1, 50.1, 20.5. ESI-MS calculated for $[M+H]^+$ 178.3, found 178.2

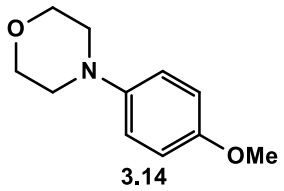


3.13

4-(4-trifluoromethylphenyl)morpholine

Compound was isolated as a white powder (105.0 mg, 91% yield) after purification by silica gel column chromatography (0 → 30% Et_2O/hexanes). ^1H NMR (300 MHz, C_6D_6)

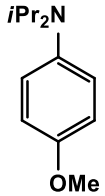
δ 7.41 (d, *J* = 8.7 Hz, 2H), 6.35 (d, *J* = 8.7 Hz, 2H), 3.55 – 3.31 (m, 4H), 2.73 – 2.45 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 128.7 (q, J = 269.1 Hz), 126.6 (q, *J* = 3.8 Hz), 120.80 (q, *J* = 13.3 Hz), 114.43 (s), 66.76 (s), 48.27 (s). ESI-MS calculated for $[M+H]^+$ 232.1, found 232.1.



3.14

4-(4-Methoxyphenyl)morpholine

Compound was isolated as a pink powder (85.4 mg, 88% yield) after purification by silica gel column chromatography (0 → 30% Et_2O/hexanes). ^{1}H NMR (300 MHz, C_6D_6) δ 6.87 (d, *J* = 8.5 Hz, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 3.72 – 3.53 (m, 4H), 3.39 (s, 3H), 2.87 – 2.59 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 145.8, 117.9, 114.6, 67.2, 55.7, 50.9. ESI-MS calculated for $[M+H]^+$ 194.1, found 194.1.

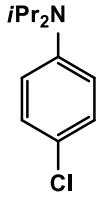


3.15

N,N-diisopropyl-4-methoxyaniline

Compound was isolated as a yellow oil (105.6 mg, 85% yield) after purification by ion exchange chromatography. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 6.94 (d, *J* = 9.1 Hz, 2H), 6.77 (d, *J* = 9.1 Hz, 2H), 3.75 (s, 3H), 3.60 – 3.46 (m, 2H), 1.02 (d, *J* = 6.5 Hz, 12H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 140.6, 127.6, 113.4, 55.5, 48.6, 21.4. HRMS

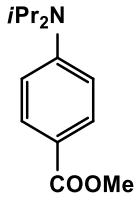
calculated for $[M]^+$ 207.1622, found 207.1619. FTIR (neat, cm^{-1}): 3037(m), 2971(s), 1464(m), 1359(m), 1286(m), 1241(s).



3.16

4-chloro-N,N-diisopropylaniline

Compound was isolated as a colorless oil (870.4 mg, 82% yield) after purification by silica gel column chromatography (0 → 5% Et_2O/hexanes over 7 CV). ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 3.73 (sept, *J* = 6.7 Hz, 2H), 1.19 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 128.3, 123.1, 120.4, 47.7, 21.3. HRMS calculated for $[M+H]^+$ 212.1206, found 212.1213. FTIR (neat, cm^{-1}): 3051(m), 2972(s), 1595(m), 1499(s), 1265(s), 740(s).

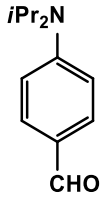


3.17

methyl 4-(diisopropylamino)benzoate

Compound was isolated as a white solid (104.8 mg, 89% yield) after purification by silica gel column chromatography (0 → 10% ethyl acetate/hexanes over 7 CV). ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 9.2 Hz, 2H), 6.77 (d, *J* = 9.2 Hz, 2H), 4.00 – 3.86 (m, 2H), 3.84 (s, 3H), 1.30 (d, *J* = 6.9 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7,

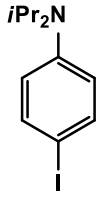
152.3, 131.1, 117.1, 114.5, 51.7, 48.0, 21.1. HRMS calculated for $[M+H]^+$ 236.1652, found 236.1646. FTIR (neat, cm^{-1}): 2971(s), 2875(m), 2251(m), 1705(s), 1605(s), 1434(s), 1278(s).



3.18

4-(diisopropylamino)benzaldehyde

Compound was isolated as a yellow oil (106.0 mg, 94% yield) after purification by silica gel column chromatography (0 → 10% ethyl acetate/hexanes over 6 CV). ^1H NMR (300 MHz, CD_2Cl_2) δ 9.67 (s, 1H), 7.64 (d, J = 9.1 Hz, 2H), 6.86 (d, J = 9.1 Hz, 2H), 4.00 (hept, J = 6.8 Hz, 2H), 1.33 (d, J = 6.9 Hz, 12H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 190.1, 153.6, 131.7, 125.5, 114.6, 48.3, 21.1. HRMS calculated for $[M+H]^+$ 206.1545, found 206.1543. FTIR (neat, cm^{-1}): 2972(s), 2930(s), 2872(m), 2853(m), 1867(w), 1681(s), 1423(s).

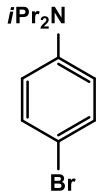


3.19

4-iodo-N,N-diisopropylaniline

Compound was isolated as a white-pink solid (125.0 mg, 83% yield) after purification by silica gel column chromatography (0 → 10% ethyl acetate/hexanes over 8

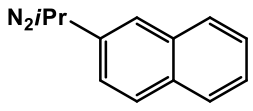
CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 9.0 Hz, 2H), 6.63 (d, *J* = 9.0 Hz, 2H), 3.76 (hept, *J* = 6.8 Hz, 2H), 1.21 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 148.5, 137.6, 120.4, 78.4, 48.1, 21.5. ESI-MS calculated for $[M]^+$ 303.0, found 303.0. FTIR (neat, cm^{-1}): 3047(w), 2970(s), 2873(m), 2611(w), 1582(s), 1495(s), 1367(s), 1328(s), 1288(s), 591(w), 553(m).



3.20

4-bromo-N,N-diisopropylaniline

Compound was isolated as off white solid (107.6 mg, 84% yield) after purification by silica gel column chromatography (0 → 10% ethyl acetate/hexanes over 6 CV). ^{1}H NMR (300 MHz, C_6D_6) δ 7.27 (d, *J* = 9.1 Hz, 2H), 6.51 (d, *J* = 9.1 Hz, 2H), 3.32 (hept, *J* = 6.7 Hz, 2H), 0.91 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.3, 131.3, 120.6, 110.2, 47.8, 21.4. ESI-MS calculated for $[M+H]^+$ 256.1, found 257. FTIR (neat, cm^{-1}): 3038(w), 2970(s), 2872(m), 2612(w), 1588(s), 1496(s), 1367(s), 1287(s), 732(m).

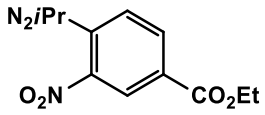


3.21

N,N-diisopropylnaphthalen-2-amine

Compound was isolated as a yellow oil (94.9 mg, 84% yield) after purification by ion exchange chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.57 (m, 3H), 7.46

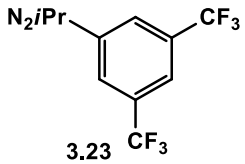
– 7.33 (m, 1H), 7.32 – 7.17 (m, 2H), 7.16 (d, *J* = 2.1 Hz, 1H), 3.90 (hept, *J* = 6.6 Hz, 2H), 1.30 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 147.0, 135.4, 128.0, 127.9, 127.7, 126.7, 126.3, 122.7, 122.1, 112.8, 48.3, 21.8. HRMS calculated for $[M]^+$ 227.1671, found 227.2675. FTIR (neat, cm^{-1}): 3053(s), 2970(s), 1823(w), 1627(s), 1388(s), 1283(s), 1236(s), 1147(s), 1016(m).



3.22

ethyl 4-(diisopropylamino)-3-nitrobenzoate

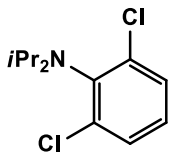
Compound was isolated as an orange oil (129.0 mg, 88% yield) after purification by silica gel column chromatography (0 → 15% ethyl acetate/hexanes over 9 CV). ^{1}H NMR (300 MHz, C_6D_6) δ 8.18 (d, *J* = 2.1 Hz, 1H), 7.91 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.22 (hept, *J* = 6.6 Hz, 2H), 0.96 (t, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR (126 MHz, CD_3CN) δ 165.4, 150.4, 146.6, 132.4, 130.2, 126.8, 125.7, 62.2, 51.4, 21.7, 14.5. HRMS calculated for $[M+H]^+$ 295.1655, found 295.1660. FTIR (neat, cm^{-1}): 3690(w), 3053(s), 2985(s), 2684(w), 1719(m), 1610(m), 1367(w).



3.23

N,N-diisopropyl-3,5-bis(trifluoromethyl)aniline

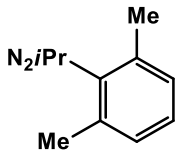
Compound was isolated as a yellow oil (133.6 mg, 85% yield) after purification by silica gel column chromatography (0 → 5% ethyl acetate/hexanes over 9 CV). ^{1}H NMR (300 MHz, C_6D_6) δ 7.28 (s, 1H), 7.11 (s, 2H), 3.26 (hept, *J* = 6.8 Hz, 2H), 0.80 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 149.5, 132.2 (q, *J* = 32.2 Hz), 124.7 (q, *J* = 272.4 Hz), 115.5, 109.3 (m), 48.5, 21.3. ESI-MS calculated for $[M]^+$ 313.2, found 313.1. FTIR (neat, cm^{-1}): 3054(m), 2976(s), 1615(s), 1550(w), 1488(s), 1429(s), 1361(s), 1276(s), 1179(s), 1130(s).



3.24

2,6-dichloro-N,N-diisopropylaniline

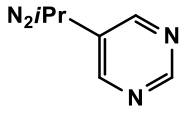
Compound was isolated as a white solid (103.7 mg, 84% yield) after purification by silica gel column chromatography (100% hexanes over 1 CV). ^{1}H NMR (500 MHz, C_6D_6) δ = 7.01 (d, *J*= 8.0, 2H), 6.41 (t, *J* = 8.0, 1H), 3.75 – 3.62 (hept, *J* = 6.5 Hz, 2H), 1.11 (d, *J* = 6.5, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ = 144.2, 140.9, 128.5, 126.9, 50.0, 22.9. ESI-MS calculated for $[M+H]^+$ 246.2, found 246.2. FTIR (neat, cm^{-1}): 3052(m), 2971(s), 1429(s), 1264(s), 1192(m), 743(s).



3.25

N,N-diisopropyl-2,6-dimethylaniline

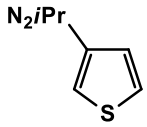
Compound was isolated as a yellow oil (96.7 mg, 94% yield) after purification by ion exchange chromatography. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.02 – 6.96 (m, 2H), 6.96 – 6.90 (m, 1H), 3.55 (hept, *J* = 6.6 Hz, 2H), 2.26 (s, 6H), 1.02 (d, *J* = 6.4 Hz, 12H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 147.0, 141.4, 128.3, 125.4, 50.2, 23.7, 20.7. ESI-MS calculated for $[M+H]^+$ 206.2, found 206.1. FTIR (neat, cm^{-1}): 4197(w), 3054(s), 2987(s), 2855(m), 2855(w), 2305(m), 1422(m), 1266(s),



3.26

N,N-diisopropylpyrimidin-5-amine

Compound was isolated as a yellow solid (77.8 mg, 87% yield) after purification by silica gel column chromatography (0 → 30% ethyl acetate/hexanes over 12 CV). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.45 (s, 1H), 8.29 (s, 2H), 3.84 (hept, *J* = 6.8 Hz, 2H), 1.27 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (126 MHz, CD_3CN) δ 147.9, 144.6, 48.0, 21.0. ESI-MS calculated for $[M+H]^+$ 180.1, found 180.1. FTIR (neat, cm^{-1} 3052(s), 2985(s), 2886(m), 2688(w), 1367(w), 1264(s).

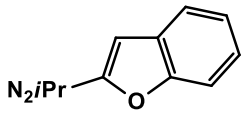


3.27

N,N-diisopropylthiophen-3-amine

Compound was isolated as a yellow brown oil (80.8 mg, 88% yield) after purification by silica gel column chromatography (0 → 10% diethyl ether/hexanes over 6

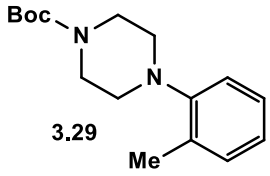
CV). ^{1}H NMR (300 MHz, C_6D_6) δ 6.89 (dd, *J* = 5.2, 3.1 Hz, 1H), 6.72 (dd, *J* = 5.2, 1.5 Hz, 1H), 6.06 (dd, *J* = 3.1, 1.5 Hz, 1H), 3.34 (hept, *J* = 6.7 Hz, 2H), 0.99 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (126 MHz, CD_3CN) δ 148.9, 124.2, 124.0, 102.6, 49.2, 21.4. ESI-MS calculated for $[M+H]^+$ 183.1, found 183.1. FTIR (neat, cm^{-1}): 3052(s), 2971(s), 2871(m), 1537(s), 1264(s), 1126(m).



3.28

N,N-diisopropylbenzofuran-2-amine

Compound was isolated as a light orange solid (95.0 mg, 87% yield) after purification by silica gel column chromatography (0 → 5% ethyl acetate/hexanes over 6 CV). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.20 (d, *J* = 7.6 Hz, 2H), 7.03 (td, *J* = 7.6, 1.0 Hz, 1H), 6.95 – 6.82 (m, 1H), 5.34 (s, 1H), 3.76 (hept, *J* = 6.7 Hz, 2H), 1.30 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (126 MHz, CD_3CN) δ 161.5, 151.0, 132.3, 123.5, 119.9, 118.0, 109.9, 79.7, 49.1, 21.4. ESI-MS calculated for $[M]^+$ 217.2, found 217.1. FTIR (neat, cm^{-1}): 3853(s), 2984(s), 2305(m), 1581(s), 1368(m), 1264(s), 1130(m).

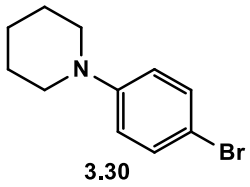


3.29

tertbutyl 4-(o-tolyl)piperazine-1-carboxylate

Compound was isolated as a yellow solid (105.2 mg, 76% yield) after purification by silica gel column chromatography (0 → 10% ethyl acetate/hexanes over 6 CV). ^{1}H NMR

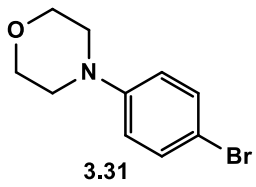
(300 MHz, MeOD) δ 7.25 – 7.11 (m, 2H), 7.03 – 6.77 (m, 2H), 3.61 – 3.54 (m, 4H), 2.98 – 2.56 (m, 4H), 2.31 (s, 3H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, CD_3CN) δ 155.5, 152.5, 133.5, 131.9, 127.6, 124.3, 120.1, 80.0, 52.6, 28.5, 21.8, 17.9. ESI-MS calculated for $[M]^+$ 276.2, found 276,0. FTIR (neat, cm^{-1}): 3053(s), 2984(m), 2053(m), 1685(m), 1366(m), 1265(s), 1171(m).



3.30

1-(4-bromophenyl)piperidine

Compound was isolated as a white solid (96.2 mg, 80% yield) after purification by ion exchange chromatography. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.30 (d, *J* = 9.1 Hz, 2H), 6.79 (d, *J* = 9.1 Hz, 2H), 3.15 – 3.08 (m, 4H), 1.71 – 1.64 (m, 4H), 1.62 – 1.54 (m, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 151.9, 132.2, 118.3, 111.0, 50.8, 26.3, 24.8. ESI-MS calculated for $[M]^+$ 240.1, found 240.0. FTIR (neat, cm^{-1}): 3053(s), 2986(s), 2940(s), 1856(m), 2827(m), 2305(s), 1588(m), 1421(s), 1264(s), 1130(m), 895(s).

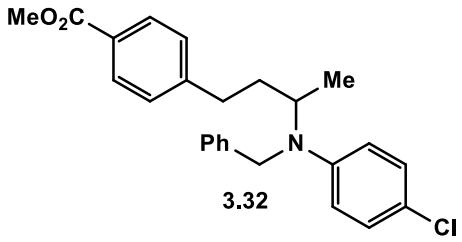


3.31

4-(4-bromophenyl)morpholine

Compound was isolated as a white solid (98.1 mg, 81% yield) after purification by silica gel column chromatography (0 → 17% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.35 (d, *J* = 9.1 Hz, 2H), 6.79 (d, *J* = 9.1 Hz, 2H), 3.91 – 3.66 (m, 4H),

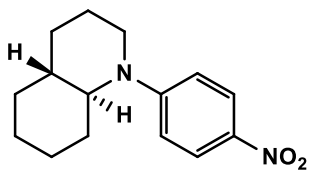
3.21 – 2.94 (m, 4H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 151.1, 132.4, 117.7, 112.2, 67.3, 49.6. ESI-MS calculated for $[M+H]^+$ 242.1, found 242.9. FTIR (neat, cm^{-1}): 3684(w), 3053(s), 2986(s), 1494(m), 1265(s), 522(w).



3.32

methyl 4-(3-(benzyl(4-chlorophenyl)amino)butyl)benzoate

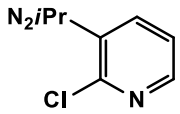
Compound was isolated as a colorless oil (178.2 mg, 87% yield) after purification by silica gel column chromatography (0 → 20% ethyl acetate/hexanes over 8 CV), then ion exchange chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.16 (m, 5H), 7.11 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 9.2 Hz, 2H), 6.55 (d, *J* = 9.1 Hz, 2H), 4.38 (s, 2H), 3.98 (dq, *J* = 13.6, 6.7 Hz, 1H), 3.89 (s, 3H), 2.69 (t, *J* = 7.9 Hz, 2H), 1.99 – 1.91 (m, 1H), 1.83 – 1.74 (m, 1H), 1.21 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 147.9, 147.3, 139.6, 129.8, 128.9, 128.6, 128.4, 128.1, 126.8, 126.5, 121.7, 115.2, 53.6, 52.0, 48.4, 36.2, 33.4, 17.8. HRMS calculated for $[M+H]^+$ 408.1730, found 408.1738. FTIR (neat, cm^{-1}): 3053(m), 2986(w), 1718(s), 1496(m), 1265(s), 738(s).



3.33

(4aR,8aS)-1-(4-nitrophenyl)decahydroquinoline

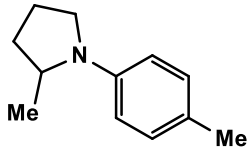
Compound was isolated as a yellow solid (123.7 mg, 95% yield) after purification by silica gel column chromatography (0 → 4% ethyl acetate/hexanes over 4 CV). ^{1}H NMR (300 MHz, C_6D_6) δ 8.03 (d, *J* = 9.3 Hz, 2H), 6.32 (d, *J* = 9.3 Hz, 2H), 2.94 – 2.92 (m, 2H), 2.84 – 2.58 (m, 1H), 2.34 (td, *J* = 10.6, 3.0 Hz, 1H), 1.77 – 1.22 (m, 6H), 1.22 – 0.95 (m, 3H), 0.95 – 0.63 (m, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 155.5, 138.2, 126.2, 114.5, 65.0, 44.1, 40.1, 33.7, 30.5, 27.7, 26.8, 25.8, 23.5. ESI-MS calculated for $[M+H]^+$ 260.1, found 260.1. FTIR (neat, cm^{-1}): 3053(m), 2986(m), 2934(m), 1594(m), 1421(m), 1312(m), 1264(s), 1113(w), 895(m), 705(s).



3.34

2-chloro-N,N-diisopropylpyridin-3-amine

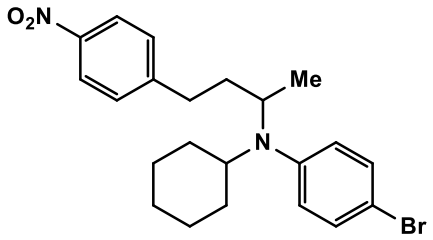
Compound was isolated as a yellow oil (82.4 mg, 78% yield) after purification by silica gel column chromatography (0 → 10% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (500 MHz, C_6D_6) δ 7.98 (dd, *J* = 4.5, 1.7 Hz, 1H), 7.04 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.51 (dd, *J* = 7.8, 4.6 Hz, 1H), 3.28 (hept, *J* = 6.6 Hz, 2H), 0.89 (d, *J* = 6.5 Hz, 12H). ^{13}C NMR (126 MHz, CD_3CN) δ 155.2, 146.7, 142.9, 141.2, 123.5, 51.0, 21.5. ESI-MS calculated for $[M+H]^+$ 213.1, found 213.0. FTIR (neat, cm^{-1}): 3053(s), 2974(s), 1443(m), 1398(s), 1265(s).



3.35

2-methyl-1-(p-tolyl)pyrrolidine

Compound was isolated as a colorless oil (79.1 mg, 90% yield) after purification by silica gel column chromatography (0 → 5% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (300 MHz, C_6D_6) δ 7.13 (d, *J* = 8.7 Hz, 2H), 6.56 (d, *J* = 8.7 Hz, 2H), 3.80 – 3.49 (m, 1H), 3.13 (dt, *J* = 12.4, 6.1 Hz, 1H), 2.88 (dt, *J* = 14.6, 6.9 Hz, 1H), 2.28 (s, 3H), 1.74 – 1.57 (m, 2H), 1.55 – 1.42 (m, 1H), 1.32 – 1.18 (m, 1H), 0.98 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.4, 129.7, 124.3, 112.0, 53.8, 48.5, 33.2, 23.4, 20.3, 19.6. HRMS calculated for $[M+H]^+$ 176.1439, found 176.1441. FTIR (neat, cm^{-1}): 3053(m), 2985(w), 1521(w), 1265(s).

