Anti-Markovnikov Hydroarylation of Alkenes with Aryl Halides and Synthesis and Characterization of a Monomeric Copper Hydride complex

Andrea Chong

A thesis submitted in a partial fulfillment of the requirements for the degree of

Master of Science

University of Washington

2018

Committee:

Dr. Gojko Lalic

Dr. Michael Heinekey

Program Authorized to offer Degree:

Department of Chemistry

Abstract

Anti-Markovnikov Hydroarylation of Alkenes with Aryl Halides and Synthesis and Characterization of a Monomeric Copper Hydride complex

Andrea Chong

Chairperson of the Supervisory Committee:
Professor Gojko Lalic
Department of Chemistry

Chapter 1 describes the nickel-catalyzed hydroarylation of alkenes. This reaction involves reductive cross coupling of alkenes and aryl halides in the presence of a silane as the hydride donor. High anti-Markovnikov selectivity is achieved in this reaction, and broad functional group compatibility demonstrates its utility, coupling a wide range of alkene substrates, such as alkyl- and aryl-substituted alkenes as well as enol ethers and diene.

Chapter 2 describes efforts to synthesize monomeric copper hydride complexes. Preparation and characterization of various copper complexes using tris(pyrazolyl)borate (Tp), - methane (Tpm), - ethane (Tpe) and *N*-heterocyclic carbene (NHC) ligands were performed. Reaction of Tp ligated copper (II) methoxide complex with silane showed evidence of the existence of copper (II) hydride in the reaction.

Table of Contents

List of Abbrevations

Ad:	Adamantyl
Ar:	Aryl
C:	Celcius
COD:	1,5-cyclooctadiene
dba:	Dibenzylideneacetone
DCM:	Dichloromethane
DFT:	Density functional theory
dme:	Dimethoxyethane
DTBM-SEGPHOS:	5,5’-bis[di(3,5-di-t-butyl-4-methoxyphenyl)phosphino]-4,4’-bi-1,3-benzodioxole
Equiv:	Equivalent
EtOAc:	Ethyl Acetate
Et_2O:	Diethyl ether
ESI-MS:	Electrospray ionization mass spectrometry
Et:	Ethyl
FTIR:	Fourier transform infrared spectroscopy
Abbreviations for IR peaks	
s:	Strong
m:	Medium
w:	Weak
b:	broad
GC:	Gas Chromatography

HBpin:	Pinacolborane
Hr:	Hour
HPLC:	High performance liquid chromatography
HRMS:	High resolution mass spectrometry
Hz:	Hertz
iPr:	Isopropyl
IPr:	1,3-Bis-(2,6-diisopropylphenyl)imidazolium
Me:	Methyl
MHz:	Megahertz
mol:	Mole
NHC:	N-heterocyclic carbene
NMR:	Nuclear magnetic resonance

Abbreviations for NMR splitting patterns

s:	Singlet
d:	Doublet
t:	Triplet
q:	Quartet
m:	Multiplet
br:	Broad
dd:	Doublet of doublets
dt:	Doublet of triplets
ddt:	Doublet of doublet of triplets

ORTEP:	Oak Ridge Thermal Ellipsoid Plot Program (molecular modeling)

OTf:	Trifluoromethanesulfonate
Ph:	Phenyl
PMHS:	polymethylhydrosiloxane
PNP:	p-nitrophenyl
ppm:	Parts per million
Pz:	Pyrazole
rt:	Room temperature
tBu:	Tert-butyl
THF:	tetrahydrofuran
TLC:	Thin layer chromatography
TMB:	1,3,5-Trimethoxy benzene
TMDSO:	Tetramethyldisiloxane
Tp:	Tris(pyrazolyl)borate
Tpe:	Tris(pyrazolyl)ethane
Tpm:	Tris(pyrazolyl)methane
X-ray:	Energetic High-Frequency Electromagnetic Radiation

List of Figures

List of Schemes

Scheme 2.1. Synthesis of copper (II) hydroxo complexes with Tp ligands

Scheme 2.2. Synthesis of hydrotris(pyrazolyl) ligand

Scheme 2.3. Synthesis of copper (II) methoxide, [Cu(OMe){HB(3-Ad-5-Mepz)$_3$}]

Scheme 2.4. Synthesis of copper (II) hydride complex, [HCu{HB(3-Ad-5-Mepz)$_3$}]

Scheme 2.5. General scheme to synthesize copper (I) hydride

Scheme 2.6. Synthesis of imidazolium salt, IPr*$^{(2\text{-Np})\cdot}$ HCl

List of Tables

Acknowledgement

Firstly, I would like to express my gratitude to my advisor, Prof. Gojko Lalic, for his support and mentorship. He has taught me so much about practice of science, and I am deeply grateful for the patience and encouragement he has given me.