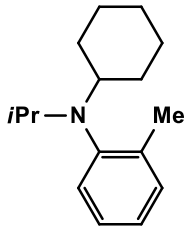


3.36

4-bromo-N-cyclohexyl-N-(4-(4-nitrophenyl)butan-2-yl)aniline

Compound was isolated as a yellow oil (86.8 mg, 80% yield) after purification by silica gel column chromatography (0 → 15% ethyl acetate/hexanes over 9 CV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.9 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.66 (d, *J* = 9.0 Hz, 2H), 3.48 – 3.39 (m, 1H), 3.19 – 3.09 (m, 1H), 2.59 (t, *J* = 8.1 Hz, 2H), 1.92 – 1.82 (m, 1H), 1.79 – 1.63 (m, 5H), 1.59 – 1.52 (m, 1H), 1.42 – 1.35 (m, 2H), 1.25 – 1.14 (m, 5H), 1.05 – 0.95 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.2, 147.4, 146.4, 131.4, 129.1, 123.7, 121.0, 110.7, 58.7, 52.1, 37.2, 33.6, 32.8, 31.9, 26.3,

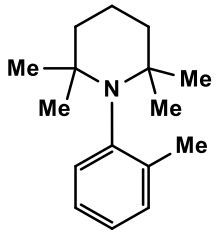
26.0, 25.9, 19.8. HRMS calculated for $[M+H]^+$ 431.1334, found 431.1342. FTIR (neat, cm^{-1}): 3053(m), 2988(w), 1420(w), 1267(s), 918(s).



3.37

N-cyclohexyl-N-isopropyl-2-methylaniline

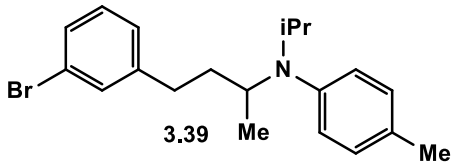
Compound was isolated as a yellow oil (110.0 mg, 95% yield) after purification by ion exchange chromatography. ^{1}H NMR (300 MHz, CD_3CN) δ 7.26 – 7.18 (m, 2H), 7.12 – 7.00 (m, 2H), 3.53 (hept, *J* = 6.8 Hz, 1H), 3.06 (tt, *J* = 10.7, 3.3 Hz, 1H), 2.14 (s, 3H), 1.90 – 1.80 (m, 2H), 1.74 – 1.59 (m, 2H), 1.59 – 1.48 (m, 1H), 1.37 – 1.10 (m, 2H), 1.04 (m, 3H), 0.94 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 147.5, 140.8, 130.7, 130.3, 125.8, 125.3, 59.4, 49.8, 32.1, 26.9, 26.5, 21.4, 19.4. ESI-MS calculated for $[M]^+$ 231.2, found 231.2. FTIR (neat, cm^{-1}): 3052(m), 2931(s), 1379(m), 1361(w), 1264(s), 1109(m), 1066(w).



3.38

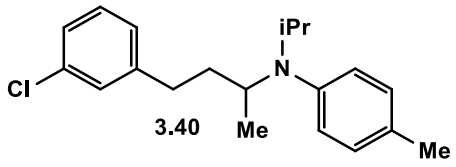
2,2,6,6-tetramethyl-1-(o-tolyl)piperidine

Compound was isolated as a yellow oil (102.9 mg, 89% yield) after purification by silica gel column chromatography (100% hexanes over 2 CV). ^{1}H NMR (300 MHz, C_6D_6) δ 7.34 – 7.27 (m, 1H), 7.21 (dd, *J* = 5.5, 3.8 Hz, 1H), 7.10 – 7.01 (m, 2H), 2.37 (s, 3H), 1.93 – 1.71 (m, 1H), 1.70 – 1.42 (m, 5H), 1.25 (s, 6H), 0.79 (s, 6H). ^{13}C NMR (75 MHz, C_6D_6) δ 145.9, 141.5, 132.4, 130.9, 125.8, 125.5, 55.3, 42.4, 32.0, 25.7, 19.9, 19.0. ESI-MS calculated for $[M]^+$ 231.2, found 231.2. FTIR (neat, cm^{-1}): 3053(s), 2971(s), 1486(m), 1349(m), 1265(s), 895(m).



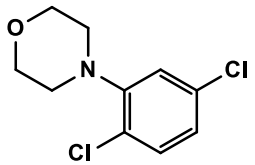
N-(4-(3-bromophenyl)butan-2-yl)-N-isopropyl-4-methylaniline

Compound was isolated as a colorless oil (166.3 mg, 92% yield) after purification by silica gel column chromatography (0 → 5% Et_2O/hexanes over 9 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.18 (m, 2H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.79 – 6.70 (m, 2H), 3.50 – 3.36 (m, 1H), 3.28 – 3.17 (m, 1H), 2.49 – 2.29 (m, 2H), 2.21 (s, 3H), 1.78 – 1.65 (m 1H), 1.47 – 1.34 (m, 1H), 1.16 – 0.91 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.7, 145.0, 131.5, 129.9, 129.1, 128.9, 128.7, 127.1, 122.5, 121.0, 52.2, 48.4, 37.7, 33.2, 22.6, 21.4, 20.6, 19.2. HRMS calculated for $[M+H]^+$ 360.1326, found 360.1325. FTIR (neat, cm^{-1}): 3047(w), 2968(m), 1514(m), 1265(s), 739(s).



N-(4-(3-chlorophenyl)butan-2-yl)-N-isopropyl-4-methylaniline

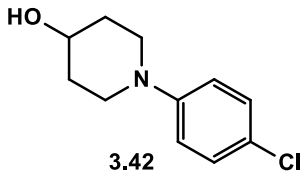
Compound was isolated as a colorless oil (128.9 mg, 81% yield) after purification by silica gel column chromatography (0 → 15% ethyl acetate/hexanes over 7 CV, then 0 → 5% Et_2O/hexanes over 7 CV. ^1H NMR (300 MHz, C_6D_6) δ 7.19 (s, 1H), 7.17 – 7.09 (m, 3H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.91 (t, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 3.52 (dq, *J* = 13.2, 6.6 Hz, 1H), 3.38 – 3.30 (m, 1H), 2.53 – 2.46 (m, 2H), 2.31 (s, 3H), 1.85 – 1.75 (m, 1H), 1.59 – 1.45 (m, 1H), 1.25 – 1.00 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.7, 144.7, 134.1, 129.5, 129.1, 128.7, 128.6, 126.6, 125.9, 121.0, 52.2, 48.4, 37.6, 33.2, 22.5, 21.5, 20.5, 19.1. ESI-MS calculated for $[M+H]^+$ 315.2, found 315.3. FTIR (neat, cm^{-1}): 3054(m), 2987(w), 1419(w), 1265(s), 741(s).



3.41

4-(2,5-dichlorophenyl)morpholine

Compound was isolated as a colorless oil (105.8 mg, 91% yield) after purification by silica gel column chromatography (0 → 5% Et_2O/hexanes over 7 CV). ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 2.2 Hz, 1H), 6.61 (dd, *J* = 8.4, 2.1 Hz, 1H), 3.64 – 3.43 (m, 4H), 2.60 – 2.36 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.0, 133.2, 131.5, 127.0, 123.7, 120.8, 67.0, 51.5. ESI-MS calculated for $[M+H]^+$ 232.0, found 232.1. FTIR (neat, cm^{-1}): 3054(s), 2986(m), 1421(w), 1265(s), 736(s).



3.42

4-hydroxy-1-(4-chlorophenyl)piperidine

Compound was isolated as white needles (79.2 mg, 75% yield) after purification by silica gel column chromatography (40 → 70% Et_2O/hexanes over 7 CV). ^1H NMR (300 MHz, C_6D_6) δ 7.13 (d, *J* = 9.1 Hz, 2H), 6.43 (d, *J* = 9.0 Hz, 2H), 3.29 (m, 1H), 3.15 – 2.97 (m, 2H), 2.39 (ddd, *J* = 12.6, 9.6, 3.2 Hz, 2H), 1.61 – 1.41 (m, 2H), 1.36 – 1.21 (m, 2H), 0.66 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 129.1, 124.4, 117.8, 67.8, 47.4, 34.1. HRMS calculated for $[M+H]^+$ 212.0842, found 212.0846. FTIR (neat, cm^{-1}): 3404(br), 2951(m), 1635(br), 1495(s), 1041(s), 733(m)

Section 5: References

1. Carey, J. S.; Laffan, D.; Thomas, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

2. Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599.

3. For selected seminal publications see: (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382. (b) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1995**, *34*, 1348. (c) Louie, J. Hartwig, J. F. *Tetrahedron Lett*. **1995**, *36*, 3609.

4. For recent reviews of palladium-catalyzed reactions see: (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338. (b) Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 57. (c). Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534.

5. For example, the 20 % yield reported by Sattar et al. is the highest yield reported for the coupling of aryl halides with diisopropylamine. Iyer, S.; Kulkarni, G. M.; Ramesh, C.; Sattar, A. K. *Indian J. Chem. Sect. B*, **2005**, *44B*, 1894.

6. Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 2716.

7. Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680.

8. (a) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521. (b) Berman, A. M. Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219.

9. Del, A. V.; Dubbaka, S. R.; Krasovsky, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 7838.

10. For other catalytic methods for electrophilic amination of organometallic nucleophiles see: (a) Barker, T. J.; Jarvo, E. R. *Synthesis* **2011**, 3954. (b) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc*. **2009**, *131*, 15598. (c) Barker, T. J.; Jarvo, E. R. *Angew. Chem. Int. Ed*. **2011**, *50*, 8325. (d) Yu, Y.; Srogl, J.; Liebeskind, L. S. *Org. Lett*. **2004**, *6*, 2631. (e) Zhang, Z.; Yu, Z.; Liebeskind, L. S. *Org. Lett*. **2008**, *10*, 3005. (f) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc*. **2008**, *130*, 6918.

11. Hall, D. G. *Boronic Acids* **2005,** Wiley-VCH: Weinheim, Germany.

12. He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 6414.

13. Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933.

14. Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M.; Chan, D. M. T.; Combs, A.; *Tetrahedron Lett.* **1998**, *39*, 2941.

15. Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937.

16. (a) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397. (b) Yu, X. Q.; Yamamoto, Y.; Miyaura, N. *Chem. Asian J*. **2008**, *3*, 1517.

17. Batey et al. (ref. 16a) have shown that the use of hindered amines, results in lower yields of the coupling products (37% yield in a reaction with *tert*-butyl amine and phenyl boronic acid).

18. Rucker, R. P.; Whittaker, A, M.; Dang, H.; Lalic, G. *J. Am. Chem. Soc.* **2012**, *134*, 6571-6574.

19. Rucker, R. P.; Whittaker, A, M.; Dang, H.; Lalic, G. *Angew. Chem. Int. Ed.* **2012,** *51*, 3953-3957.

20. Uehling, M. R.; Marionni, S. T.; Lalic, G. *Org. Lett.* **2012**, *14*, 362. (c) Whittaker, A. M.; Rucker, R. P.; Lalic, G. *Org. Lett.* **2010**, *12*, 3216. Also see references 23d and 23e.

21. See ref 18

22. (a) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116. (b) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936. (c) Shintani, R.; Takatsu, K.; Hayashi, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 3735.

23. (a) Dang, L.; Lin, Z.; Marder, T. B. *Organometallics* **2010**, *29*, 917. (b) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687. (c) Tomita, D.; Kanai, M.; Shibasaki, M. *Chem. Asian J.* **2006**, *1*, 161. (d) Ohishi, T.; Nishiura, M.; Hou, Z. *Angew. Chem. Int. Ed.* **2008**, *47*, 5792. (e) Ohmiya, H.; Yokokawa, N.; Sawamura, M. *Org. Lett.* **2010**, *12*, 2438.

24. See ref 8

25. Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 3369.

26. See ref 8

27. For selected examples that extended this work see: Zhu, C.; Li, G.; Ess, D. H.; Falck, J. R.; Kurti, L. *J. Am. Chem. Soc.* **2012,** *134*, 18253. (b) Xiao, Q.; Tian, L.; Tan, R.; Xia, Y.; Qiu, D.; Zhang, Y.; Wang, J. *Org. Lett.* **2012,** *14*, 4230. (c) Zhou, Y.; Xie, Y.; Yang, L.; Xie, P.; Huang, H. *Tetrahedron Lett.* **2013,** *54*, 2713.

28. See ref 8b.

29. Schnürch, M.; Holzweber, M.; Mihovilovic, M. D.; Stanetty, P. *Green. Chem.* **2007**, *9*, 139.

30. Lemmon, T. H.; Goeden, G. V.; Huffman, J. C.; Geerts, R. L.; Kaulton, K. G. *Inorg. Chem.* **1990**, *29*, 3680.

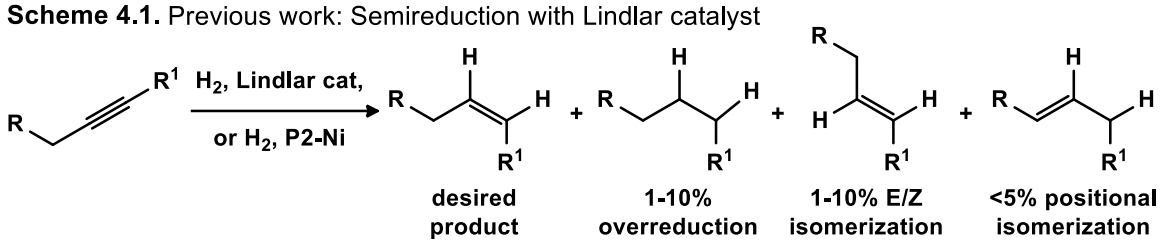
31. See ref 20

Chapter 4 – Monophasic Catalytic System for the Selective Semireduction of Alkynes

Section 1: Introduction

One of the most important transformations of alkynes is their semireduction to alkenes. This transformation is usually accomplished using Lindlar[1] or P2 nickel[2] catalysts. However, both catalysts have significant limitations. P2 nickel is not selective in reductions of terminal alkynes, and the catalyst has to be prepared fresh before each reaction.[3] Lindlar catalyst, on the other hand, induces E-Z isomerization[4] and further reduction of the alkene products,[5] and as result, strict monitoring of the reaction progress is necessary in order to minimize over-reduction and isomerization. Even when the reaction progress is carefully monitored, small amounts of alkane are formed (typically 1-10%) through a direct reduction of alkynes to alkanes, making purification of the desired alkenes challenging. Over-reduction is even more pronounced with terminal alkynes and with alkynes that adsorb well to the catalyst surface, such as arylacetylenes, diarylacetylenes, en-ynes, and alkynes containing polar functional groups.[6] In addition, undesirable reduction of other functional groups, such as nitro or aryliodo, often accompanies the reduction of alkynes. Finally, the notorious batch variability further complicates the use of Lindlar catalyst.[7]

Scheme 4.1. Previous work: Semireduction with Lindlar catalyst

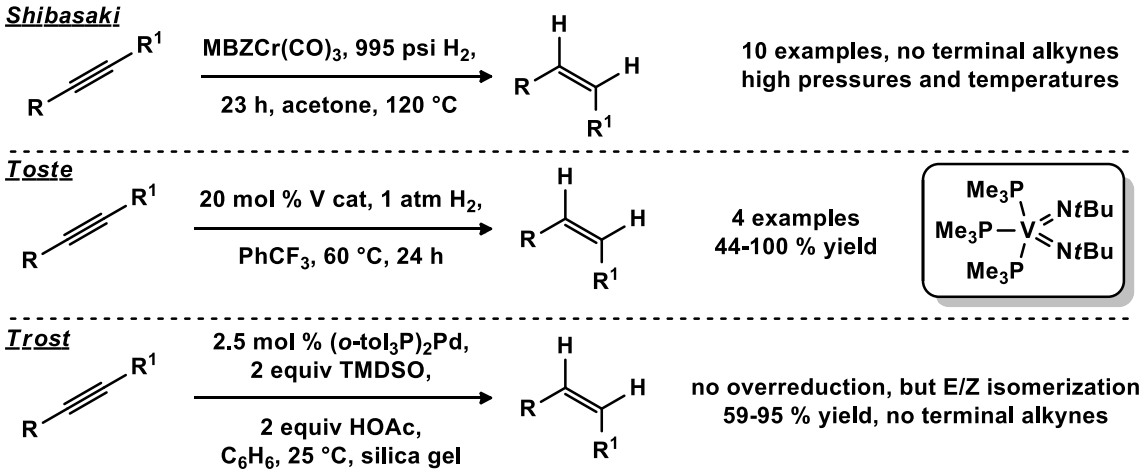


To address these problems, numerous attempts have been made at developing new catalysts. Most efforts have been devoted to controlling the reactivity of solid state catalysts by modifications of the catalyst surface.[8] Using this approach, significant progress has been made in developing catalysts for the reduction of arylacetylenes.[9] However, few reports also describe selective reduction of terminal alkynes,[10] which is still a major challenge.[11] Similarly, it is rare that catalysts are developed for the reduction of alkynes in the presence of nitro or aryl iodo groups.[12]

Considerable effort has also been devoted to the development of molecular catalysts to circumvent these limitations. Complexes of rhodium,[13] chromium,[14] palladium,[15] vanadium,[16] and other metals[17] have been explored as catalysts for the semireduction of alkynes. Although most homogenous catalysts developed so far are inferior to Lindlar, some show remarkable selectivity. For example, a palladium catalyst reported by Trost allows selective reduction of an alkyne in the presence of a nitro group, although low yields of the alkene products are often obtained.[18] Similarly, a chromium catalyst developed by Shibaskaki shows remarkable selectivity for the reduction of alkynes without over-reduction to alkanes.[19] Unfortunately, the high temperature and hydrogen pressure (120 °C, 1000 psi) required for this reaction make this catalyst impractical to use. The most notable progress on this topic has been achieved in

semireduction of aryl- and diaryl acetylenes using palladium[20] and copper complexes.[21] With these types of substrates, selectivities significantly higher than with Lindlar catalyst can be obtained.

Scheme 4.2. Previous work: Semireduction using homogeneous catalysis

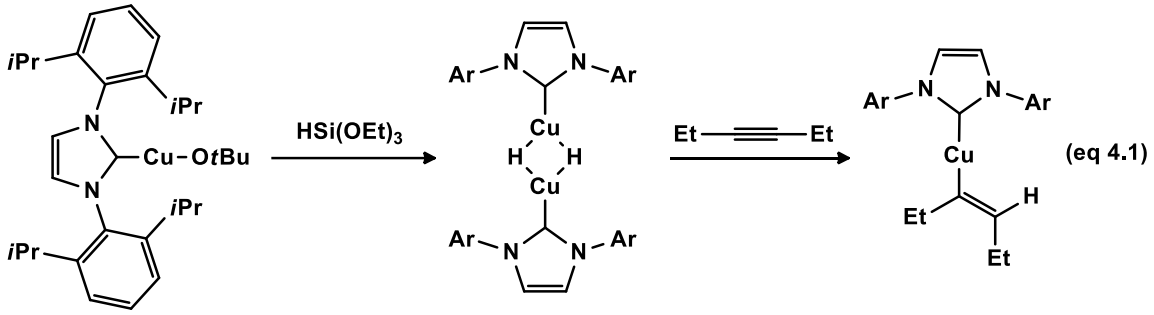


Overall, while significant progress has been made in developing both homogenous and heterogeneous catalysts for the semireduction of individual substrate classes, none of the catalysts developed so far offer a practical alternative to Lindlar catalyst in terms of substrate scope, selectivity, and the ease of use. As a result, and despite the problems associated with its use, Lindlar catalyst remains the reagent of choice for the semireduction of most alkynes.

Our approach to the development of a catalyst that would address problems encountered in reactions with Lindlar catalyst was inspired by Sadighi's report describing copper hydride formation by transmetalation with silane, and the stoichiometric hydrocupration of an alkyne using the isolated copper hydride complex (equation 4.1).[22] Prompted by these two stoichiometric reactions, we decided to explore a strategy for the

catalytic semireduction of alkynes that involves hydrocupration followed by protonation of the alkenyl copper intermediate.

Scheme 4.3. Hydrocupration of an alkyne using a silane

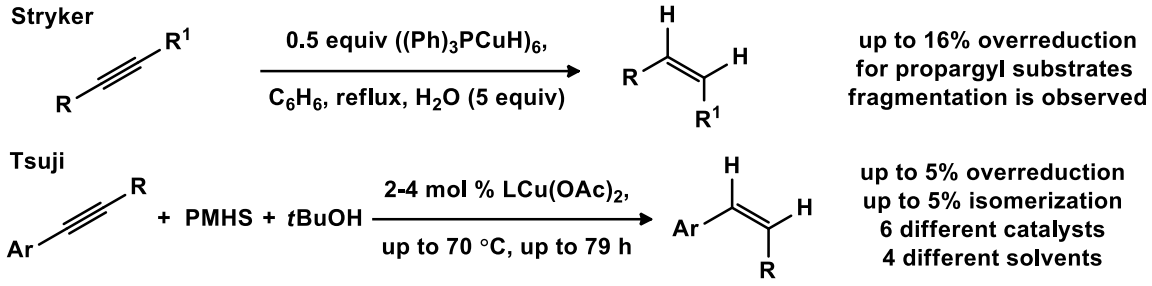


The most appealing aspect of this approach is that it is fundamentally different from the standard approach in which hydrogen is delivered by a metal dihydride intermediate through alkyne insertion and reductive elimination. Furthermore, hydrocupration has barely been explored in the context of semireduction of alkynes. Stryker has reported a stoichiometric reduction of alkynes using 0.5 equivalents of $((PPh_3)Cu\text{-}H)_6$ and water as the proton source.[23] In Stryker's report, over-reduction was a significant problem with most substrates, while derivatives of propargylic alcohols gave significant amount of allene products or fragmented products.