I would also like to extend my thanks to my other advisor in Copper hydride project, Prof. Michael Heinekey, for his patience, guidance and engagement through the learning process of this project.

Furthermore, I would like to thank the members of the Lalic Lab who have helped me during my time in the group: Dr. Melrose Mailig, Julia Nguyen, Megan Armstrong, Mitchell Lee, Avijit Hazra, Madison Goodstein and Jason Chen. They have made the lab environment efficient and enjoyable to work in. I would also like to thank the post-doc of the Heinekey Lab, Dr. Louise Guard, for all her helps and encouragement.

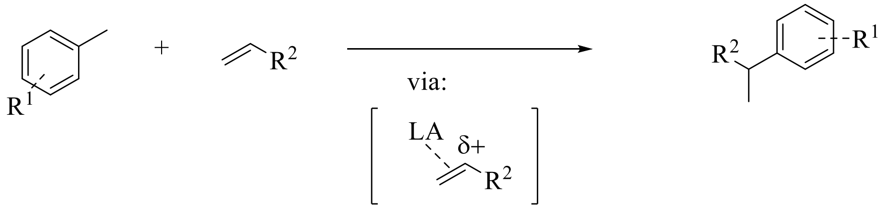
Finally, I must express my very profound gratitude to my parents and family for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. Thank you for always being there.

Chapter 1: Anti-Markovnikov hydroarylation of alkenes with aryl halides

1.1 Introduction

Alkenes are widely available and inexpensive feedstock materials. Thus, catalytic hydroarylation of alkenes has become a versatile approach for the preparation of alkylarenes, a prevalent motif in medicinal chemistry and materials science. The classical method of alkene hydroarylation is Friedel-Crafts acid catalyzed hydroarylation (Figure 1.1a).[1–3] This reaction forms carbocationic intermediates, and therefore, requires electron rich arenes as coupling partners and favors the formation of the branched product. Additionally, metal catalyzed aryl C-H bond cleavage has been utilized as another strategy to generate aryl alkenes.[4] The aryl C-H bond cleavage reaction goes through a metal hydride intermediate and can provide access to both Markovnikov and anti-Markovnikov products (Figure 1.1b). This method, however, is associated with harsh reaction conditions and requires the presence of a directing group or a very specific aryl coupling partner to achieve good regioselectivity.

a. Friedel-craft acid catalyzed reaction



b. Metal-catalyzed aryl C-H bond cleavage

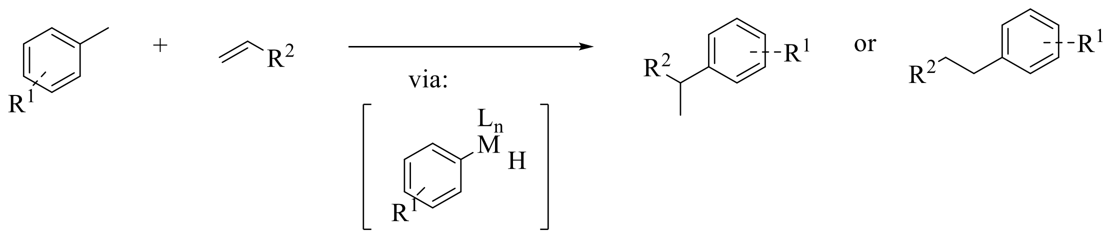


Figure 1.1. Hydroarylation reactions of alkenes

Reductive cross coupling has demonstrated that hydride reagents such as silanes and H_2 can be used to generate metal hydrides, which can undergo olefin insertion to form reactive alkyl metal species. These alkyl metal species can then be intercepted by an aryl electrophile. Therefore, the reductive cross coupling strategy provides opportunities to achieve better stereospecificity without relying on aryl substituent groups. Whereas most examples of reductive cross coupling lead to Markovnikov hydroarylation,[5,6] Buchwald et al. reported the anti-Markovnikov hydroarylation of alkenes using reductive cross coupling promoted by dual copper and palladium catalysis (Figure 1.2). His work employs unactivated alkenes as coupling partners with aryl halides and generates linear products.[7] Interestingly, they observed opposite regioselectivity when aryl alkenes are used.[8]

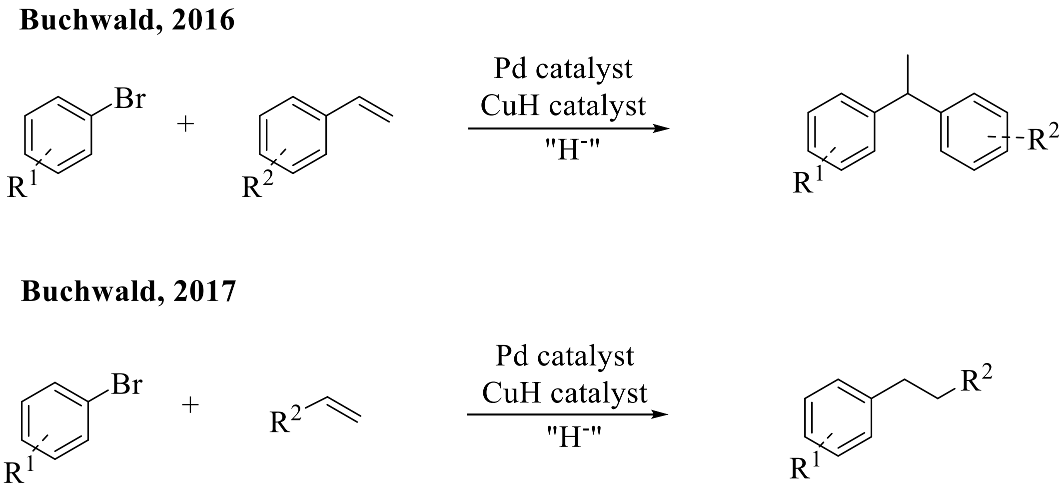


Figure 1.2. Previous works of hydroarylation of alkenes

This thesis reports the development of a method to achieve the anti-Markovnikov hydroarylation of alkenes and styrenes using a single catalyst. On the basis of a report by Lee et al. demonstrating the 1,2-insertion of 1-hexene into the Ni-H bond of an amido diphosphine supported Ni complex,[9] it is hypothesized that nickel alone could achieve the hydroarylation reaction.

Previous work demonstrated that, when a nickel hydride complex supported by PNP pincer ligand [N(o-C6H4PPh2)2]- (Ph-PNP) is involved, the addition of 1-hexene to this nickel hydride complex could quantitatively generate the alkyl nickel complex (Figure 1.3).[10] Reaction of this isolated alkyl nickel complex with an aryl electrophile lead to observation of anti-Markovnikov hydroarylation product. However, in preliminary optimization work, it was found that a ligand-less nickel catalyst gives highest yield.

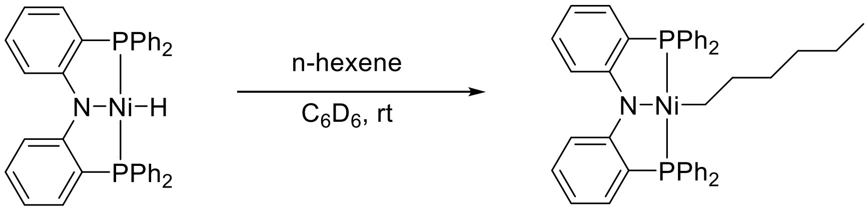
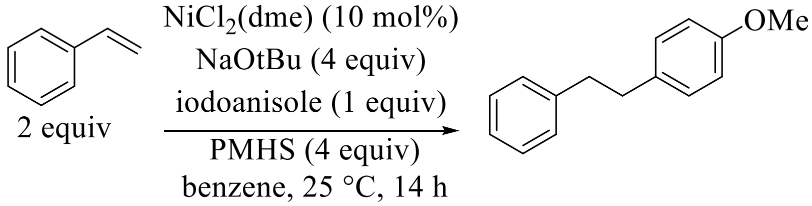


Figure 1.3. Stoichiometric olefin insertion reaction with nickel hydride complex

1.2 Reaction Optimization

Using styrene as standard substrate, reaction optimization was started by screening different nickel sources, such as $NiCl_2$(dme), $Ni(COD)_2$ and $NiCl_2$. While $NiCl_2$(dme) emerged as a competent catalyst in this reaction, other nickel catalysts showed poor yields. Meanwhile, in screening nitrogen- and phosphine-based ligands, we only observed negligible yields. As an example, NHC based- ligand (IPr) not only led to low yield of the product, but also showed poor regioselectivity. A solvent screen showed that only aromatic based solvents give a satisfying result, and benzene works better than toluene. Polymethylhydrosilane (PMHS) was found to be the best hydride source, and sodium *tert*-Butoxide (NaOtBu) worked as the best base. Overall, this optimized reaction condition (Table 1.1, Entry 1) provides good yield and good regioselectivity. Notably, exclusion of any component in this reaction will result in no product formation.