Earlier this year, the first report of a catalytic semireduction of alkynes involving copper hydride was reported.[24] Tsuji et al. have shown that copper alkoxide supported by a diphosphine ligand can be used as a catalyst in a highly selective semireduction of activated aryl and diaryl acetylenes. Unfortunately, this catalyst was ineffective in reductions of less reactive simple terminal and internal alkynes, which could only be reduced in the presence of NHC-based copper catalysts. With these substrates, yields

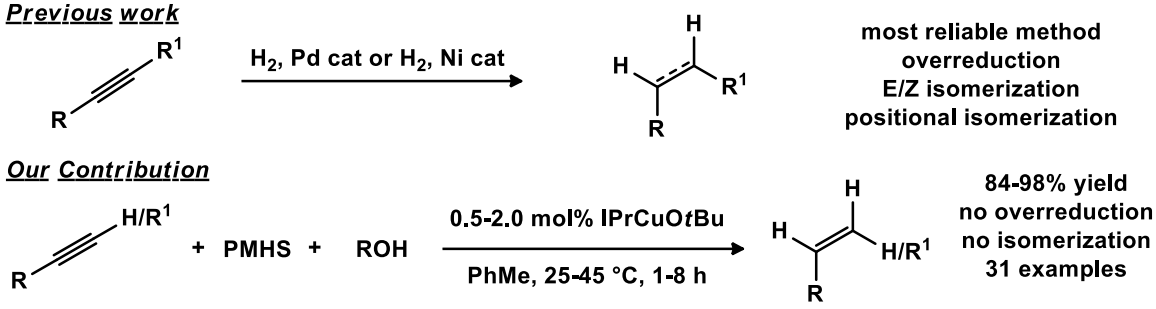
were relatively low, especially for internal alkynes (78% yield for reduction of 6-dodecyne). More importantly, for reduction of six simple unfunctionalized substrates (three internal and three terminal alkynes), three different catalysts and four sets of reaction conditions were used. The variety of conditions in Tsuji's reaction reflects the difficulties associated with the development of a general catalyst using an approach involving hydrocupration followed by protonation.

Scheme 4.4. Previous work: Copper hydride in alkyne semireduction



In this chapter, I provide a full account of our efforts that resulted in the development of a catalyst that offers a practical alternative to Lindlar and P2-nickel catalysts as a general reagent for the semireduction of both terminal and internal alkynes. Extensive studies of the major processes competing with the desired semireduction, and the optimization of the catalytic system based on this insight is discussed. The exploration of the reaction scope and an extension of this reaction to gram scale reactions outside of a glove box will also be described. Finally, the results of our studies of the reaction mechanism including catalyst resting state determination, and deuterium labelling experiments will be discussed.

Scheme 4.5. Summary: Catalytic semireduction of alkynes

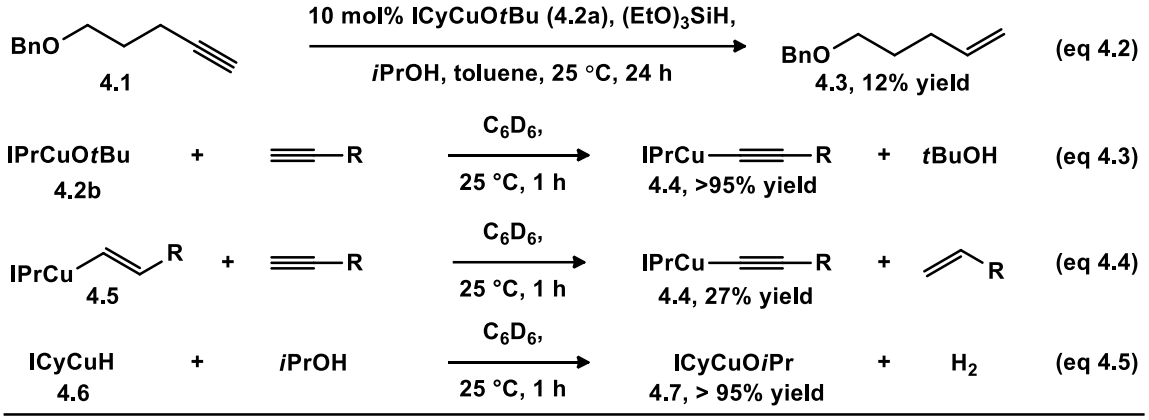


Section 2: Results and Discussion

4.2.a. Optimization

In initial experiments, we focused on the reduction of terminal alkynes and decided to explore the reduction of 4.1 using conditions similar to the stoichiometric reactions by Sadighi.[25] Unfortunately, we observed only 12% of the desired alkene product 4.3 (equation 4.2, scheme 4.6). Through a combination of stoichiometric and competition experiments, we identified three side reactions responsible for the low yield of the catalytic reaction. The major problem was the formation of catalytically inactive copper acetylide by deprotonation of the alkyne, by the copper alkoxide (equation 4.3), or by the alkenyl copper complex (equation 4.4). Another obstacle was the protonation of the copper hydride by *i*PrOH (equation 4.5). Although the copper isopropoxide formed in this reaction is catalytically active, this side reaction consumes both the silane and the alcohol.

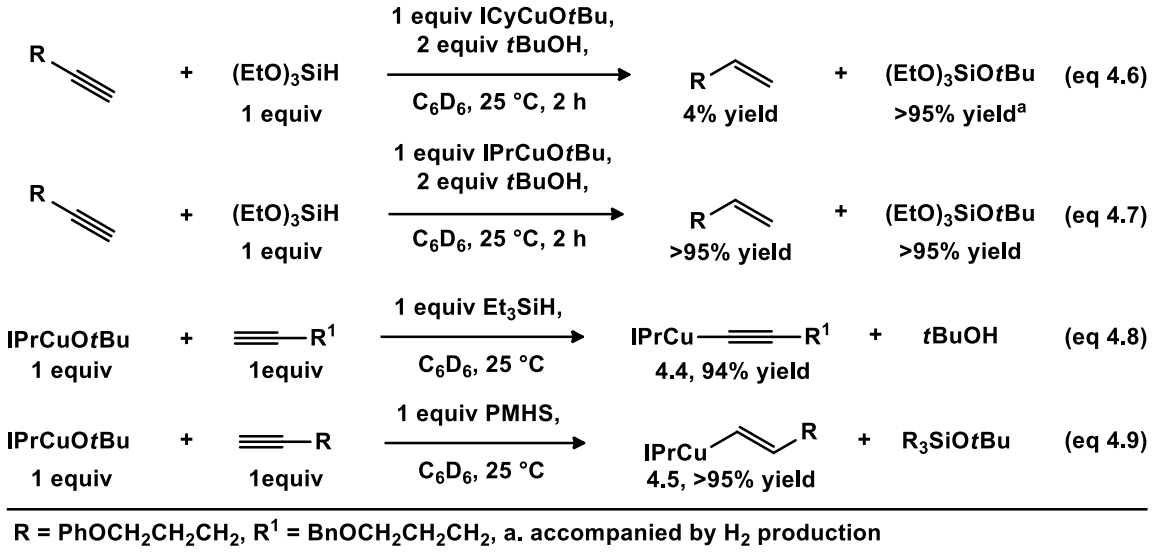
Scheme 4.6. Identification of the possible side reactions



R = $BnOCH_2CH_2CH_2$

Through optimization of several components of the catalytic system we were able to suppress all three side reactions. The formation of hydrogen could be suppressed by the use of sterically demanding NHC ligands. For example, in stoichiometric reactions with silane, alcohol and alkyne, the use an ICyCuO*t*Bu complex resulted in silane consumption by the formation of hydrogen gas (equation 4.6, scheme 4.7), while a complex supported by a sterically demanding IPr ligand suppressed hydrogen formation, and resulted in alkene as the major product (equation 4.7). As shown in the equations 4.8 and 4.9 in scheme 4.7, the choice of silane had a significant effect on the formation of the copper acetylide. With highly reactive PMHS (polymethylhydrosiloxane) the copper alkoxide is engaged in a fast transmetalation, and deprotonation of the alkyne is completely suppressed.

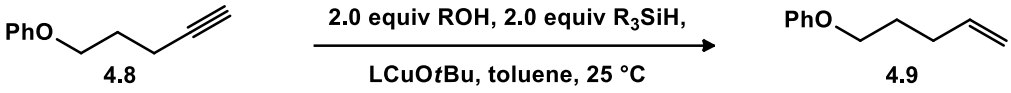
Scheme 4.7. Competition experiments with terminal alkynes



R = $PhOCH_2CH_2CH_2$, R^1 = $BnOCH_2CH_2CH_2$, a. accompanied by H_2 production

The results of the experiments shown in scheme 4.7 guided our optimization of the catalyst and the silane, and allowed us to achieve complete conversion in the catalytic semireduction of alkyne (table 4.1). Increasing the amount of *t*BuOH to 10 equivalents resulted in an increase in the rate of the reduction, but for complete conversion, 2 mol % of the catalyst was still necessary (entries 7 and 8). We suspected that the side reaction shown in equation 4.4, although slow, was responsible for removing the active catalyst from the reaction mixture. Indeed, we found that in the presence of a stronger acid (*i*BuOH) that increases the rate of protonation of alkenyl copper intermediate, 0.5 mol % of the catalyst was sufficient for the complete reduction of the alkyne in less than 1 hour (entry 9, table 4.1).

Table 4.1. Reaction optimization: Terminal alkynes



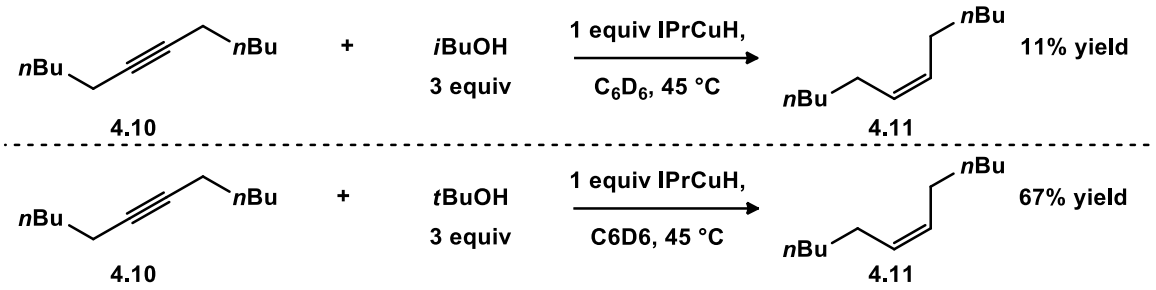
4.8 4.9

entry	catalyst	mol %	silane	ROH	t (h)	yield (%)
1	ICy	2.0	$(EtO)_3Si$	*t*BuOH	8	19
2	IMes	2.0	$(EtO)_3Si$	*t*BuOH	8	69
3	SiPr	2.0	$(EtO)_3Si$	*t*BuOH	8	61
4	IPr	2.0	$(EtO)_3Si$	*t*BuOH	8	90
5	IPr	2.0	Et_3Si	*t*BuOH	8	<5
6	IPr	2.0	PMHS	*t*BuOH	8	>98
7[b]	IPr	2.0	PMHS	*t*BuOH	1	>98
8[b]	IPr	0.5	PMHS	*t*BuOH	1	65
9[c]	IPr	0.5	PMHS	*i*BuOH	1	>98

a. Determined by GC. b. 10 equiv of *t*BuOH used. c. 1.2 equiv *i*BuOH, 1.2 equiv PMHS.

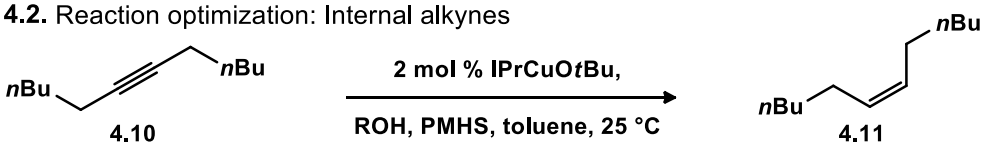
The best results for semireduction of terminal alkynes, as shown in table 4.1, are obtained using just 0.5 mol % of the catalyst and a slight excess of PMHS and isobutanol, which facilitates complete conversion of the alkyne and isolation of the alkene product. It is worth noting that PMHS is readily available, air stable, cost-effective, and nontoxic, and has a minimal environmental impact.[26] Although these conditions gave excellent results in the reduction of terminal alkynes, an attempt to accomplish semireduction of internal alkynes using the same conditions resulted in complete recovery of the starting alkyne. Only at the increased reaction temperature (45 °C) did we observe a 15% yield of the desired product together with a complete consumption of the alcohol and the silane (table 4.2). A control experiment showed that the major problem in the reaction was the formation of hydrogen. In a competition experiment, copper hydride reacts almost exclusively with *i*BuOH in the presence of an internal alkyne, and the result of the reaction was the exclusive formation of hydrogen. However, in a similar experiment performed with the less acidic *t*BuOH, alkene was the major product, suggesting that the copper hydride reacts preferentially with the alkyne (scheme 4.8).

Scheme 4.8. Competition experiments with internal alkynes



With *t*BuOH as a proton source in a catalytic reaction, we observed a significant improvement in the overall yield of the reaction (60% yield, table 4.2, entry 3). Finally, by increasing the amount of alcohol and silane used in the reaction we could accomplish quantitative reduction of dodecyne as shown in entry 4. Overall, by adjusting the acidity of the proton source we could achieve the reduction of both internal and terminal alkynes using the same, readily available catalyst.

Table 4.2. Reaction optimization: Internal alkynes



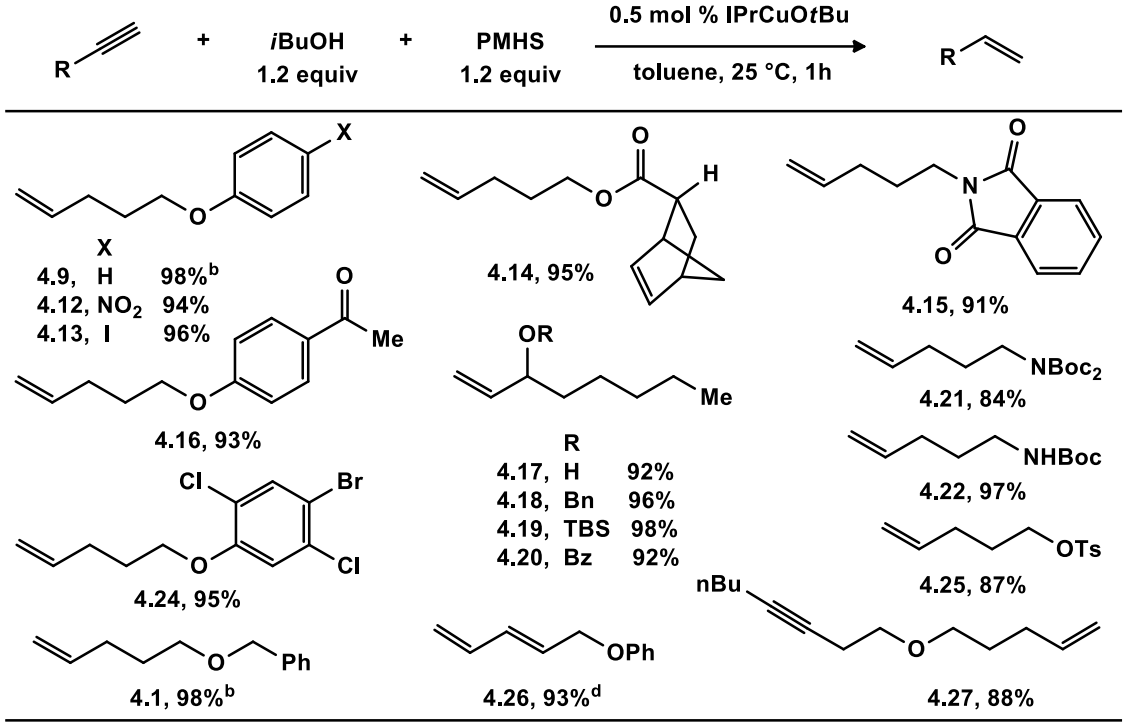
entry	PMHS equiv	ROH	ROH equiv	T(°C)	GC yield (%)
1	1.2	*i*BuOH	1.2	25	0
2	1.2	*i*BuOH	1.2	45	15
3	1.2	*t*BuOH	1.2	45	60
4	2.0	*t*BuOH	2.5	45	>98

4.2.b. Scope

Under optimized reaction conditions, selective semireduction of a wide range of terminal alkynes can be accomplished within one hour at room temperature (Table 4.3). The semireduction can be achieved in the presence of nitroarenes, aryl halides, esters, sulfonates, carbamates, imides, alcohols, and ethers. Although very similar conditions

have been used for the reduction of ketones, they are also well tolerated in this reaction (**4.16**).[27] Terminal alkynes are selectively reduced in the presence of both strained alkenes and internal alkynes. These two transformations are particularly difficult to accomplish using the currently available reagents. A propargylic alcohol and a variety of its derivatives were reduced to the corresponding allylic derivatives without any over-reduction, a common problem with most catalysts (**4.17-4.20**).[28] The formation of the corresponding allene product was not observed either, although similar conditions have been used in transformations of propargylic carbonates to allenes.[29] Finally, terminal 1,3-enynes are selectively reduced to 1,3-dienes (**4.26**). Overall, the remarkable chemoselectivity of our catalytic system is complementary to the chemoselectivity of catalysts currently used for semireduction of alkynes.

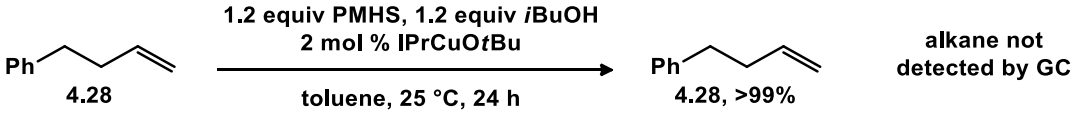
Table 4.3. Scope: Terminal alkynes



a. Reactions were performed on 1 mmol scale. Yields of isolated products are reported, unless otherwise noted. b. Determined by GC analysis. c. IPrCuO*t*Bu (2 mol %). d. From 5-phenoxy-pent-3-ene-1-yne.

It is important to note that alkenes were the only products formed in the reactions shown in table 4.3, and that we did not observe the formation of alkane products in any of the reactions, as evidenced by GC analysis of crude reaction mixtures. In fact, when we exposed 1-phenyl-1-butene to the standard reaction conditions for 24 h, we did not observe even a trace amount of the corresponding alkane, as judged by GC and GC/MS analysis of the crude reaction mixture (Scheme 4.9). This result suggests that a close monitoring of the reaction progress is not necessary for highly selective semireduction of alkynes under these reaction conditions.

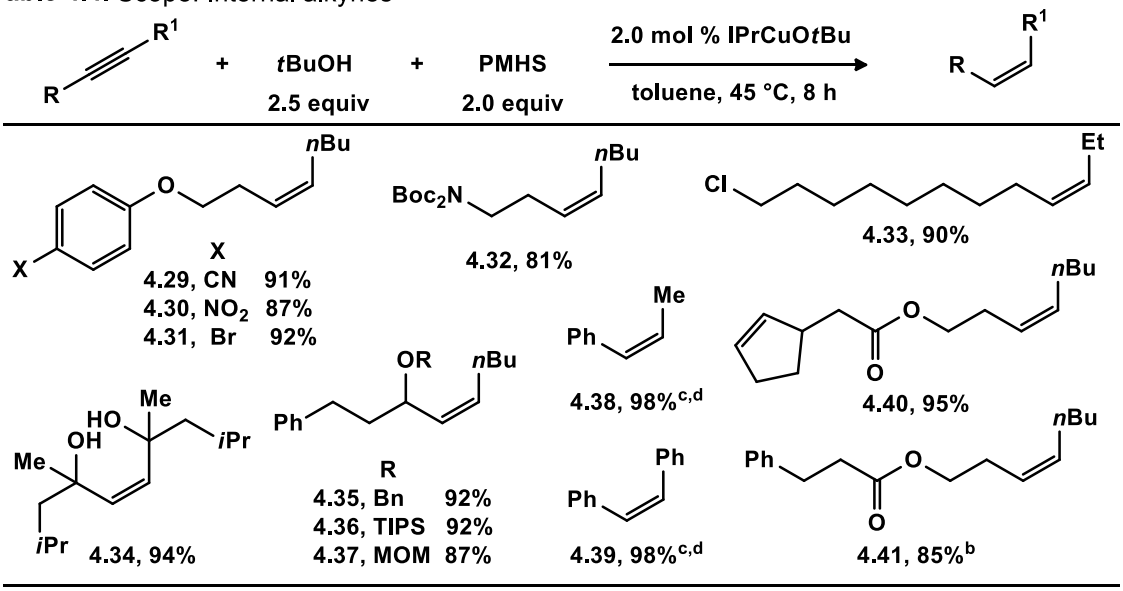
Scheme 4.9. submitting an alkene to the standard reaction conditions



Using the optimized set of reaction conditions for internal alkyne reduction (table 4.2, entry 4), we set out to explore the scope of this reaction. We found that even internal alkynes can be reduced in the presence of a wide range of functional groups. Most notable is the reduction in the presence of nitroarenes and aryl bromides which is usually difficult to achieve. Benzyl ethers, nitriles, alkyl chlorides, imides, esters, alkenes, and alcohols are also compatible with the reaction condition. Unfortunately, ketones are not compatible with the reduction of internal alkynes.

Various ether derivatives of propargylic alcohols could be reduced to *Z*-allylic alcohol derivatives without formation of the corresponding allenes. This result suggests that even with a less acidic alcohol as a proton source and at higher temperature, protonation of the alkenyl copper intermediate was faster than the elimination of the alkoxides.

Table 4.4. Scope: Internal alkynes

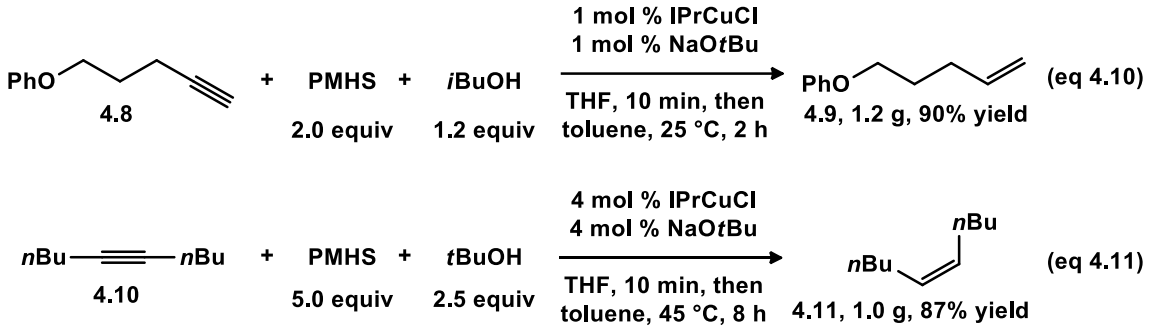


a. Reactions were performed on a 1 mmol scale. Yields of isolated products are reported, unless otherwise stated. b. 3.5 equiv *t*BuOH, 3 equiv PMHS, α,β-unsaturated ester also reduced. c. GC yield. d. Reaction performed at 25 °C.