Table 1.1. Reaction optimization of anti-Markovnikov hydroarylation of alkenes



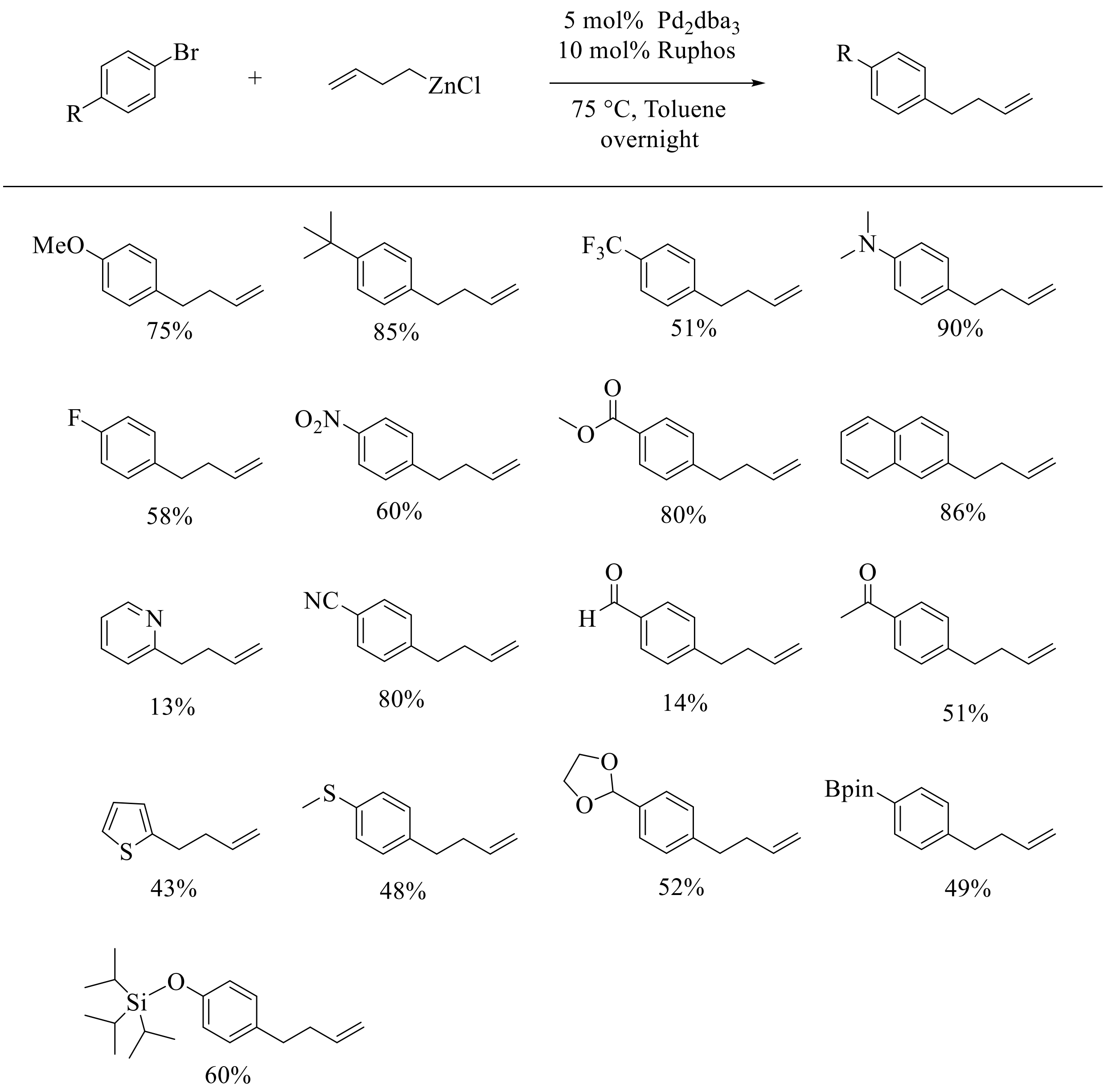
Entry	Variations from above	Yield (%)[a]	L:B[b]
1	none	89 (81)	55:1
2	bipyridine as a ligand	24	56:44
3	IPr as a ligand	0	-
4	$NiCl_2$ instead of $NiCl_2$(dme)	44	-
5	$Ni(COD)_2$ instead of $NiCl_2$(dme)	39	-
6	toluene instead of benzene	80	-
7	THF instead of benzene	8	71:29
8	LiOtBu instead of NaOtBu	30	-
9	TMDSO instead of PMHS	57	-