With all substrates, we observed the exclusive formation of the Z alkene, and we did not observe further reduction of the alkene products. A special case was the reduction of phenyl acetylenes and diphenyl acetylenes. Selective semireduction of these substrates was accomplished with complete diastereoselectivity at 25 °C. However, at higher temperatures (45 °C) we observed a small amount of over-reduction to the alkanes (< 5%). It is important to note that aryl acetylenes are the only substrates with which we observed the formation of any alkane product.

To demonstrate the synthetic utility of the new method, we have performed gram-scale reactions using commercially available and air stable IPrCuCl as a catalyst precursor. As shown in equations 4.10 and 4.11, both terminal and internal alkynes can be reduced to the corresponding alkenes using this procedure. Importantly these reactions were performed outside of a glove box using standard air free techniques.

Scheme 4.10. Gram scale reactions outside of the glove box



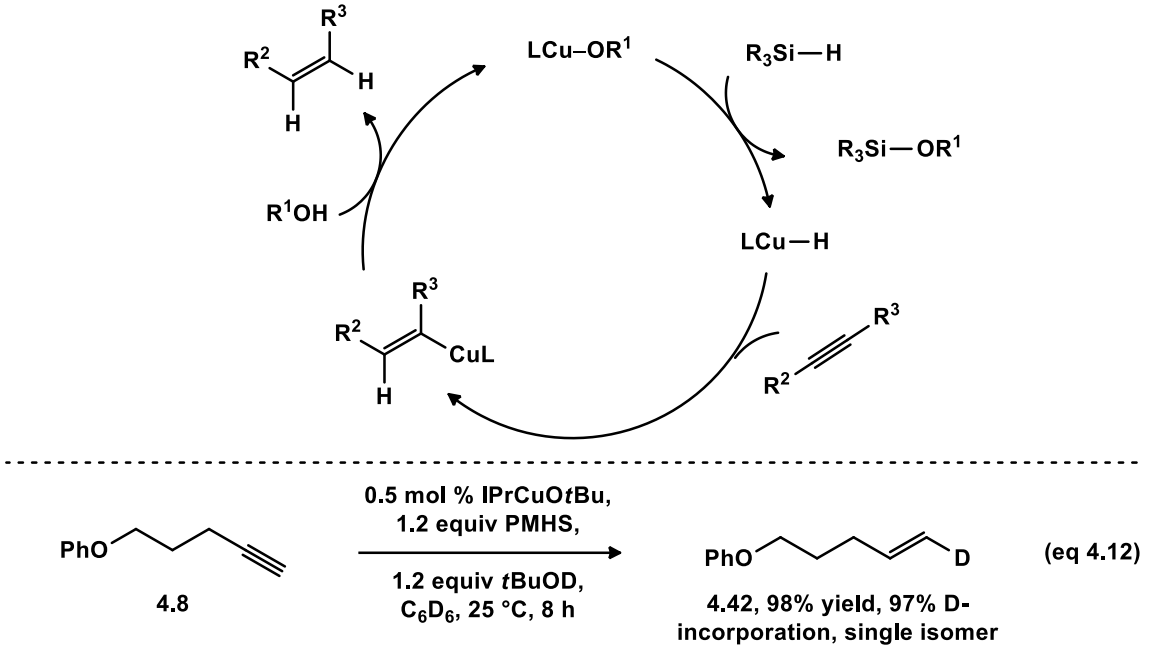
4.2.c. Mechanism

We propose that the mechanism of the semireduction method involves copper hydride formation followed by hydrocupration of the alkyne (Scheme 4.11). The alkenyl copper complex is then protonated by the alcohol to form the copper alkoxide and the desired alkene product.

Stoichiometric reactions performed by Sadighi,[30] Tsuji,[31] and us[32] support the feasibility of all the elementary steps in the proposed catalytic cycle. We have also shown that any of the three proposed intermediates can be used as catalysts in the catalytic reaction. These results are consistent with the idea that the copper hydride and the alkenyl copper complexes are intermediates in the catalytic reaction. Furthermore, through the labelling experiment shown in equation 4.12, we demonstrate the regioselectivity of the hydrocupration of terminal alkynes. High deuterium incorporation (>97%) and regioselectivity of the incorporation observed in this experiment are unusual in the context of much lower deuterium incorporation observed in similar experiments performed by Tsuji[33] and Lipshutz.[34] The high selectivity and efficiency of the deuterium incorporation suggests that under the reaction conditions there is no exchange between

copper hydride and *t*BuOH, or between silane and *t*BuOH, as observed in similar experiments performed with copper hydride.[35]

Scheme 4.11. Proposed mechanism

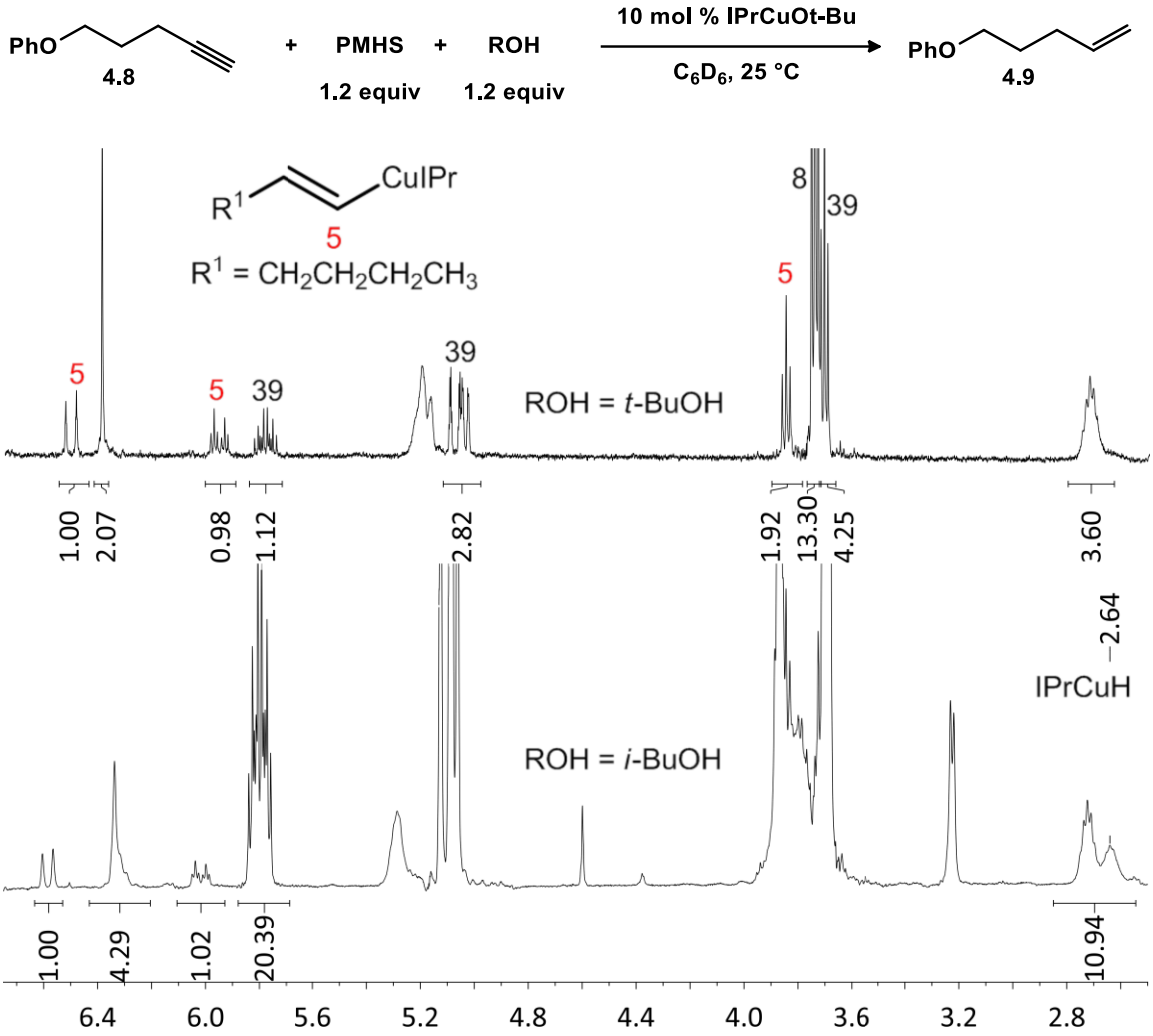


We have also explored the role of *i*BuOH in the reduction of terminal alkynes, and the difference in the reactivity of terminal and internal alkyne. When a reduction of terminal alkyne performed in the presence of 10 mol % of IPrCuO*t*Bu and *t*BuOH was monitored by in situ ^{1}H NMR, 10 mol % of alkenyl copper intermediate was observed throughout the course of the reaction (figure 4.1).

This observation indicates that the alkenyl copper intermediate is the resting state of the catalyst. Considering the irreversible nature of the subsequent protonation step, this observation also suggests that the rate limiting step of the catalytic cycle is the protonation of the alkenyl copper intermediate. Interestingly, when the same experiment was performed with *i*BuOH, alkenyl copper intermediate accounted for only 46% of the

copper catalyst present in the reaction mixture (scheme 4.12). This observation suggests that in the presence of *i*BuOH protonation of the alkenyl copper intermediate is only partially rate limiting. The change in the rate limiting step of the reduction with a change from *t*BuOH to *i*BuOH provides an explanation for the dramatic effect *i*BuOH has on the rate of the semireduction of terminal alkynes.

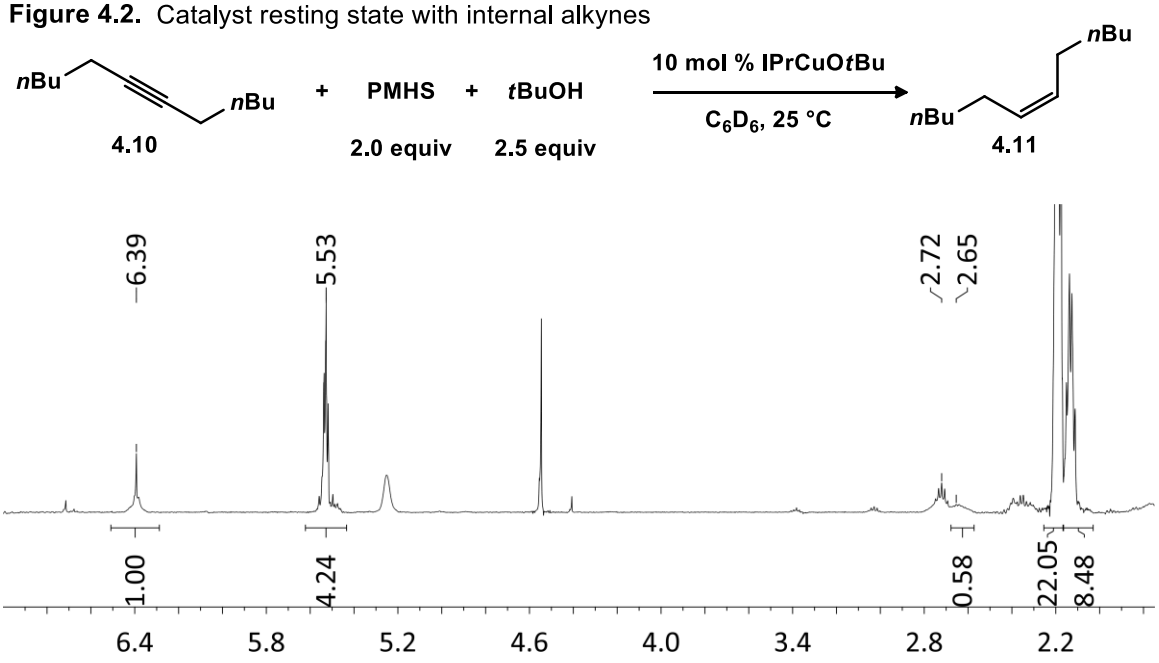
Scheme 4.12. Catalyst resting state with terminal alkynes



We also explored the resting state of the catalyst in the reduction of the internal alkynes. In situ ^{1}H NMR analysis of the reaction shown in scheme 4.13 revealed that

alkenyl copper intermediate was not present in significant quantities during the course of the reaction. Instead, IPrCu-H was identified as the major copper species present in the reaction mixture as indicated by the peak at 6.39 in figure 4.2. These observations suggest that IPrCu-H is the resting state of the catalyst and that hydrocupration is the rate limiting step of the reaction. Such a conclusion is also consistent with a negative impact *i*BuOH has on the reaction of internal alkynes and the competition experiments presented in scheme 4.8.

Figure 4.2. Catalyst resting state with internal alkynes



Overall, the difference in the rate of hydrocupration of terminal and internal alkynes allows us to understand the use of two different alcohols in reactions of these two classes of substrates. With terminal alkynes, best results are obtained with a primary alcohol. If a less acidic proton source is used, the protonation of the alkenyl copper intermediate becomes rate-limiting and can lead to the catalyst deactivation according to equation 4.4. In reactions of internal alkynes, hydrocupration is rate-limiting, and faster

protonation of the alkenyl copper intermediate does not affect the rate of the reaction. Instead, protonation of the copper hydride intermediate, which is the resting state of the catalyst, is the major concern. As a result, less acidic *t*BuOH is the optimal proton source in reactions of internal alkynes.

Section 3: Conclusions

In conclusion, we have developed a highly efficient catalytic method for the selective semireduction of alkynes. Essential for the reaction development was a thorough understanding of the processes competing with the alkyne reduction, made possible by systematically identifying each possible side reaction. The new method can be used with a wide range of substrates, including both internal and terminal alkynes, as well as aryl and diaryl acetylenes. Furthermore, the new method has excellent chemoselectivity, which is complementary to the chemoselectivity of Lindlar and P2-nickel catalysts. Practical reaction conditions (25 °C or 45 °C, low catalyst loading, monophasic reaction mixture), together with commercial availability of a catalyst precursor and the ability to scale the reaction add to the appeal of the new catalytic system.

Section 4: Experimental

4.4.a. General

Reactions were performed under a nitrogen atmosphere with flame-dried glassware, using standard Schlenk techniques, or in a glove box (Nexus II from Vacuum

Atmospheres). Column chromatography was performed using a Biotage Iso-1SV flash purification system with silica gel from Agela Technologies Inc. (60Å, 40-60 μm, 230-400 mesh). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to the residual proteated solvent peak ($CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), CD_2Cl_2 (5.32 ppm), or MeOD (3.31 ppm)). ^{13}C chemical shifts (δ) are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$ (77.2 ppm), or CD_2Cl_2 (54.0 ppm)). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet), integration, and coupling constants in Hertz (Hz). Mass spectra were collected on a Bruker Esquire Liquid Chromatograph - Ion Trap Mass Spectrometer, Hewlett Packard 5971A Gas Chromatograph - Mass Spectrometer, or JEOL HX-110 mass spectrometer. GC analysis was performed on a Shimadzu GC-2010 instrument with a flame ionization detector and a SHRXI-5MS column (15 m, 0.25 mm inner diameter, 0.25 μm film thickness). The following temperature program was used: 2 min @ 60 °C, 13 °C/min to 160 °C, 30 °C/min to 250 °C, 5.5 min @ 250 °C.

THF, CH_2Cl_2, diethyl ether, and toluene were degassed and dried by passing through columns of neutral alumina. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. Deuterated solvents were degassed before use.

Commercial reagents were purchased from Sigma-Aldrich Co., VWR International, LLC., or STREM Chemicals, Inc., and were used as received unless otherwise noted. Alkynes used were commercially available with the exception of 1-nitro-4-(pent-4-yn-1-yloxy)benzene, 1-iodo-4-(pent-4-yn-1-yloxy)benzene, 1-(4-(pent-4-yn-1-yloxy)phenyl)ethanone, N,N-di(*tert*-butylcarbamate)-N-(pent-4-yn-1-yl) amine, 1-bromo-2,5-dichloro-4-(pent-4-yn-1-yloxy)benzene, (E)-(penta-2-en-4-yn-1-yloxy)benzene, 4-(oct-3-yn-1-yloxy)benzonitrile, 1-nitro-4-(oct-3-yn-1-yloxy)benzene, 1-bromo-4-(oct-3-yn-1-yloxy)benzene, N,N-di(*tert*-butyl carbamate)-N-(oct-3-yn-1-yl) amine,[36] (rac)-pent-4-yn-1-yl bicyclo[2.2.1]hept-5-ene-2-carboxylate, (Z)-oct-3-yn-1-yl 3-phenylpropanoate, oct-3-yn-1-yl 2-(cyclopent-2-en-1-yl)acetate, oct-1-yn-3-yl benzoate,[37] 1-(pent-4-yn-1-yloxy)oct-3-yne,[38] (3-(methoxymethoxy)non-4-en-1-yl)benzene,[39] and 12-chlorododec-3-ene.[40] All of which were synthesized according to known literature procedures.

4.4.b. Experimental Details

Competition Experiment: Protonation of alkenyl copper by alkyne or ROH

In a glove box, a dram vial was charged with alkyne (1.00 equiv, 3.5 mg, 0.02 mmol), C_6D_6 (1.0 mL), and the alkenyl copper complex (1.00 equiv, 12.6 mg, 0.02 mmol). The mixture was then transferred to an NMR tube and the progress of the reaction was monitored by NMR at 25 °C. Disappearance of a ^{1}H NMR signal at 6.15 ppm with concommitment appearance of a signal at 5.90 ppm was used to determine the conversion of the alkenyl copper complex to the alkene. See section VIIIc for a representative ^{1}H NMR spectrum.

Competition Experiment: Protonation of LCu-H vs. Hydrocupration

Terminal alkynes

In a glove box, a dram vial equipped with a stir bar was charged with triethoxy silane (1.00 equiv, 16.4 mg, 0.10 mmol), C_6D_6 (0.70 mL), alkyne (1.00 equiv, 16.0 mg, 0.10 mmol), and *tert*-butanol (2.00 equiv, 15.0 mg, 0.20 mmol), and the solution was stirred for 1 min before adding LCuO*t*Bu (1.00 equiv, 0.10 mmol). The reaction mixture was allowed to stir at 25 °C for 2 h then filtered through a plug of silica using C_6D_6 (0.5 mL) to elute all components. The conversion of the silane was determined using the disappearance of a quartet at 3.78 ppm with the appearance of a quartet at 3.87 ppm in the ^{1}H NMR spectrum. The yield of the alkene was determined using 1,3,5-trimethoxy benzene as an internal standard (0.20 equiv, 3.4 mg, 0.02 mmol).

Internal alkynes

In a glove box IPrCu-H (1.00 equiv, 0.10 mmol) was pre-formed using a known procedure.[6] The resulting yellow solution was added to a dram vial containing 6-dodecyne (1 equiv, 16.6 mg, 0.1 mmol), C_6D_6 (1 mL), alcohol (1 equiv,7.4 mg, 0.1 mmol) and 1,3,5-trimethoxybenzene (0.2 equiv, 3.4 mg, 0.02 mmol). A stir bar was added to the vial and the reaction heated to 40 °C with stirring for 3 h prior to obtaining a ^{1}H NMR. In both reactions, the IPrCu-H was consumed as indicated by the disappearance of a singlet at ~2.65 ppm in the ^{1}H NMR spectrum of the crude reaction mixture.[41] Further screening for internal alkynes was performed according to the general optimization procedure. The results of these screens are contained in table S1 of section IVa.

Competition Experiments: Alkyne Deprotonation vs. Transmetalation

In a glove box, a dram vial was charged with silane (3.00 equiv, 0.15 mmol), C_6D_6 (1 mL), and alkyne (3.00 equiv, 26.1 mg, 0.15 mmol). The mixture was then transferred to an NMR tube and cooled to -196 °C before injecting IPrCuO*t*Bu (1.00 equiv, 26.3 mg, 0.05 mmol, in 0.2 mL C_6D_6) and flame sealing the NMR tube. The mixture was gradually warmed to 25 °C and the progress of the reaction was monitored by NMR. Disappearance of a triplet at δ 2.15 with concomitant appearance of a triplet at δ 2.33 was used to determine conversion of the alkyne to copper acetylide. With PMHS as the silane, the alkenyl copper product **X** was obtained as a white solid (38.0 mg, 62% isolated yield, >95% by NMR) after the volatiles were removed and the resulting solid was washed with pentane.

Prolonged Exposure of an Alkene to the Standard Reaction Conditions

In a glove box, a dram vial equipped with a stir bar was charged with 4-phenyl-1-butene (1.00 equiv, 13.2 mg, 0.10 mmol), polymethylhydrosiloxane (1.20 equiv, 8.9 mg, 0.12 mmol), toluene (2 mL), and *tert*-butanol (1.20 equiv, 7.2 mg, 0.12 mmol), and IPrCuO*t*Bu (0.05 equiv, 2.6 mg, 0.005 mmol). The reaction was stirred at 25 °C for 24 h, and the conversion of the alkene was determined using 1,3,5-trimethoxy benzene (0.20 equiv, 3.4 mg, 0.02 mmol) as an internal standard. There was no indication of any alkane product formed during the course of the reaction.

Optimization Reactions

All optimization reactions shown in Table 1 were performed in a glove box. A 1-dram vial was charged with a stir bar. To the vial were added alkyne (1.00 equiv, 0.10 mmol), silane, solvent, alcohol as specified, and 1,3,5-trimethoxybenzene as an internal

standard (0.20 equiv, 0.02 mmol). To the resulting mixture, the copper catalyst in 100 µL of toluene was added before the reaction vial was capped and stirred at the specified temperature for the indicated time. Product yield was determined by GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

Semireduction of Terminal Alkynes

In a glove box, a dram vial equipped with a stir bar was charged with alkyne (1.00 equiv, 1.00 mmol), polymethylhydrosiloxane (1.20 equiv, 71.7 mg, 1.20 mmol), toluene (10 mL), and isobutanol (1.00 equiv, 88.9 mg, 1.20 mmol). IPrCuO*t*Bu (0.005 equiv, 2.6 mg, 0.005 mmol) was added and the reaction capped while stirring for 60 min at 25 °C. The mixture was then diluted with hexanes (20 mL), and filtered through a silica plug using a 50% ethyl acetate/hexane mixture to elute the product before the solvent was removed under reduced pressure. The crude product was purified by distillation, silica gel column chromatography, or with an aqueous workup. The aqueous workup was conducted as follows: The product was stirred in a solution of sodium hydroxide (10 mL, 0.1 M in tetrahydrofuran/H_2O 5:1) for 30 min. The solution was then extracted with diethyl ether (3x20 mL), and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced procedure.

Semi-reduction of Internal Alkynes

In a glove box, a dram vial equipped with a stir bar was charged with alkyne (1.00 equiv, 1.00 mmol), polymethylhydrosiloxane (2.00 equiv, 120.1 mg, 2.00 mmol), toluene (2 mL), and *tert*-butanol (2.50 equiv, 185.3 mg, 2.50 mmol). IPrCuO*t*Bu (0.02 equiv, 10.5 mg, 0.02 mmol) was added and the reaction mixture was stirred for 8 h at 40 °C in a

capped vial. The mixture was then diluted with hexanes (20 mL), and filtered through a silica plug using a 50% ethyl acetate/hexane mixture to elute the product. The solvent was removed under reduced pressure and the crude product was purified by distillation, silica gel column chromatography, or with an aqueous workup. The aqueous workup was performed as follows: The product was stirred in a solution of sodium hydroxide (20 mL, 0.1 M in tetrahydrofuran/H2O 5:1) for 30 min. The solution was extracted with diethyl ether (3x20 mL), and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced procedure.

Gram Scale Reactions Outside of a Glove Box.

Gram scale reaction of (pent-4-yn-1-yloxy)benzene

To a flame dried Schlenk flask under a nitrogen atmosphere was added IPrCuCl (0.01 equiv, 39.0 mg, 0.08 mmol), NaO*t*Bu (0.01 equiv, 7.7 mg, 0.08 mmol), and THF (2 mL). The catalyst solution was allowed to stir vigorously for 20 min while a reaction flask equipped with a stir bar under a nitrogen atmosphere was charged with (pent-4-yn-1-yloxy)benzene (1.00 equiv, 1281.7 mg, 8.00 mmol), polymethylhydrosiloxane (2.00 equiv, 0.955 mL, 16.00 mmol), toluene (40 mL), and isobutanol (1.20 equiv, 0.887 mL, 9.60 mmol). The catalyst solution was then transferred to the reaction mixture, which was stirred at 25 °C for 60 min. The mixture was then diluted with hexanes (20 mL), and filtered through a silica plug using a 50% ethyl acetate/hexane mixture to elute the product before the solvent was removed under reduced pressure. Short path distillation (80 °C, 100 mtorr) afforded (pent-4-en-1-yloxy) benzene as a colorless oil (1168 mg, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, *J* = 7.4, 1.9 Hz, 2H), 7.03 –

6.86 (m, 3H), 5.91 – 5.56 (m, 1H), 5.18 – 4.93 (m, 2H), 3.98 (t, *J* = 6.4 Hz, 2H), 2.25 (dt, *J* = 14.0, 7.3 Hz, 2H), 1.95 – 1.86 (m, *J* = 13.4, 6.6 Hz, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 159.2, 138.0, 129.5, 120.7, 115.3, 114.6, 67.2, 30.3, 28.6. ESI-MS calculated for $[M+H]^+$ 163.1, found 164.2. FTIR (neat, cm^{-1}): 3074(w), 2945(m), 1601(m), 1245(s), 1079(s).

Gram scale reaction of 6-dodecyne

To a flame dried Schlenk flask under a nitrogen atmosphere was added IPrCuCl (0.04 equiv, 136.5 mg, 0.28 mmol), NaO*t*Bu (0.04 equiv, 26.9 mg, 0.28 mmol), and THF (5 mL). The catalyst solution was allowed to stir vigorously for 20 min while a reaction flask equipped with a stir bar under a nitrogen atmosphere was charged with 6-dodecyne (1.00 equiv, 0.1479 mL, 7.00 mmol), polymethylhydrosiloxane (5.00 equiv, 2.090 mL, 35.00 mmol), toluene (20 mL), and *tert*-butanol (2.50 equiv, 1297.1 mg, 17.50 mmol). The catalyst solution was transferred to the reaction flask at 25 °C and the reaction mixture was heated to 40 °C for 8 h with stirring. The mixture was then diluted in hexanes (20 mL), and filtered through a silica plug using a 50% ethyl acetate/hexane mixture to elute the product before the solvent was removed under reduced pressure. Short path distillation (70 °C, 100 mtorr) afforded (6Z)-dodecene as a colorless oil (1021 mg, 87% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (t, *J* = 4.9 Hz, 2H), 2.02 (dt, *J* = 12.2, 6.6 Hz, 4H), 1.43 – 1.23 (m, 12H), 0.89 (t, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.1, 31.7, 29.6, 27.3, 22.7, 14.2. GC-MS calculated for $[M]^+$ 168, found 168.

Deuterium labeling experiment

All glassware used in deuterium labeling experiments was rinsed with methanol-d4, followed by C_6D_6 prior to the experiments. In a glove box, stock solutions of Alkyne (1.00 equiv, 16.0 mg, 0.10 mmol), and PMHS (2.00 equiv, 12.0 mg, 0.20 mmol) were dried over sieves for 4 h. these solutions were decanted into a dram vial containing a stir bar and *tert*-butanol-d1 (2.00 equiv, 15.0 mg, 0.20 mmol) before IPrCuO*t*Bu (0.02 equiv, 1.0 mg, 0.002 mmol) was added. The reaction was capped, and allowed to stir for 24 h at 25 °C. The mixture was then diluted in hexanes (20 mL), and filtered through a silica plug using a 50% ethyl acetate/hexane mixture to elute the product before the solvent was removed under reduced pressure.

IPrCu-H as a Competent Catalyst

In a glove box, a dram vial equipped with a stir bar was charged with alkyne (1.00 equiv, 16.0 mg, 0.10 mmol), polymethylhydrosiloxane (1.20 equiv, 9.0 mg, 0.12 mmol), toluene (2 mL), and isobutanol (1.20 equiv, 7.2 mg, 0.12 mmol). IPrCu-H (0.01 equiv, 0.5 mg, 0.002 mmol) was pre-formed in C_6D_6 and confirmed by NMR. IPrCu-H was then added to the solution containing the alkyne and the reaction capped while stirring for 1 h at 25 °C. The completion of the reaction was determined by GC-FID.

Alkenyl Copper as a Competent Catalyst

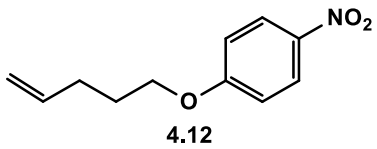
In a glove box, a dram vial equipped with a stir bar was charged with alkyne (1.00 equiv, 16.0 mg, 0.10 mmol), polymethylhydrosiloxane (1.20 equiv, 9.0 mg, 0.12 mmol), toluene (2 mL), and isobutanol (1.20 equiv, 7.2 mg, 0.12 mmol). Alkenyl copper complex 5 (0.01 equiv, 0.6 mg, 0.01 mmol) was then added and the reaction capped while stirring at 25 °C for 1 h. The completion of the reaction was determined by GC-FID.

Resting State Experiments

The reduction of terminal alkyne **X** was monitored by in situ ^{1}H NMR (equation S1). Using *t*BuOH as the proton source 10 mol % of alkenyl copper intermediate was observed throughout the course of the reaction. When the same experiment was performed with *i*BuOH, alkenyl copper intermediate **X** accounted for only 46% of the copper catalyst present in the reaction mixture. In situ ^{1}H NMR analysis of reaction **X** (Figure **X**) revealed that IPrCu-H was the major copper species present in the reaction mixture, indicating that **X** is the resting state of the catalyst and that hydrocupration is the rate limiting step of the reaction.

In a glove box, a dram vial was charged with alkyne (1.00 equiv, 0.10 mmol), polymethylhydrosiloxane, C_6D_6 (1 mL), and *tert*-butanol as indicated in the reaction scheme. The mixture was transferred to an NMR tube and cooled to -78 °C before adding IPrCuO*t*Bu (0.10 equiv, 5.3 mg, 0.01 mmol) as a 1M solution in C_6D_6. The NMR tube was allowed to warm to the indicated temperature in the NMR while collecting spectra. The resting state of the catalyst was monitored by ^{1}H-NMR at 25 °C for (pent-4-yn-1-yloxy)benzene, and 40 °C for 6-dodecyne over the course of the reaction.

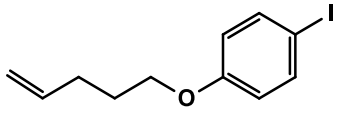
4.4.c. Characterization



4.12

1-nitro-4-(pent-4-en-1-yloxy)benzene

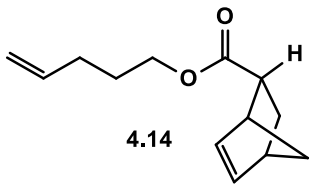
Compound was isolated as a yellow solid (194 mg, 94% yield) after purification by silica gel column chromatography (0 → 20% ethyl acetate/hexanes over 8 CV, then 0-10% diethyl ether/hexanes over 8 CV). ^{1}H NMR (500 MHz, C_6D_6) δ 8.00 (d, *J* = 9.2 Hz, 2H), 6.39 (d, *J* = 9.1 Hz, 2H), 5.91 – 5.56 (m, 1H), 5.18 – 4.93 (m, 2H), 3.39 (t, *J* = 6.4 Hz, 2H), 2.03 (dt, *J* = 14.2, 7.2 Hz, 2H), 1.70 – 1.51 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.2, 141.4, 137.4, 126.0, 115.7, 114.5, 68.1, 30.0, 28.2. ESI-MS calculated for $[M+Na]^+$ 230.1, found 230.2. FTIR (neat, cm^{-1}): 3079(w), 2942(m), 1510(s), 1341(s), 1110(m).



4.13

1-iodo-4-(pent-4-en-1-yloxy)benzene

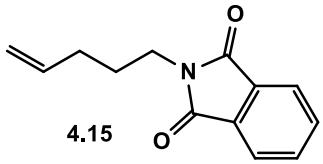
Compound was isolated as a white solid (278 mg, 96% yield) after purification by column chromatography (0 → 10% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 5.91 – 5.56 (m, 1H), 5.18 – 4.93 (m, 2H), 3.93 (t, *J* = 6.4 Hz, 2H), 2.23 (dt, *J* = 14.2, 7.1 Hz, 2H), 2.00 – 1.81 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 138.3, 137.8, 117.0, 115.5, 82.7, 67.3, 30.2, 28.4. GC-MS calculated for $[M+H]^+$ 288, found 288. FTIR (neat, cm^{-1}): 3076(w), 2944(m), 1641(w), 1243(s), 1075(s).



4.14

(±)-pent-4-en-1-yl bicyclo[2.2.1]hept-5-ene-2-carboxylate

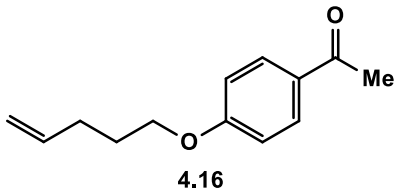
Compound was isolated as a colorless liquid (196 mg, 95% yield) after purification by column chromatography (0 → 10% diethyl ether/hexanes with a 5% benzene additive over 8 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (dd, *J* = 5.7, 3.1 Hz, 1H), 5.92 (dd, *J* = 5.4, 2.8 Hz, 1H), 5.88 – 5.72 (m, 1H), 5.13 – 4.93 (m, 2H), 4.03 (td, *J* = 6.6, 2.1 Hz, 2H), 3.31 – 3.11 (m, 1H), 3.04 – 2.82 (m, 2H), 2.13 (dt, *J* = 6.8, 2.3 Hz, 2H), 1.97 – 1.84 (m, 1H), 1.80 – 1.63 (m, 2H), 1.43 (d, *J* = 9.7 Hz, 2H), 1.38 – 1.16 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 137.9, 137.7, 132.5, 115.4, 63.7, 49.8, 45.9, 43.5, 42.7, 30.2, 29.3, 28.0. HRMS calculated for $[M+Na]^+$ 229.1204, found 229.1215. FTIR (neat, cm^{-1}): 3063(w), 2975(m), 1732(s), 1336(s), 1186(s).



4.15

2-(pent-4-en-1-yl)isoindoline-1,3-dione

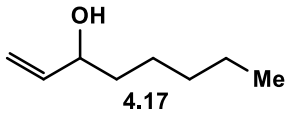
Compound was isolated as a white solid (196 mg, 91% yield) after a tetrahydrofuran/sodium hydroxide workup followed by column chromatography (0 → 20% diethyl ether/hexanes over 8 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.94 – 5.68 (m, 1H), 5.16 – 4.90 (m, 2H), 3.88 – 3.57 (m, 2H), 2.12 (dt, *J* = 14.1, 7.3 Hz, 2H), 1.94 – 1.68 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 137.5, 134.0, 132.3, 123.3, 115.5, 37.7, 31.1, 27.7. HRMS calculated for $[M+Na]^+$ 238.0843, found 238.0852. FTIR (neat, cm^{-1}): 3061(w), 2938(m), 1712(s), 1397(m).



4.16

1-(4-(pent-4-en-1-yloxy)phenyl)ethanone

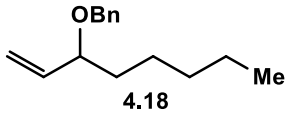
Compound was isolated as a colorless oil (189 mg, 93% yield) after purification by column chromatography (0 → 5% diethyl ether/hexanes with a 5% benzene additive, over 8 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 5.91 – 5.89 (m, 1H), 5.18 – 4.95 (m, 2H), 4.03 (t, *J* = 6.4 Hz, 2H), 2.56 (s, 3H), 2.43 – 2.17 (m, 2H), 2.09 – 1.79 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.9, 163.1, 137.7, 130.7, 130.3, 115.6, 114.3, 67.5, 30.1, 28.4, 26.5. HRMS calculated for $[M+H]^+$ 205.1228, found 205.1233. FTIR (neat, cm^{-1}): 3076(w), 2944(m), 1675(s), 1255(s), 1019(s).



4.17

oct-1-en-3-ol

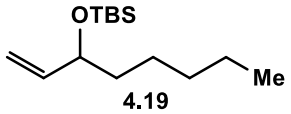
Compound was isolated as a colorless oil (118 mg, 92% yield) after a tetrahydrofuran/sodium hydroxide workup followed by column chromatography (0 → 30% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 – 5.76 (m, 1H), 5.26 – 5.05 (m, 2H), 4.15 – 4.05 (m, 1H), 1.66 – 1.19 (m, 9H), 0.88 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.5, 114.6, 73.4, 37.1, 31.9, 25.1, 22.7, 14.1. GC-MS calculated for $[M+H]^+$ 129.1, found 129.6. FTIR (neat, cm^{-1}): 3365(br), 3078(w), 2930(m), 1457(m), 1010(m).



4.18

((oct-1-en-3-yloxy)methyl)benzene

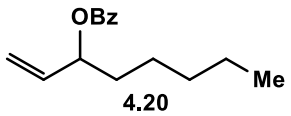
Compound was isolated as a yellow liquid (210 mg, 96% yield) after a tetrahydrofuran/sodium hydroxide workup. ^{1}H NMR (300 MHz, MeOD) δ 7.46 – 7.16 (m, 5H), 5.80 – 5.62 (m, 1H), 5.39 – 5.06 (m, 2H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.34 (d, *J* = 11.8 Hz, 1H), 3.75 (dt, *J* = 13.4, 7.0 Hz, 1H), 1.65 – 1.55 (m, 1H), 1.50 – 1.20 (m, 7H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.4, 139.0, 128.4, 127.8, 127.5, 117.1, 80.7, 70.1, 35.6, 31.9, 25.2, 22.7, 14.2. GC-MS calculated for $[M]^+$ 218, found 218. FTIR (neat, cm^{-1}): 3065(m), 2930(s), 1742(m), 1454(s), 1092(s).



4.19

tert-butyldimethyl(oct-1-en-3-yloxy)silane

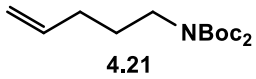
Compound was isolated as a colorless liquid (238 mg, 98% yield) after purification by column chromatography (0 → 10% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 – 5.61 (m, 1H), 5.17 – 5.00 (m, 2H), 4.15 (dt, *J* = 13.4, 7.0 Hz, 1H), 1.55 – 1.35 (m, *J* = 6.3 Hz, 2H), 1.38 – 1.18 (m, 6H), 0.95 – 0.79 (m, 12H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.2, 113.5, 74.1, 38.3, 32.0, 26.1, 25.0, 22.8, 18.4, 14.2, -4.2, -4.6. GC-MS calculated for $[M]^+$ 242, found 242. FTIR (neat, cm^{-1}): 8078(w), 2929(m), 1472(m), 1251(m), 1081(m).



4.20

oct-1-en-3-yl benzoate

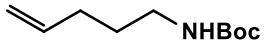
Compound was isolated as a colorless oil (213 mg, 92% yield) after purification by column chromatography (0 → 10% diethyl ether/hexanes over 8 CV, then 0-10% ethyl acetate/hexanes with a 5% chloroform additive over 8 CV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.63 – 7.51 (m, 1H), 7.44 (dd, *J* = 10.8, 4.7 Hz, 2H), 5.99 – 5.82 (m, 1H), 5.55 – 5.44 (m, 1H), 5.32 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.20 (dd, *J* = 10.5, 1.1 Hz, 1H), 1.87 – 1.65 (m, 2H), 1.47 – 1.24 (m, 6H), 0.88 (t, *J* = 9.8, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 136.8, 133.0, 130.8, 129.7, 128.5, 116.7, 75.5, 34.4, 31.7, 24.9, 22.7, 14.1. ESI-MS calculated for $[M+H]^+$ 233.2, found 233.3.



4.21

N,N-di(tert-butylcarbamate)-N-(pent-4-en-1-yl) amine

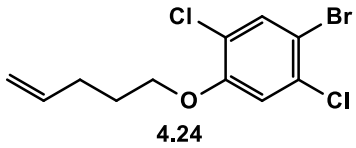
Compound was isolated as a white solid (240 mg, 84% yield) after purification by column chromatography (0 → 10% ethyl acetate/hexanes over 8 CV, then 0-5% diethyl ether/hexanes with a 5% chloroform additive). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 – 5.71 (m, 1H), 5.16 – 4.86 (m, 2H), 3.67 – 3.44 (m, 2H), 2.06 (q, *J* = 7.2 Hz, 2H), 1.68 (dd, *J* = 14.9, 7.4 Hz, 2H), 1.52 (d, *J* = 10.1 Hz, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.8, 138.0, 115.1, 82.2, 46.2, 31.1, 28.2, 28.1. HRMS calculated for $[M+H]^+$ 286.2018, found 286.2010. FTIR (neat, cm^{-1}): 3077(w), 2980(m), 1785(m), 1700(s), 1128(s).



4.22

tert-butyl pent-4-en-1-ylcarbamate

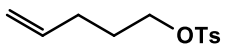
Compound was isolated as a colorless oil (180 mg, 97% yield) after purification by column chromatography (0 → 30% diethyl ether/hexanes over 8 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 – 5.70 (m, 1H), 5.12 – 4.95 (m, 2H), 4.52 (s, 1H), 3.25 – 3.03 (m, 2H), 2.08 (dt, *J* = 14.6, 6.9 Hz, 2H), 1.59 (tt, *J* = 14.6, 7.4 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 156.1, 138.0, 115.2, 81.9, 40.2, 31.1, 29.4, 28.5. HRMS calculated for $[M+Na]^+$ 208.1313, found 208.1322. FTIR (neat, cm^{-1}): 3349(br), 3077(w), 2977(m), 1701(s), 1172(s).



4.24

1-bromo-2,5-dichloro-4-(pent-4-en-1-yloxy)benzene

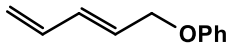
Compound was isolated as a yellow solid (295 mg, 95% yield) after purification by column chromatography (0 → 10% ethyl acetate/hexanes with a 5% chloroform additive over 8 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 6.99 (s, 1H), 5.85 (ddt, *J* = 16.9, 10.0, 6.7 Hz, 1H), 5.15 – 4.98 (m, *J* = 14.7 Hz, 2H), 4.00 (t, *J* = 6.3 Hz, 2H), 2.27 (dt, *J* = 7.2, 3.4 Hz, 2H), 2.05 – 1.85 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4, 137.5, 133.9, 133.3, 122.4, 115.8, 114.8, 112.6, 68.9, 30.0, 28.1. GC-MS calculated for $[M]^+$ 310, found 310. FTIR (neat, cm^{-1}): 3076(w), 2942(m), 1076(s), 739(m), 661(m).



4.25

pent-4-en-1-yl 4-methylbenzenesulfonate

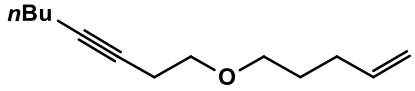
Compound was isolated as a colorless oil (210 mg, 87% yield) after purification by column chromatography (0 → 20% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.79 – 5.60 (m, 1H), 5.09 – 4.83 (m, 2H), 4.03 (t, *J* = 6.4 Hz, 2H), 2.55 – 2.35 (m, 3H), 2.08 (dt, *J* = 7.2 Hz, 2H), 1.85 – 1.64 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8, 136.8, 133.3, 130.0, 128.1, 116.0, 69.9, 29.5, 28.1, 21.8. ESI-MS calculated for $[M+H]^+$ 241.1, found 241.3.