[a] Yields were determined by GC analysis of the crude reaction mixture using 1,3,5-trimethylbenzene as the internal standard. Numbers in parentheses are yields of isolated products. [b] L:B is the ratio of the linear product to the branched product as determined by GC analysis of the crude reaction mixture.

1.3 Reaction Scope

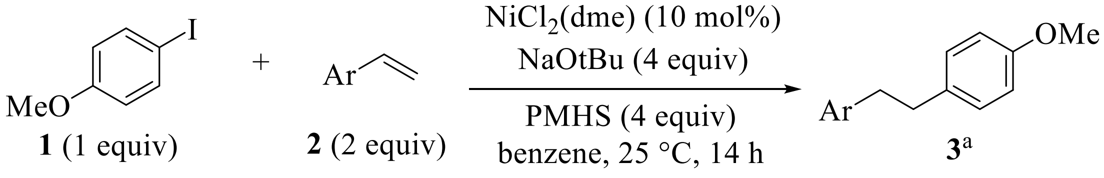
Using the optimal reaction condition, the substrate scope was expanded by exploration of different alkenes and aryl coupling partners. Prior to this, a wide range of alkene starting materials was synthesized and further used for substrate scope purpose. As modified from literature[11], a general procedure for the cross coupling of an alkenyl zinc halide with an aryl bromide was developed in the synthesis of alkenes. (Table 1.2).

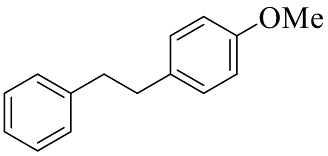
Table 1.2. General procedure to synthesize olefin substrates and the substrate scope



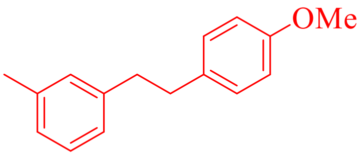
A variety of styrene coupling partners were investigated under the optimal reaction condition. As shown in Table 1.3, electron-rich styrene substrates were found to provide high product yields, while electron-withdrawing groups showed decreased yields. Exceptionally, the acetal product **3j** was isolated in high yield (94%). Then, isolation of methyl-substituted styrene showed that both ortho- and meta-substituted substrates were well tolerated. However, α-methyl-styrene afforded relatively lower yield from others, likely due to increased steric hindrance.

Table 1.3. Substrate scope of styrene coupling partners

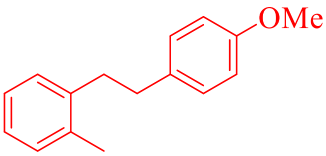




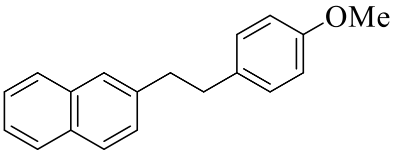
3a, 81%
(55:1)



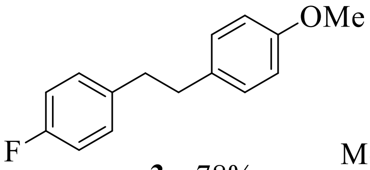
3b, 73%
(66:1)



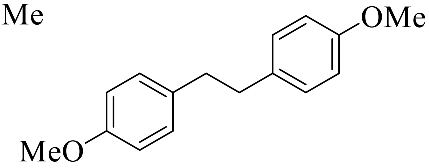
3c, 80%
(20:1)



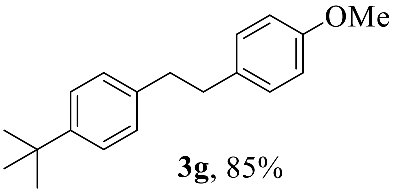
3d, 83%
(34:1)