4.26

(E)-(penta-2,4-dien-1-yloxy)benzene

Compound was isolated as a colorless oil (149 mg, 93% yield) after purification by column chromatography (0 → 50% benzene/hexanes over 8 CV). ^{1}H NMR (300 MHz, MeOD) δ 7.32 – 7.18 (m, 2H), 6.97 – 6.85 (m, 3H), 6.62 – 6.20 (m, 2H), 6.02 – 5.85 (m, 1H), 5.23 (dd, *J* = 15.5, 3.2 Hz, 1H), 5.10 (dd, *J* = 8.1, 3.5 Hz, 1H), 4.57 (d, *J* = 5.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 136.2, 133.8, 129.6, 128.6, 121.0, 118.3, 114.8, 68.1. GC-MS calculated for $[M]^+$ 160, found 160. FTIR (neat, cm^{-1}): 3084(w), 3071(w), 2944(m), 1243(s), 1079(s).

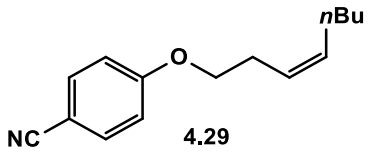


4.27

1-(pent-4-en-1-yloxy)oct-3-yne

Compound was isolated as a colorless oil (171 mg, 88% yield) after purification by short path distillation (50 °C, 100 mtorr). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 – 5.70

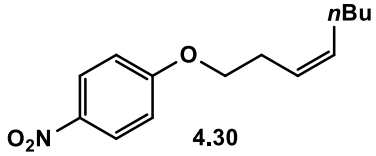
(m, 1H), 5.09 – 4.88 (m, 2H), 3.63 – 3.37 (m, 4H), 2.53 – 2.33 (m, 2H), 2.24 – 2.35 (m, 4H), 1.80 – 1.62 (m, 2H), 1.54 – 1.28 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 138.7, 114.8, 81.3, 77.5, 70.2, 70.0, 31.5, 30.7, 29.4, 22.2, 20.7, 18.8, 13.8. ESI-MS calculated for $[M+Na]^+$ 217.3, found 217.4. FTIR (neat, cm^{-1}): 3075(w), 2933(m), 2278 (m), 1260(w), 1115(s).



4.29

(Z)-4-(oct-3-en-1-yloxy)benzonitrile

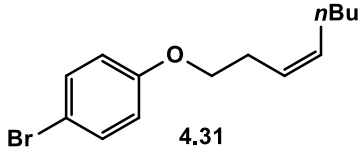
Compound was isolated as a colorless oil (208 mg, 91% yield) after a tetrahydrofuran/sodium hydroxide workup followed by column chromatography (0 → 10% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 5.54 (dt, *J* = 8.8, 7.1 Hz, 1H), 5.44 (dt, *J* = 8.5, 7.3 Hz, 1H), 4.00 (t, *J* = 6.8 Hz, 2H), 2.56 (q, *J* = 6.3 Hz, 2H), 2.18 – 2.00 (m, 2H), 1.40 – 1.28 (m, 4H), 0.91 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4, 134.1, 133.4, 124.0, 119.4, 115.3, 103.9, 68.0, 31.9, 27.3, 27.2, 22.5, 14.1. GC-MS calculated for $[M]^+$ 229, found 229. FTIR (neat, cm^{-1}): 3010(w), 2927(m), 2224(s), 1606(s), 1257(s), 1023(s).



4.30

(Z)-1-nitro-4-(oct-3-en-1-yloxy)benzene

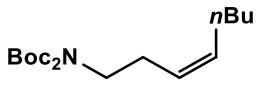
Compound was isolated as a yellow oil (218 mg, 87% yield) after purification by column chromatography (0 → 10% ethyl acetate/hexanes with a 5% chloroform additive over 8 CV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.1 Hz, 2H), 5.57 (dt, *J* = 17.2, 8.0 Hz, 1H), 5.43 (dt, *J* = 17.0, 7.7 Hz, 1H), 4.05 (t, *J* = 6.8 Hz, 2H), 2.58 (dt, *J* = 7.5, 6.7 Hz, 2H), 2.18 – 2.02 (m, 2H), 1.40 – 1.25 (m, 4H), 0.91 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.2, 141.5, 133.6, 126.1, 123.9, 114.6, 68.5, 31.9, 27.3, 27.2, 22.5, 14.1. HRMS calculated for $[M+Na]^+$ 272.1262, found 272.1274. FTIR (neat, cm^{-1}): 3011(w), 2955(m), 1513(s), 1342(s), 1021(s).



4.31

(Z)-1-bromo-4-(oct-3-en-1-yloxy)benzene

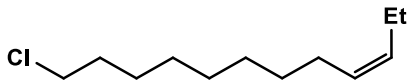
Compound was isolated as a colorless oil (261 mg, 92% yield) after a tetrahydrofuran/sodium hydroxide workup followed by column chromatography (0 → 5% diethyl ether/hexanes with a 5% benzene additive over 8 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 9.0 Hz, 2H), 6.77 (d, *J* = 9.0 Hz, 2H), 5.70 – 5.26 (m, 2H), 3.92 (t, *J* = 6.9 Hz, 2H), 2.52 (dt, *J* = 7.3, 6.8 Hz, 2H), 2.16 – 2.01 (m, 2H), 1.43 – 1.25 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 158.2, 133.1, 132.4, 124.5, 116.5, 112.9, 67.9, 31.9, 27.5, 27.2, 22.5, 14.1. GC-MS calculated for $[M]^+$ 282, found 282. FTIR (neat, cm^{-1}): 3010(w), 2925(m), 1489(s), 1031(s), 821(s).



4.32

(Z)-N,N-di(tert-butyl carbamate)-N-(oct-3-en-1-yl) amine

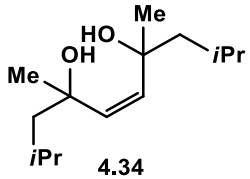
Compound was isolated as a colorless oil (281 mg, 81% yield) after purification by column chromatography (0 → 10% diethyl ether/hexanes with a 5% chloroform additive over 8 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 (dt, *J* = 18.3, 7.6 Hz, 1H), 5.32 (dt, *J* = 18.3, 7.6 Hz, 1H), 3.69 – 3.47 (m, 2H), 2.32 (dt, *J* = 7.2, 6.5 Hz, 2H), 2.12 – 1.98 (m, 2H), 1.50 (s, 18H), 1.38 – 1.27 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 132.7, 125.5, 82.2, 46.1, 32.0, 28.2, 27.3, 27.1, 22.5, 14.1. ESI-MS calculated for $[M+Na]^+$ 350.3, found 350.3. FTIR (neat, cm^{-1}): 3010(w), 2979(m), 1751(s), 1700(s), 1128(s).



4.33

(Z)-12-chlorododec-3-ene

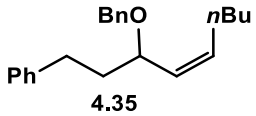
Compound was isolated as a colorless liquid (182 mg, 90% yield) after purification by column chromatography (0 → 30% benzene/hexanes over 8 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 – 5.02 (m, 2H), 3.53 (t, *J* = 6.7 Hz, 2H), 2.12 – 1.95 (m, 4H), 1.83 – 1.70 (m, 2H), 1.49 – 1.25 (m, 10H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.7, 129.4, 45.4, 32.8, 29.9, 29.5, 29.3, 29.0, 27.2, 27.0, 20.7, 14.5. GC-MS calculated for $[M]^+$ 202, found 202. FTIR (neat, cm^{-1}): 3004(m), 2926(s), 1463(m), 725(s).



4.34

(Z)-2,4,7,9-tetramethyldec-5-ene-4,7-diol

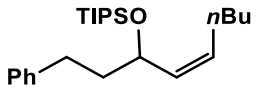
Compound was isolated as a white solid (227 mg, 99% yield) after a tetrahydrofuran/sodium hydroxide workup followed by column chromatography (0 → 40% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (s, 2H), 4.32 (s, 2H), 1.83 (qt, *J* = 12.9, 6.4 Hz, 2H), 1.51 (d, *J* = 6.0 Hz, 4H), 1.34 (s, 6H), 0.96 (d, 4.7 Hz, 6H), 0.94 (d, *J* = 6.6, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.4, 74.1, 52.8, 31.0, 24.9, 24.8, 24.7. HRMS calculated for $[M+Na]^+$ 251.1987, found 251.1991. FTIR (neat, cm^{-1}): 3219(br), 3004(w), 2954(s), 1158(s).



4.35

(Z)-(3-(benzyloxy)non-4-en-1-yl)benzene

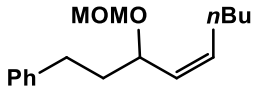
Compound was isolated as a colorless oil (283 mg, 92% yield) after a tetrahydrofuran/sodium hydroxide workup followed by column chromatography (0 → 15% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (300 MHz, MeOD) δ 7.59 – 6.88 (m, 10H), 5.64 (dt, *J* = 11.1, 7.5 Hz, 1H), 5.35 (dt, *J* = 11.0, 7.1 Hz, 1H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.31 (d, *J* = 11.8 Hz, 1H), 4.15 (dt, *J* = 13.7, 8.3 Hz, 1H), 2.80 – 2.55 (m, 2H), 2.08 – 1.81 (m, 3H), 1.77 – 1.60 (m, 1H), 1.39 – 1.15 (m, 4H), 0.86 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3, 139.1, 133.9, 130.7, 128.6, 128.4, 128.3, 127.9, 127.5, 125.8, 73.6, 70.0, 37.5, 32.0, 31.9, 27.7, 22.5, 14.1. HRMS calculated for $[M+Na]^+$ 331.2037, found 331.2030. FTIR (neat, cm^{-1}): 3026(w), 2955(m), 1603(m), 1453(m), 1068(s).



4.36

(Z)-triisopropyl((1-phenylnon-4-en-3-yl)oxy)silane

Compound was isolated as a colorless oil (172 mg, 92% yield) after a tetrahydrofuran/sodium hydroxide workup followed by column chromatography (0 → 10% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (300 MHz, MeOD) δ 7.35 – 7.06 (m, 5H), 5.50 – 5.32 (m, 2H), 4.73 – 4.53 (m, 1H), 2.78 – 2.52 (m, 2H), 2.12 – 1.65 (m, 4H), 1.44 – 1.27 (m, 4H), 1.12 – 1.02 (m, 21H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 133.9, 129.5, 128.5, 128.4, 125.7, 68.7, 41.0, 32.0, 31.4, 27.9, 22.6, 18.2, 14.2, 12.5. ESI-MS calculated for $[M+Na]^+$ 397.7, found 397.6. FTIR (neat, cm^{-1}): 3026(m), 2941(s), 1604(w), 1463(s), 1091(s).

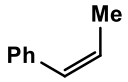


4.37

(Z)-(3-(methoxymethoxy)non-4-en-1-yl)benzene

Compound was isolated as a colorless liquid (229 mg, 87% yield) after purification by column chromatography (0 → 10% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (300 MHz, MeOD) δ 7.40 – 6.99 (m, 5H), 5.63 (dt, *J* = 11.6, 7.6 Hz, 1H), 5.36 – 5.13 (m, 1H), 4.67 (d, *J* = 6.7 Hz, 1H), 4.55 – 4.32 (m, 2H), 3.36 (s, 3H), 2.80 – 2.58 (m, 2H), 2.13 – 1.83 (m, 3H), 1.81 – 1.59 (m, 1H), 1.39 – 1.20 (m, 4H), 0.89 (t, *J* = 5.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3, 134.3, 129.7, 128.5, 125.9, 93.7, 70.7, 55.5,

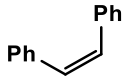
37.5, 32.0, 31.9, 31.5, 27.5, 22.4, 14.1. ESI-MS calculated for $[M+Na]^+$ 285.3, found 285.6. FTIR (neat, cm^{-1}): 3026(w), 2929(m), 1453(m), 1095(s), 1035(s).



4.38

(Z)-prop-1-en-1-ylbenzene

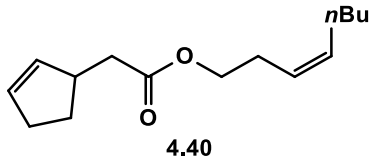
Compound was isolated as a colorless liquid (62 mg, 52% isolated yield, 98% by GC) after purification by vacuum transfer (100 mtorr). ^{1}H NMR (300 MHz, MeOD) δ 7.35 – 7.25 (m, 4H), 7.24 – 7.15 (m, 1H), 6.42 (dd, *J* = 11.6, 1.7 Hz, 1H), 5.78 (dq, *J* = 11.6, 7.2 Hz, 1H), 1.87 (dd, *J* = 7.2, 1.8 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 137.7, 130.0, 129.0, 128.2, 126.9, 126.5, 14.7. GC-MS calculated for $[M]^+$ 118, found 118. FTIR (neat, cm^{-1}): 3016(s), 2940(m), 1599(m), 1491(s), 1366(m).



4.39

(Z)-1,2-diphenylethene

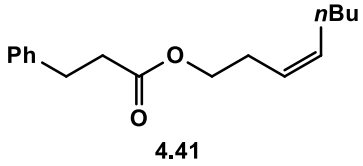
Compound was isolated as a colorless oil (177 mg, 98% yield) after purification by column chromatography (0 → 30% benzene/hexanes over 8 CV). ^{1}H NMR (300 MHz, MeOD) δ 7.25 – 7.15 (m 10H), 6.61 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.4, 130.4, 129.0, 128.4, 127.2. GC-MS calculated for $[M]^+$ 180, found 180. FTIR (neat, cm^{-1}): 3070(w), 3054(s), 3022(s), 1494(s), 1448(s).



4.40

(Z)-oct-3-en-1-yl 2-(cyclopent-2-en-1-yl)acetate

Compound was isolated as a colorless oil (225 mg, 95% yield) after purification by column chromatography (0 → 10% diethyl ether/hexanes with a chloroform additive over 8 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (dt, *J* = 4.3, 2.1 Hz, 1H), 5.67 (dd, *J* = 3.7, 2.1 Hz, 1H), 5.56 – 5.45 (m, 1H), 5.40 – 5.29 (m, 1H), 4.08 (t, *J* = 6.9 Hz, 2H), 3.17 – 3.00 (m, *J* = 6.1 Hz, 1H), 2.45 – 2.24 (m, 6H), 2.18 – 2.00 (m, 3H), 1.53 – 1.41 (m, 1H), 1.38 – 1.26 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 133.9, 133.0, 131.6, 124.5, 63.9, 42.2, 40.6, 32.0, 31.9, 29.8, 27.2, 27.0, 22.5, 14.1. GC-MS calculated for $[M]^+$ 236, found 236. FTIR (neat, cm^{-1}): 3021(w), 3010 (m), 2952(m), 1730(s), 1167(s).

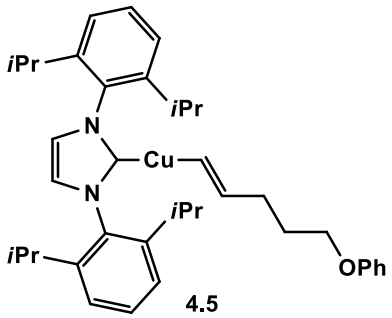


4.41

(Z)-oct-3-en-1-yl 3-phenylpropanoate

Compound was isolated as a colorless oil (222 mg, 85% yield) after purification by column chromatography (0 → 10% diethyl ether/hexanes over 8 CV then 0-10% ethyl acetate/hexanes with a benzene additive over 8 CV). ^{1}H NMR (300 MHz, MeOD) δ 7.53 – 6.88 (m, 5H), 5.48 (dt, *J* = 18.2, 7.4 Hz, 1H), 5.31 (dt, *J* = 18.1, 7.2 Hz, 1H), 4.03 (t, *J* = 6.9 Hz, 2H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.33 (dt, *J* = 7.2, 6.6 Hz,

2H), 2.18 – 2.00 (m, 2H), 1.40 – 1.28 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 140.7, 133.1, 128.6, 128.4, 126.4, 124.4, 64.1, 36.1, 31.9, 31.1, 27.1, 26.9, 22.5, 14.1. HRMS calculated for $[M+H]^+$ 261.1854, found 261.1865. FTIR (neat, cm^{-1}): 3063(w), 3010(m), 2956(s), 1732(s), 1161(s).



4.5

(5-phenoxy-1-penten-1-yl)[1,3-dihydro-1,3-bis(2,6-diisopropylphenyl)-2H-imidazol-2-ylidene]-Copper

The alkenyl copper product **X** was obtained as a white solid (38.0 mg, 62% isolated yield, >95% by NMR) after the volatiles were removed and the resulting solid was washed with pentane. ^{1}H NMR (300 MHz, C_6D_6) δ 7.41 – 7.11 (m, 11H), 6.58 (d, J = 19.7 Hz, 1H), 6.39 (s, 2H), 6.05 (dt, J = 19.6, 5.8 Hz, 1H), 3.49 (t, J = 7.0 Hz,PhH), 2.73 (sept, J = 9.2 Hz, 4H), 2.43 (tt, J = 13.5, 7.2 Hz, 2H), 2.03 – 1.85 (m, 2H), 1.53 (d, J = 9.4 Hz, 12H), 1.18 (d, J = 9.4 Hz, 12H).

Section 5: References

1. (a) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446. (b) Lindlar, H.; Dubuis, R. *Org. Synth. Coll.* **1973**, *5*, 880.

2. Brown, C. A. *Chem. Commun.* **1970**, 139.

3. Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226.

4. Molnár, Á.; Sárkány, A.; Varga, M. *J. Mol. Catal. A: Chem.* **2001**, *173*, 185.

5. Ulan, J. G.; Maier, W. F.; Smith, D. A. *J. Org. Chem.* **1987**, *52*, 3132.

6. Van Laren, M. W.; Elsevier, C. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3715.

7. Kluwer, A. M.; Koblenz, T. S.; Jonischkeit, T.; Woelk, K.; Elsevier, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 15470.

8. Selected examples: (a) Campos, K. R.; Cai, D.; Journet, M.; Kowal, J. J.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2001**, *66*, 3634. (b) Gruttadauria, M.; Noto, R.; Deganello, G.; Liotta, L. F. *Tetrahedron Lett.* **1999**, *40*, 2857. (c) Khan, N. A. *J. Am. Chem. Soc.* **1952**, *74*, 3018. (d) Nitta, Y.; Imanaka, T.; Teranishi, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3579. (e) Brunet, J. J.; Gallois, P.; Caubere, P. *J. Org. Chem.* **1980**, *45*, 1937. (f) Gallois, P.; Brunet, J. J.; Caubere, P. *J. Org. Chem.* **1980**, *45*, 1946. (g) Brunet, J. J.; Caubere, P. *J. Org. Chem.* **1984**, *49*, 4058. (h) Yoon, N. M.; Park, K. B.; Lee, H. J.; Choi, J. *Tetrahedron Lett.* **1996**, *37*, 8527. (i) Armbrüster, M.; Kovnir, K.; Behrens, M.; Teschner, D.; Grin, Y.; Schlögl, R. *J. Am. Chem. Soc.* **2010**, *132*, 14745. (j) Gruttadauria, M.; Liotta, L. F.; Noto, R.; Deganello, G. *Tetrahedron Lett.* **2001**, *42*, 2015. (k) Mastalir, Á.; Király, Z.; Szöllosi, G.; Bartók, M. *J. Catal.* **2000**, *194*, 146. (l) Mastalir, Á.; Király, Z. *J. Catal.* **2003**, *220*, 372. (m) Panpranot, J.; Phandinthong, K.; Sirikajorn, T.; Arai, M.; Praserthdam, P. *J. Mol. Catal. A: Chem.* **2007**, *261*, 29.

9. (a) Weerachawanasak, P.; Mekasuwandumrong, O.; Arai, M.; Fujita, S.-I.; Praserthdam, P.; Panpranot, J. *J. Catal.* **2009**, *262*, 199. (b) Dominguez-Dominguez, S.; Berenguer-Murcia, A.; Pradhan, B. K.; Linares-Solano, A.; Cazorla-Amoros, D. *J. Phys. Chem. C* **2008**, *112*, 3827.

10. Hori, J.; Murata, K.; Sugai, T.; Shinohara, H.; Noyori, R.; Arai, N.; Kurono, N.; Ohkuma, T. *Adv. Synth. Catal.* **2009**, *351*, 3143.

11. (a) Nishio, R.; Sugiura, M.; Kobayashi, S. *Org. Biomol. Chem.* **2006**, *4*, 992. (b) Alonso, F.; Osante, I.; Yus, M. *Adv. Synth. Catal.* **2006**, *348*, 305. (c) Shao, Z.; Li, C.; Chen, X.; Pang, M.; Wang, X.; Liang, C. *ChemCatChem* **2010**, *2*, 1555.

12. Yabe, Y.; Yamada, T.; Nagata, S.; Sawama, Y.; Monguchi, Y.; Sajiki, H. *Adv. Synth. Catal.* **2012**, *354*, 1264.

13. Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 2143.

14. Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1985**, *50*, 1147.

15. Li, J.; Hua, R.; Liu, T. *J. Org. Chem.* **2010**, *75*, 2966.

16. La Pierre, H. S.; Arnold, J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 3900.

17. Belger, C.; Neisius, N. M.; Plietker, B. *Chem. Eur. J.* **2010**, *16*, 12214.

18. Trost, B. M.; Braslau, R. *Tetrahedron Lett.* **1989**, *30*, 4657.

19. See reference 14

20. Hauwert, P.; Maestri, G.; Sprengers, J. W.; Catellani, M.; Elsevier, C. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3223.

21. Semba, K.; Fujihara, T.; Xu, T.; Terao, J.; Tsuji, Y. *Adv. Synth. Catal.* **2012**, *354*, 1542.

22. Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 3369.

23. Daeuble, J. F.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1990,** *31*, 2397.

24. See reference 21

25. See reference 22.

26. (a) Klyaschitskaya, A. L.; Krasovskii, G. N.; Fridlyand, S. A. *Gig. Sanit.* **1970**, *35*, 28. (b) Lawrence, J. N.; Drew, D. M.; Bushell, M. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381. (c) Jacquet, O.; Das Neves Gomes, C.; Ephritikhine, M.; Cantat, T. *J. Am. Chem. Soc.* **2012**, *134*, 2934.

27. Díez-González, S.; Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *J. Org. Chem.* **2005**, *70*, 4784.

28. See references 6, 7, 8a, 10, 11b, and 12.

29. Deutsch, C.; Lipshutz, B. H.; Krause, N. *Org. Lett.* **2009**, *11*, 5010.

30. See reference 22.

31. See reference 21.

32. As described in section 4.2.a.

33. See reference 22.

34. Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352.

35. See references 21-23, and

36. Davidson, M. H.; McDonald, F. E. *Org. Lett.* **2004**, *6*, 1601.

37. Konrad, T. M.; Fuentes, J. A.; Slawin, A. M.; Clarke, M. L. *Angew. Chem. Intl. Ed.* **2010**, *49*, 9197.

38. Fukino, T.; Fujita, N.; Aida, T. *Org. Lett.* **2010**, *12*, 3074.

39. Bender, C. F.; Yoshimoto, F. K.; Paradise, C. L.; De Brabander, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 11350.

40. Della, E. W.; Taylor, D. K. *J. Org. Chem.* **1994**, *59*, 2986.

41. See ref 22.

List of References in Alphabetical Order

1. Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008,** *108*, 2796.
2. Alonso, F.; Osante, I.; Yus, M. *Adv. Synth. Catal.* **2006**, *348*, 305.
3. Armbrüster, M.; Kovnir, K.; Behrens, M.; Teschner, D.; Grin, Y.; Schlögl, R. *J. Am. Chem. Soc.* **2010**, *132*, 14745.
4. Backvall, J. E.; Persson, E. S.; Bombrun, A. *J. Org. Chem.* **1994,** *59*, 4126.
5. Backvall, J. E.; Sellen, M.; Grant, B. *J. Am. Chem. Soc.* **1990,** *112*, 6615–6621.
6. Barker, T. J.; Jarvo, E. R. *Angew. Chem. Int. Ed*. **2011**, *50*, 8325.
7. Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598.
8. Barker, T. J.; Jarvo, E. R. *Synthesis* **2011**, 3954.
9. Belger, C.; Neisius, N. M.; Plietker, B. *Chem. Eur. J.* **2010**, *16*, 12214.
10. Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368.
11. Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Herwig, J.; Müller, T. E.; Thiel, O. R. *Chem. Eur. J.* **1999**, *5*, 1306.
12. Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070.
13. Bender, C. F.; Yoshimoto, F. K.; Paradise, C. L.; De Brabander, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 11350.
14. Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680.
15. Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219.
16. Bertz, S. H.; Cope, S.; Dorton, D.; Murphy, M.; Ogle, C. A. *Angew. Chem. Int. Ed.* **2007,** *46*, 7082.
17. Brown, C. A. *Chem. Commun*. **1970**, 139.
18. Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226.
19. Brown, H. C.; Cole, T. E.; Srebnik, M.; Kim, K. W. *J. Org. Chem.* **1986**, *51*, 4925.
20. Brown, H. C.; Heydkamp, W. R.; Breuer, E.; Murphy, W. S. *J. Am. Chem. Soc.* **1964**, *86*, 3565.
21. Brown, H. C.; Kim, K.-W.; Srebnik, M.; Bakthan, S. *Tetrahedron* **1987**, *43*, 4071.
22. Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 1097.

23. Brown, H. C.; Srebnik, M.; Cole, T. E. *Organometallics* **1986**, *5*, 2300.

24. Brunet, J. J.; Caubere, P. *J. Org. Chem.* **1984**, *49*, 4058.

25. Brunet, J. J.; Chu, N. C.; Rodriguez-Zubiri, M. *Eur. J. Inorg. Chem.* **2007**, *2007*, 4711.

26. Brunet, J. J.; Gallois, P.; Caubere, P. *J. Org. Chem.* **1980**, *45*, 1937.

27. Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521.

28. Campos, K. R.; Cai, D.; Journet, M.; Kowal, J. J.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2001**, *66*, 3634.

29. Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

30. Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116.

31. Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738.

32. Casarini, A.; Dembech, P.; Lazzari, D.; Marini, E.; Reginato, G.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1993**, *58*, 5620.

33. Castonguay, A.; Spasyuk, D. M.; Madern, N.; Beauchamp, A. L.; Zargarian, D. *Organometallics* **2009**, *28*, 2134.

34. Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933.

35. Cochran, B. M.; Michael, F. E. *J. Am. Chem. Soc.* **2008**, *130*, 2786.

36. Daeuble, J. F.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1990,** *31*, 2397.

37. Dang, L.; Lin, Z.; Marder, T. B. *Organometallics* **2010**, *29*, 917.

38. Davidson, M. H.; McDonald, F. E. *Org. Lett.* **2004**, *6*, 1601.

39. Del, A. V.; Dubbaka, S. R.; Krasovsky, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 7838.

40. Della, E. W.; Taylor, D. K. *J. Org. Chem.* **1994**, *59*, 2986.

41. Demel, P.; Keller, M.; Breit, B. *Chem. Eur. J.* **2006,** *12*, 6669.

42. Deutsch, C.; Lipshutz, B. H.; Krause, N. *Org. Lett.* **2009**, *11*, 5010.

43. Díez-González, S.; Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *J. Org. Chem.* **2005**, *70*, 4784.

44. Dominguez, D. S.; Berenguer, M. A.; Pradhan, B. K.; Linares, S. A.; Cazorla, A. D. *J. Phys. Chem. C* **2008**, *112*, 3827.

45. Dorta, R.; Egli, P.; Zürcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857.

46. Drege, T. Glorius, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 2.

47. Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937.

48. Fadini, L.; Togni, A. *Chem. Commun.* **2003**, 30.

49. Falciola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008,** 3765.

50. Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 2716.

51. Fukino, T.; Fujita, N.; Aida, T. *Org. Lett.* **2010**, *12*, 3074.

52. Gade, L. H.; Laponnaz, S. B. *Coord. Chem. Rev.* **2007**, *251*, 718.

53. Gallois, P.; Brunet, J. J.; Caubere, P. *J. Org. Chem.* **1980**, *45*, 1946.

54. Gao, F.; Carr, J. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2012,** *51*, 6613.

55. Gao, F.; Lee, Y.; Mandai, K.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2010,** *49*, 8370.

56. Goj, L. A.; Blue, E. D.; Delp, S. A.; Gunnoe, T. B.; Cundari, T. R.; Pierpont, A. W.; Petersen, J. L.; Boyle, P. D. *Inorganic Chemistry* **2006**, *45*, 9032.

57. Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748.

58. Gruttadauria, M.; Liotta, L. F.; Noto, R.; Deganello, G. *Tetrahedron Lett.* **2001**, *42*, 2015.

59. Gruttadauria, M.; Noto, R.; Deganello, G.; Liotta, L. F. *Tetrahedron Lett.* **1999**, *40*, 2857.

60. Guin, J.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 779.

61. Guin, J.; Mück-Lichtenfeld, C.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2007**, *129*, 4498.

62. Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1995**, *34*, 1348.

63. Hall, D. G. *Boronic Acids* **2005,** Wiley-VCH, Weinheim, Germany.

64. Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747.

65. Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534.

66. Hauwert, P.; Maestri, G.; Sprengers, J. W.; Catellani, M.; Elsevier, C. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3223.

67. Hatakeyama, T.; Yoshimoto, Y.; Ghorai, S. K.; Nakamura, M. *Org. Lett.* **2010**, *12*, 1516.

68. He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6414.

69. Henkel, T.; Brunne, R. M.; Muller, H.; Reichel, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 643.

70. Hesp, K. D.; Tobisch, S.; Stradiotto, M. *J. Am. Chem. Soc.* **2009**, *132*, 413.

71. Hill, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284.

72. Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673.

73. Hong, S.; Tian, S.; Metz, M. V.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 14768.

74. Hori, J.; Murata, K.; Sugai, T.; Shinohara, H.; Noyori, R.; Arai, N.; Kurono, N.; Ohkuma, T. *Adv. Synth. Catal.* **2009**, *351*, 3143.

75. Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367.

76. Hupe, E.; Marek, I.; Knochel, P. *Org. Lett.* **2002**, *4*, 2861.

77. Iyer, S.; Kulkarni, G. M.; Ramesh, C.; Sattar, A. K. *Indian J. Chem. Sect. B*, **2005**, *44B*, 1894

78. Jacquet, O.; Das Neves Gomes, C.; Ephritikhine, M.; Cantat, T. *J. Am. Chem. Soc.* **2012**, *134*, 2934.

79. Julian, L. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 13813.

80. Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007,** *46*, 4554.

81. Kabalka, G. W.; Sastry, K. A. R.; McCollum, G. W.; Yoshioka, H. *J. Org. Chem.* **1981**, *46*, 4296.

82. Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936.

83. Kawatsura, M.; Hartwig, J. F. *Organometallics* **2001**, *20*, 1960.

84. Khan, N. A. *J. Am. Chem. Soc.* **1952**, *74*, 3018.

85. Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 1737.

86. Kluwer, A. M.; Koblenz, T. S.; Jonischkeit, T.; Woelk, K.; Elsevier, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 15470.

87. Klyaschitskaya, A. L.; Krasovskii, G. N.; Fridlyand, S. A. *Gig. Sanit.* **1970**, *35*, 28.

88. Konrad, T. M.; Fuentes, J. A.; Slawin, A. M.; Clarke, M. L. *Angew. Chem. Intl. Ed.* **2010**, *49*, 9197.

89. La Pierre, H. S.; Arnold, J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 3900.

90. Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M.; Chan, D. M. T.; Combs, A.; *Tetrahedron Lett.* **1998**, *39*, 2941.

91. Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130.

92. Lawrence, J. N.; Drew, D. M.; Bushell, M. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381.

93. Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008,** *130,* 446.

94. Leitch, D. C.; Payne, P. R.; Dunbar, C. R.; Schafer, L. L. *J. Am. Chem. Soc.* **2009**, *131*, 18246.

95. Lemmon, T. H.; Goeden, G. V.; Huffman, J. C.; Geerts, R. L.; Kaulton, K. G. *Inorg. Chem.* **1990**, *29*, 3680.

96. Li, J.; Hua, R.; Liu, T. *J. Org. Chem.* **2010**, *75*, 2966.

97. Li, X.; Xing, J.; Zhao, J.; Huynh, P.; Zhang, W.; jiang, P.; Zhang, Y. J. *Org.Lett.* **2012,** 14, 390.

98. Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446.

99. Lindlar, H.; Dubuis, R. *Org. Synth. Coll.* **1973**, *5*, 880.

100. Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352.

101. Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc*. **2008**, *130*, 6918.

102. Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570.

103. Loiseau, F.; Clavette, C.; Raymond, M.; Roveda, J.-G.; Burrell, A.; Beauchemin, A. M. *Chem. Commun.* **2011**, *47*, 562.

104. Louie, J. Hartwig, J. F. *Tetrahedron Lett*. **1995**, *36*, 3609.

105. Magid, R. M. *Tetrahedron* **1980,** *36*, 1901.

106. Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 57.

107. Maj, A. M. Delaude, L.; Demonceau, A.; Noels, A. F. *J. Organomet. Chem.* **2007,** *692*, 3048.

108. Manna, K.; Xu, S.; Sadow, A. D. *Angew. Chem., Int. Ed*. **2011**, *50*, 1865.

109. Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004,** *23,* 3369.

110. Mastalir, Á.; Király, Z. *J. Catal.* **2003**, *220*, 372

111. Mastalir, Á.; Király, Z.; Szöllosi, G.; Bartók, M. *J. Catal.* **2000**, *194*, 146.

112. Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2012,** *51*, 11827.

113. Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2013,** *135*, 4934.

114. Matteson, D. S.; Kim, G. Y. *Org. Lett.* **2002**, *4*, 2153.

115. McBee, J. L.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2008**, *130*, 16562.

116. Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246.

117. Molnár, Á.; Sárkány, A.; Varga, M. *J. Mol. Catal. A: Chem.* **2001**, *173*, 185.

118. Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M.-E.; Bédard, A.-C.; Séguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893.

119. Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

120. Munro-Leighton, C.; Blue, E. D.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2006**, *128*, 1446.

121. Munro-Leighton, C.; Delp, S. A.; Alsop, N. M.; Blue, E. D.; Gunnoe, T. B. *Chem. Commun.* **2008**, 111.

122. Nishio, R.; Sugiura, M.; Kobayashi, S. *Org. Biomol. Chem.* **2006**, *4*, 992.

123. Nitta, Y.; Imanaka, T.; Teranishi, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3579.

124. Ohishi, T.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2008,** *47*, 5792.

125. Ohmiya, H.; Makida, Y.; Li, D.; Tanabe, M.; Sawamura, M. *J. Am. Chem. Soc.* **2009,** *131*, 17276.

126. Ohmiya, H.; Moriya, T.; Sawamura, M. *Org. Lett.* **2009**, *11*, 2145.

127. Ohmiya, H.; Tanabe, M.; Sawamura, M. *Org. Lett.* **2011**, *13*, 1086.

128. Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 2895.

129. Ohmiya, H.; Yokokawa, N.; Sawamura, M.*Org. Lett.* **2010,** *12*, 2438.

130. Ohmiya, H.; Yoshida, M.; Sawamura, M. *Org. Lett.* **2011**, *13*, 482.

131. Panpranot, J.; Phandinthong, K.; Sirikajorn, T.; Arai, M.; Praserthdam, P. *J. Mol. Catal. A: Chem.* **2007**, *261*, 29.

132. Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; McQuade, T. *J. Am. Chem. Soc.*, **2011**, *133*, 2410.

133. Park, J. K.; Lackey, H. H.; Rexford, M. D.; Kovnir, K.; Shatruk, M.; McQuade, T. *Org. Lett.*, **2010**, *12*, 5008.

134. Piarulli, U.; Daubos, P.; Claverie, C.; Roux, M.; Gennari, C. *Angew. Chem., Int. Ed.* **2003,** *42*, 234.

135. Polet, D.; Rathgeb, X.; Falciola, C. A.; Langlois, J. B.; El Hajjaji,S.; Alexakis, A. *Chem. Eur. J.* **2009,** *15*, 1205.

136. Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397.

137. Rappoport, Z.; Marek, I; *The Chemistry of Organocopper Compounds.* **2009,** Wiley, Hoboken, NJ. Krause, N. *Modern organocopper chemistry* **2002,** Wiley, Hoboken, NJ.

138. Reznichenko, A. L.; Nguyen, H. N.; Hultzsch, K. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 8984.

139. Ronal, P.; Tokes, J. T.; Crabee, P.J. *Chem. Soc. D.* **1969,** *8*, 43.

140. Rossi, S. A.; Shimkin, K. W.; Xu, Q.; Mori-Quiroz, L. M. Watson, D. A. *Org. Lett.* **2013,** *15*, 2314.

141. Rucker, R. P.; Whittaker, A, M.; Dang, H.; Lalic, G. *Angew. Chem. Int. Ed.* **2012,** *51*, 3953-3957.

142. Rucker, R. P.; Whittaker, A, M.; Dang, H.; Lalic, G. *J. Am. Chem. Soc.* **2012,** *134*, 6751.

143. Ryu, J.-S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584.

144. Scott, H. K.; Aggarwal, V. K. *Chem. Eur. J.* **2011**, *17*, 13124.

145. Seligson, A. L.; Trogler, W. C. *Organometallics* **1993**, *12*, 744.

146. Selim, K. B.; Matsumoto, Y.; Yamada, K.; Tomioka, K. *Angew. Chem. Int. Ed.* **2009,** *48*, 8733.

147. Semba, K.; Fujihara, T.; Xu, T.; Terao, J.; Tsuji, Y. *Adv. Synth. Catal.* **2012**, *354*, 1542.

148. Shao, Z.; Li, C.; Chen, X.; Pang, M.; Wang, X.; Liang, C. *ChemCatChem* **2010**, *2*, 1555.

149. Shen, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 564.

150. Shido, Y.; Tanabe, M.; Ohima, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012,** *134*, 18573.

151. Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem. Int. Ed.* **2011**, *37*, 8656.

152. Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 2143.

153. Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599.

154. Schnürch, M.; Holzweber, M.; Mihovilovic, M. D.; Stanetty, P. *Green. Chem.* **2007**, *9*, 139.

155. Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1985**, *50*, 1147.

156. Streitwieser, A.; Jayasree, E. G.; Hasanayn, F.; Leung, S. S. *J. Org. Chem.* **2008**, *73*, 9426.

157. Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338.

158. Takaya, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 5756.

159. Tanabe, M.; Ohima, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012,** *134*, 11896.

160. Tominaga, S.; Oi, Y.; Kato, T.; An, D. K.; Okamoto, S. *Tetrahedron Lett.* **2004,** *45*, 5585.

161. Tomita, D.; Kanai, M.; Shibasaki, M. *Chem. Asian J.* **2006**, *1*, 161.

162. Trost, B. M.; Braslau, R. *Tetrahedron Lett.* **1989**, *30*, 4657.

163. Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996,** *96*, 395.

164. Uehling, M. R.; Marionni, S. T.; Lalic, G. *Org. Lett.* **2012**, *14*, 362.

165. Ulan, J. G.; Maier, W. F.; Smith, D. A. *J. Org. Chem.* **1987**, *52*, 3132.

166. Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382.

167. Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2702.

168. Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 5608.

169. Van Klaveren, M.; Persson, E. S.; Villar, A. D.; Grove, D. M.; Backvall, J. E.; Van Koten, G. *Tetrahedron Lett.* **1995,** *36*, 3059.

170. Van Laren, M. W.; Elsevier, C. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3715.

171. Van Veldhuizen, J. J.; Campbell, J. E.; Guidici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877.

172. Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687.

173. Watson, D. A.; Chiu, M.; Bergman, R. G. *Organometallics* **2006**, *25*, 4731.

174. Weerachawanasak, P.; Mekasuwandumrong, O.; Arai, M.; Fujita, S.-I.; Praserthdam, P.; Panpranot, J. *J. Catal.* **2009**, *262*, 199.

175. Whitesides, G. M.; Stedronsky, E. R.; Casey, C. P.; San Filippo, J. *J. Am. Chem. Soc.* **1970**, *92*, 1426.

176. Whittaker, A. M.; Rucker, R. P.; Lalic, G. *Org. Lett.*, **2010**, *12*, 3216.

177. Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 354.

178. Wurtz, S.; Lohre, C.; Frohlich, R.; Bergander, K.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 8344.

179. Xiao, Q.; Tian, L.; Tan, R.; Xia, Y.; Qiu, D.; Zhang, Y.; Wang, J. *Org. Lett.* **2012,** *14*, 4230.

180. Yabe, Y.; Yamada, T.; Nagata, S.; Sawama, Y.; Monguchi, Y.; Sajiki, H. *Adv. Synth. Catal.* **2012**, *354*, 1264.

181. Yoon, N. M.; Park, K. B.; Lee, H. J.; Choi, J. *Tetrahedron Lett.* **1996**, *37*, 8527.

182. Yoshikai, N.; Zhang, S.; Nakamura, E. *J. Am. Chem. Soc.* **2008,** *130*, 12862.

183. Yu, X. Q.; Yamamoto, Y.; Miyaura, N. *Chem. Asian J.* **2008**, *3*, 1517.

184. Yu, Y.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2004**, *6*, 2631.

185. Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372.

186. Zhang, Z.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 3005.

187. Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798.

188. Zheng, B.; Srebnik, M. *J. Org. Chem.* **1995**, *60*, 1912.

189. Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220.

190. Zhou, Y.; Xie, Y.; Yang, L.; Xie, P.; Huang, H. *Tetrahedron Lett.* **2013,** *54*, 2713.

191. Zhu, C.; Li, G.; Ess, D. H.; Falck, J. R.; Kurti, L. *J. Am. Chem. Soc.* **2012,** *134*, 18253.

Appendix A: X-Ray Crystallography Information

Crystal Structure Report for G. Lalic
by Werner Kaminsky
Sample Submitted by Aaron Whittaker
ID – AW06177
X-ray Crystallography Laboratory
University of Washington
27. August 2013

Data backup accessibly through http:
URL: http://cad4.cpac.washington.edu/structures
Username: xray-user
Password: hkl-data

W.Kaminsky: tel. (206) 543 7585
(x-ray lab): tel. (206) 543 0210
Email: kaminsky@chem.washington.edu

Understanding crystallographic information is not trivial. If you discuss a structure in a publication, please let the crystallographers proof-read the final draft of that manuscript before you submit it. For many structures it is true that crystallography is an intellectual performance (like synthesis or elucidation of mechanisms) and not a routine job. In these cases, particularly when the structures contribute significantly to the content of the publication, the crystallographers should be co-authors. Do not think this is not necessary because you pay for structures. Even I have to pay for my own structures for my research.

A colorless prism, measuring 0.32 x 0.25 x 0.10 mm^3 was mounted on a glass capillary with oil. Data was collected at -173^{o}C on a Bruker APEX II single crystal X-ray diffractometer, Mo-radiation.

Crystal-to-detector distance was 40 mm and exposure time was 1 seconds per frame for all sets. The scan width was 2^o. Data collection was 100% complete to 25^o in ϑ. A total of 25392 (merged) reflections were collected covering the indices, h = -12 to 13, k = -17 to 17, l = -20 to 21. 9527 reflections were symmetry independent and the R_{int} = 0.0514 indicated that the data was good (average quality 0.07). Indexing and unit cell refinement indicated a primitive monoclinic lattice. The space group was found to be P $\bar{1}$ (No.2).

The data was integrated and scaled using SAINT, SADABS within the APEX2 software package by Bruker.

Solution by direct methods (SHELXS, SIR97) produced a complete heavy atom phasing model consistent with the proposed structure. The structure was completed by difference Fourier synthesis with SHELXL97. Scattering factors are from Waasmair and Kirfel. Hydrogen atoms were placed in geometrically idealised positions and constrained to ride on their parent atoms with C---H distances in the range 0.95-1.00 Angstrom. Isotropic thermal parameters U_{eq} were fixed such that they were $1.2U_{eq}$ of their parent atom Ueq for CH's and $1.5U_{eq}$ of their parent atom U_{eq} in case of methyl groups. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares.
The structure is of high quality and ready for publication. Table 1 summarizes the data collection details. Figure 1 shows an ORTEP of the asymmetric unit.

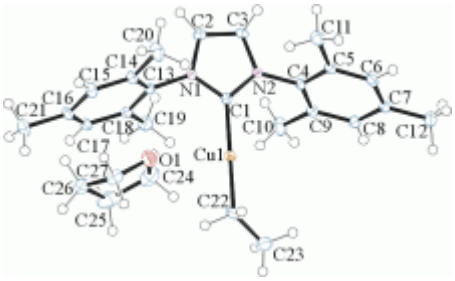


Figure A1.1. ORTEP of the structure with thermal ellipsoids at the 50% probability level.

Table A1.1: Crystallographic data for the structures provided.

Empirical formula	C27 H37 Cu N2 O	
Formula weight	469.13	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P $\bar{1}$	
Unit cell dimensions	a = 8.4829(5) Å	α= 102.238(4)°.
	b = 11.4784(6) Å	β= 98.112(4)°.
	c = 14.0410(8) Å	γ = 107.368(4)°.
Volume	1244.20(12) $Å^3$	
Z	2	
Density (calculated)	1.252 Mg/m^3	
Absorption coefficient	0.898 mm^{-1}	
F(000)	500	
Crystal size	0.32 x 0.25 x 0.10 mm^3	
Theta range for data collection	1.93 to 33.25°.	

Index ranges	-12<=h<=13, -17<=k<=17, -20<=l<=21
Reflections collected	25392
Independent reflections	9527 [R(int) = 0.0514]
Completeness to theta = 25.00°	100.0 %
Max. and min. transmission	0.9156 and 0.7621
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9527 / 0 / 287
Goodness-of-fit on F^2	1.009
Final R indices [I>2sigma(I)]	R1 = 0.0487, wR2 = 0.0856
R indices (all data)	R1 = 0.1012, wR2 = 0.1017
Largest diff. peak and hole	0.529 and -0.577 e.Å^{-3}

checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

No syntax errors found. CIF dictionary Interpreting this report

---

Datablock: aw06177_0m

Bond precision: C-C = 0.0030 A Wavelength=0.71073

Cell: a=8.4829(5) b=11.4784(6) c=14.0410(8) alpha=102.238(4) beta=98.112(4) gamma=107.368(4)

Temperature: 100 K

	Calculated	Reported
Volume	1244.20(13)	1244.20(12)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C23 H29 Cu N2, C4 H8 O	C23 H29 Cu N2, C4 H8 O
Sum formula	C27 H37 Cu N2 O	C27 H37 Cu N2 O
Mr	469.14	469.13
Dx,g cm-3	1.252	1.252
Z	2	2
Mu (mm-1)	0.898	0.898
F000	500.0	500.0
F000’	500.77	
h,k,lmax	13,17,21	13,17,21
Nref	9551	9527

Tmin,Tmax 0.764,0.914 0.762,0.916
Tmin' 0.750
Correction method= MULTI-SCAN

Data completeness= 0.997 Theta(max)= 33.250

R(reflections)= 0.0487(6173) wR2(reflections)= 0.1017(9527)

S = 1.009 Npar= 287

The following ALERTS were generated. Each ALERT has the format **test-name_ALERT_alert-type_alert-level**. Click on the hyperlinks for more details of the

---

Alert level G

PLAT005_ALERT_5_G No _iucr_refine_instructions_details in CIF .... ?
PLAT154_ALERT_1_G The su's on the Cell Angles are Equal ..... 0.00400 Deg.
PLAT794_ALERT_5_G Note: Tentative Bond Valency for Cu1 (II) 1.18 0

ALERT level A = Most likely a serious problem - resolve or explain
0 **ALERT level B** = A potentially serious problem, consider carefully
0 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
3 **ALERT level G** = General information/check it is not something unexpected

1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
0 ALERT type 2 Indicator that the structure model may be wrong or deficient
0 ALERT type 3 Indicator that the structure quality may be low

---

0 ALERT type 4 Improvement, methodology, query or suggestion
2 ALERT type 5 Informative message, check

PLATON version of 15/02/2012; check.def file version of 10/02/2012

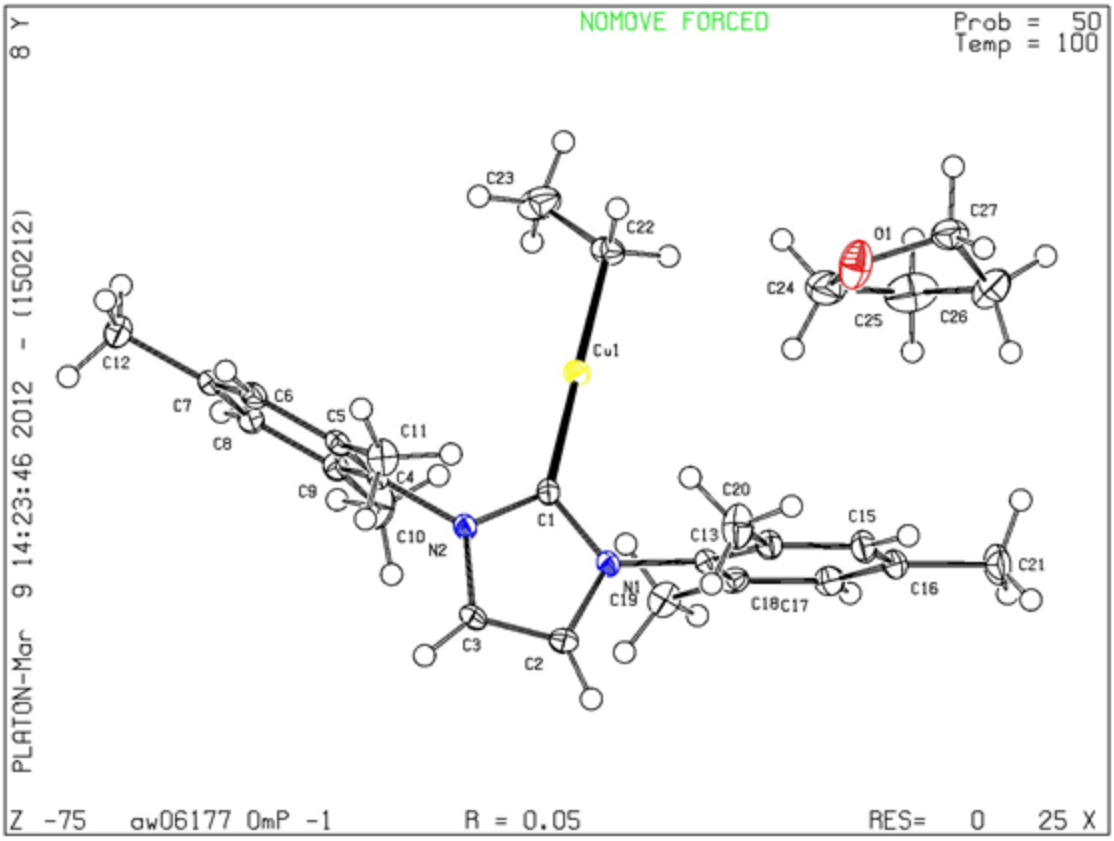


Table A1.2. Crystal data and structure refinement for aw06177_0m.

Identification code	aw06177_0m	
Empirical formula	C27 H37 Cu N2 O	
Formula weight	469.13	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P $\bar{1}$	
Unit cell dimensions	a = 8.4829(5) Å	x = 102.238(4)°.
	b = 11.4784(6) Å	y = 98.112(4)°.
	c = 14.0410(8) Å	z = 107.368(4)°.
Volume	1244.20(12) Å^3	
Z	2	
Density (calculated)	1.252 Mg/m^3	

Absorption coefficient	0.898 mm^{-1}
F(000)	500
Crystal size	0.32 x 0.25 x 0.10 mm^3
Theta range for data collection	1.93 to 33.25°.
Index ranges	-12<=h<=13, -17<=k<=17, -20<=l<=21
Reflections collected	25392
Independent reflections	9527 [R(int) = 0.0514]
Completeness to theta = 25.00°	100.0 %
Max. and min. transmission	0.9156 and 0.7621
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9527 / 0 / 287
Goodness-of-fit on F^2	1.009
Final R indices [I>2sigma(I)]	R1 = 0.0487, wR2 = 0.0856
R indices (all data)	R1 = 0.1012, wR2 = 0.1017
Largest diff. peak and hole	0.529 and -0.577 e.$Å^{-3}$

Table A1.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for aw06177_0m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	6083(2)	7074(2)	8044(1)	13(1)
C(2)	3623(2)	6191(2)	8497(1)	18(1)
C(3)	4235(2)	7424(2)	8999(2)	18(1)
C(4)	6744(2)	9267(2)	9070(1)	13(1)
C(5)	7718(2)	9735(2)	10040(1)	15(1)
C(6)	8688(2)	11018(2)	10358(1)	16(1)
C(7)	8681(2)	11813(2)	9744(1)	16(1)
C(8)	7660(2)	11313(2)	8782(1)	17(1)
C(9)	6678(2)	10036(2)	8430(1)	15(1)
C(10)	5565(3)	9501(2)	7395(2)	25(1)
C(11)	7731(3)	8904(2)	10737(2)	22(1)
C(12)	9728(2)	13200(2)	10109(2)	23(1)

C(13)	4548(2)	4792(2)	7261(1)	14(1)
C(14)	4985(2)	3890(2)	7653(1)	17(1)
C(15)	4699(2)	2715(2)	6999(2)	19(1)
C(16)	4000(2)	2442(2)	5987(1)	18(1)
C(17)	3568(2)	3368(2)	5626(1)	18(1)
C(18)	3824(2)	4555(2)	6251(1)	16(1)
C(19)	3330(2)	5538(2)	5847(2)	22(1)
C(20)	5731(3)	4152(2)	8745(2)	27(1)
C(21)	3724(3)	1169(2)	5298(2)	28(1)
C(22)	9859(2)	7446(2)	6782(2)	20(1)
C(23)	10576(3)	8652(2)	6454(2)	31(1)
C(24)	9294(3)	4222(2)	7041(2)	36(1)
C(25)	8825(3)	3236(2)	6050(2)	39(1)
C(26)	8996(3)	2076(2)	6330(2)	32(1)
C(27)	10323(2)	2644(2)	7286(2)	25(1)
N(1)	4762(2)	5993(1)	7925(1)	14(1)
N(2)	5728(2)	7945(1)	8716(1)	13(1)
Cu(1)	7945(1)	7271(1)	7407(1)	15(1)
O(1)	9986(2)	3728(1)	7784(1)	33(1)

Table A1.4. Bond lengths [Å] and angles [°] for aw06177_0m.

C(1)-N(2)	1.357(2)
C(1)-N(1)	1.360(2)
C(1)-Cu(1)	1.9022(18)
C(2)-C(3)	1.343(3)
C(2)-N(1)	1.380(2)
C(2)-H(2)	0.9500
C(3)-N(2)	1.382(2)
C(3)-H(3)	0.9500
C(4)-C(5)	1.391(2)
C(4)-C(9)	1.393(3)
C(4)-N(2)	1.440(2)

C(5)-C(6)	1.392(2)
C(5)-C(11)	1.506(3)
C(6)-C(7)	1.382(3)
C(6)-H(6)	0.9500
C(7)-C(8)	1.396(3)
C(7)-C(12)	1.506(2)
C(8)-C(9)	1.391(2)
C(8)-H(8)	0.9500
C(9)-C(10)	1.506(3)
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-C(14)	1.388(3)
C(13)-C(18)	1.397(3)
C(13)-N(1)	1.436(2)
C(14)-C(15)	1.392(3)
C(14)-C(20)	1.503(3)
C(15)-C(16)	1.390(3)
C(15)-H(15)	0.9500
C(16)-C(17)	1.389(3)
C(16)-C(21)	1.503(3)
C(17)-C(18)	1.391(3)
C(17)-H(17)	0.9500
C(18)-C(19)	1.503(3)
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(20)-H(20A)	0.9800

C(20)-H(20B)	0.9800
C(20)-H(20C)	0.9800
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
C(22)-C(23)	1.531(3)
C(22)-Cu(1)	1.9303(19)
C(22)-H(22A)	0.9900
C(22)-H(22B)	0.9900
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(24)-O(1)	1.426(3)
C(24)-C(25)	1.511(4)
C(24)-H(24A)	0.9900
C(24)-H(24B)	0.9900
C(25)-C(26)	1.507(3)
C(25)-H(25A)	0.9900
C(25)-H(25B)	0.9900
C(26)-C(27)	1.503(3)
C(26)-H(26A)	0.9900
C(26)-H(26B)	0.9900
C(27)-O(1)	1.421(3)
C(27)-H(27A)	0.9900
C(27)-H(27B)	0.9900
N(2)-C(1)-N(1)	102.89(15)
N(2)-C(1)-Cu(1)	129.69(12)
N(1)-C(1)-Cu(1)	127.42(13)
C(3)-C(2)-N(1)	106.33(16)
C(3)-C(2)-H(2)	126.8
N(1)-C(2)-H(2)	126.8
C(2)-C(3)-N(2)	106.55(16)
C(2)-C(3)-H(3)	126.7
N(2)-C(3)-H(3)	126.7

C(5)-C(4)-C(9)	122.55(16)
C(5)-C(4)-N(2)	119.08(16)
C(9)-C(4)-N(2)	118.35(15)
C(4)-C(5)-C(6)	117.57(17)
C(4)-C(5)-C(11)	122.06(16)
C(6)-C(5)-C(11)	120.37(16)
C(7)-C(6)-C(5)	121.90(17)
C(7)-C(6)-H(6)	119.0
C(5)-C(6)-H(6)	119.0
C(6)-C(7)-C(8)	118.80(16)
C(6)-C(7)-C(12)	120.88(17)
C(8)-C(7)-C(12)	120.31(17)
C(9)-C(8)-C(7)	121.36(18)
C(9)-C(8)-H(8)	119.3
C(7)-C(8)-H(8)	119.3
C(8)-C(9)-C(4)	117.79(16)
C(8)-C(9)-C(10)	121.27(17)
C(4)-C(9)-C(10)	120.94(16)
C(9)-C(10)-H(10A)	109.5
C(9)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(9)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(5)-C(11)-H(11A)	109.5
C(5)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(5)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(7)-C(12)-H(12A)	109.5
C(7)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(7)-C(12)-H(12C)	109.5

H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(14)-C(13)-C(18)	122.56(16)
C(14)-C(13)-N(1)	118.92(16)
C(18)-C(13)-N(1)	118.44(16)
C(13)-C(14)-C(15)	117.72(17)
C(13)-C(14)-C(20)	121.86(17)
C(15)-C(14)-C(20)	120.42(17)
C(16)-C(15)-C(14)	121.69(18)
C(16)-C(15)-H(15)	119.2
C(14)-C(15)-H(15)	119.2
C(17)-C(16)-C(15)	118.79(17)
C(17)-C(16)-C(21)	120.77(18)
C(15)-C(16)-C(21)	120.44(18)
C(16)-C(17)-C(18)	121.61(17)
C(16)-C(17)-H(17)	119.2
C(18)-C(17)-H(17)	119.2
C(17)-C(18)-C(13)	117.63(17)
C(17)-C(18)-C(19)	120.73(17)
C(13)-C(18)-C(19)	121.64(17)
C(18)-C(19)-H(19A)	109.5
C(18)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(18)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(14)-C(20)-H(20A)	109.5
C(14)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
C(14)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
C(16)-C(21)-H(21A)	109.5
C(16)-C(21)-H(21B)	109.5

H(21A)-C(21)-H(21B)	109.5
C(16)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
C(23)-C(22)-Cu(1)	118.71(15)
C(23)-C(22)-H(22A)	107.6
Cu(1)-C(22)-H(22A)	107.6
C(23)-C(22)-H(22B)	107.6
Cu(1)-C(22)-H(22B)	107.6
H(22A)-C(22)-H(22B)	107.1
C(22)-C(23)-H(23A)	109.5
C(22)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(22)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
O(1)-C(24)-C(25)	107.72(19)
O(1)-C(24)-H(24A)	110.2
C(25)-C(24)-H(24A)	110.2
O(1)-C(24)-H(24B)	110.2
C(25)-C(24)-H(24B)	110.2
H(24A)-C(24)-H(24B)	108.5
C(26)-C(25)-C(24)	103.87(19)
C(26)-C(25)-H(25A)	111.0
C(24)-C(25)-H(25A)	111.0
C(26)-C(25)-H(25B)	111.0
C(24)-C(25)-H(25B)	111.0
H(25A)-C(25)-H(25B)	109.0
C(27)-C(26)-C(25)	102.16(18)
C(27)-C(26)-H(26A)	111.3
C(25)-C(26)-H(26A)	111.3
C(27)-C(26)-H(26B)	111.3
C(25)-C(26)-H(26B)	111.3
H(26A)-C(26)-H(26B)	109.2

O(1)-C(27)-C(26)	105.13(17)
O(1)-C(27)-H(27A)	110.7
C(26)-C(27)-H(27A)	110.7
O(1)-C(27)-H(27B)	110.7
C(26)-C(27)-H(27B)	110.7
H(27A)-C(27)-H(27B)	108.8
C(1)-N(1)-C(2)	112.19(15)
C(1)-N(1)-C(13)	124.12(15)
C(2)-N(1)-C(13)	123.68(15)
C(1)-N(2)-C(3)	112.05(15)
C(1)-N(2)-C(4)	124.41(15)
C(3)-N(2)-C(4)	123.50(15)
C(1)-Cu(1)-C(22)	178.44(9)
C(27)-O(1)-C(24)	107.75(17)

Symmetry transformations used to generate equivalent atoms:

Table A1.5. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for aw06177_0m. The Anisotropic displacement factor exponent takes the form: $-2^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	14(1)	11(1)	13(1)	2(1)	2(1)	5(1)
C(2)	15(1)	18(1)	21(1)	4(1)	9(1)	5(1)
C(3)	17(1)	18(1)	21(1)	3(1)	11(1)	7(1)
C(4)	13(1)	11(1)	16(1)	2(1)	5(1)	5(1)
C(5)	16(1)	16(1)	14(1)	2(1)	6(1)	8(1)
C(6)	15(1)	19(1)	14(1)	-1(1)	3(1)	7(1)
C(7)	14(1)	13(1)	19(1)	0(1)	7(1)	5(1)
C(8)	18(1)	14(1)	19(1)	5(1)	7(1)	6(1)
C(9)	16(1)	15(1)	14(1)	2(1)	4(1)	7(1)
C(10)	33(1)	18(1)	19(1)	3(1)	-4(1)	6(1)
C(11)	28(1)	21(1)	17(1)	6(1)	4(1)	10(1)
C(12)	22(1)	16(1)	26(1)	1(1)	6(1)	3(1)

C(13)	13(1)	12(1)	16(1)	1(1)	5(1)	4(1)
C(14)	18(1)	16(1)	16(1)	3(1)	3(1)	6(1)
C(15)	21(1)	16(1)	20(1)	2(1)	3(1)	9(1)
C(16)	19(1)	16(1)	18(1)	-2(1)	6(1)	6(1)
C(17)	19(1)	21(1)	12(1)	1(1)	4(1)	5(1)
C(18)	14(1)	17(1)	16(1)	5(1)	6(1)	3(1)
C(19)	25(1)	21(1)	19(1)	7(1)	3(1)	6(1)
C(20)	39(1)	22(1)	19(1)	3(1)	-3(1)	13(1)
C(21)	34(1)	21(1)	25(1)	-4(1)	3(1)	12(1)
C(22)	18(1)	27(1)	14(1)	3(1)	6(1)	7(1)
C(23)	24(1)	36(1)	26(1)	7(1)	8(1)	1(1)
C(24)	26(1)	30(1)	58(2)	18(1)	13(1)	12(1)
C(25)	31(1)	51(2)	37(2)	27(1)	5(1)	9(1)
C(26)	34(1)	27(1)	25(1)	3(1)	9(1)	-2(1)
C(27)	20(1)	26(1)	32(1)	13(1)	8(1)	7(1)
N(1)	15(1)	12(1)	14(1)	2(1)	6(1)	5(1)
N(2)	15(1)	12(1)	14(1)	3(1)	6(1)	5(1)
Cu(1)	14(1)	15(1)	13(1)	2(1)	5(1)	4(1)
O(1)	51(1)	22(1)	23(1)	5(1)	10(1)	7(1)

Table A1.6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3)for aw06177_0m.

	x	y	z	U(eq)
H(2)	2608	5577	8530	22
H(3)	3739	7853	9459	21
H(6)	9374	11356	11015	20
H(8)	7636	11856	8359	20
H(10A)	5590	10190	7082	38
H(10B)	4401	9069	7437	38
H(10C)	5979	8895	6994	38
H(11A)	6767	8838	11059	33

H(11B)	8787	9274	11248	33
H(11C)	7646	8057	10358	33
H(12A)	8982	13700	10219	35
H(12B)	10357	13446	9608	35
H(12C)	10525	13356	10737	35
H(15)	4989	2083	7252	23
H(17)	3085	3186	4936	22
H(19A)	2546	5810	6216	33
H(19B)	2777	5176	5138	33
H(19C)	4344	6269	5923	33
H(20A)	6685	4953	8963	41
H(20B)	6129	3462	8854	41
H(20C)	4867	4212	9129	41
H(21A)	2965	1056	4666	42
H(21B)	3216	501	5608	42
H(21C)	4813	1120	5171	42
H(22A)	10787	7372	7252	24
H(22B)	9533	6715	6186	24
H(23A)	9704	8719	5952	46
H(23B)	11554	8616	6167	46
H(23C)	10929	9393	7033	46
H(24A)	10137	5018	7013	43
H(24B)	8279	4407	7201	43
H(25A)	7650	3074	5701	46
H(25B)	9603	3508	5614	46
H(26A)	7915	1544	6437	38
H(26B)	9374	1561	5811	38
H(27A)	10237	2034	7696	30
H(27B)	11471	2889	7146	30