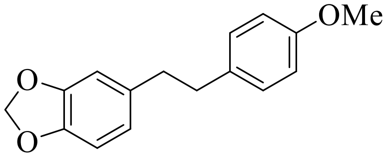
3e, 78%
(26:1)



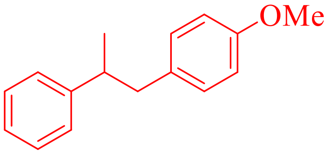
3f, 81%
(45:1)



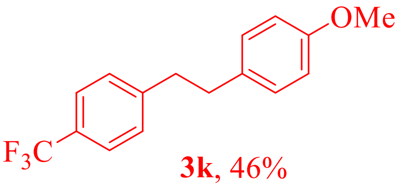
3g, 85%
(46:1)



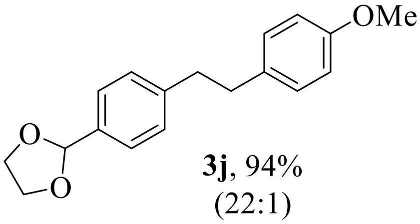
3h, 84%
(79:1)



3i, 56%
(30:1)



3k, 46%
(15:1)

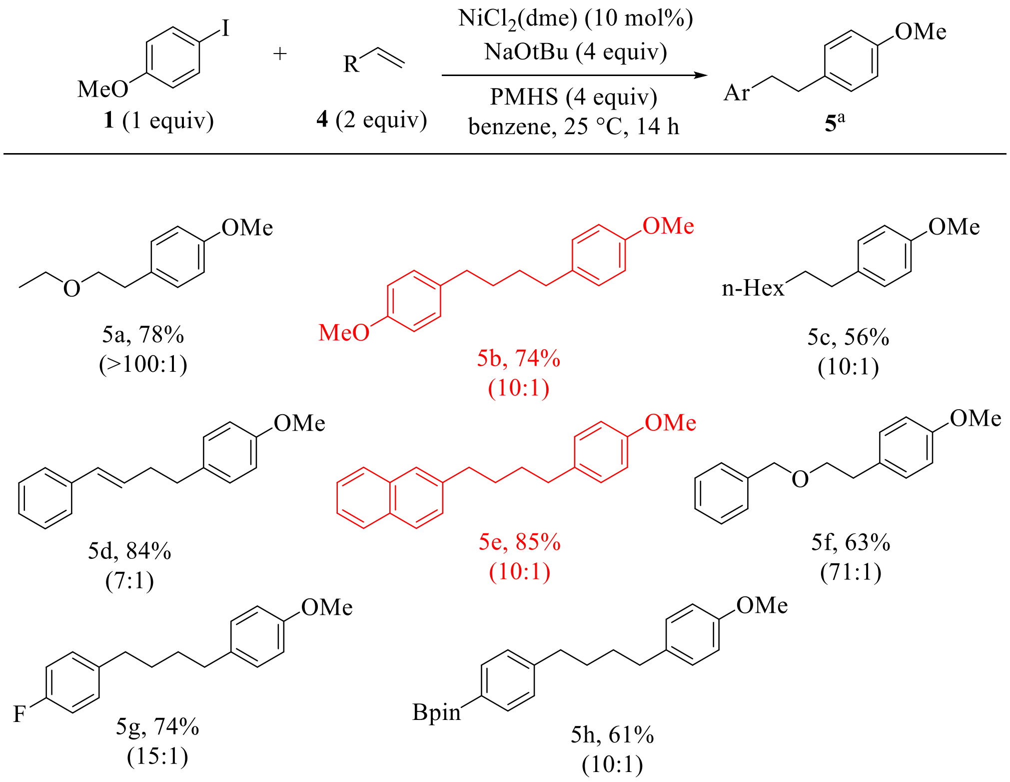


3j, 94%
(22:1)

[a] Yields of isolated products are reported. The ratio of linear to branched products were determined by GC analysis of the crude reaction mixture and are given in parenthesis.

Unactivated olefins were found to be compatible under the reaction conditions. In addition, the scope of various terminal olefins was explored in the nickel-catalyzed hydroarylation reaction. A diene substrate **5d** provided the product in high yield (84%) and good regioselectivity (7:1). In addition, products of enol ether substrates were isolated with reasonably good yields, such as ethyl vinyl ether and benzyl protected ether.

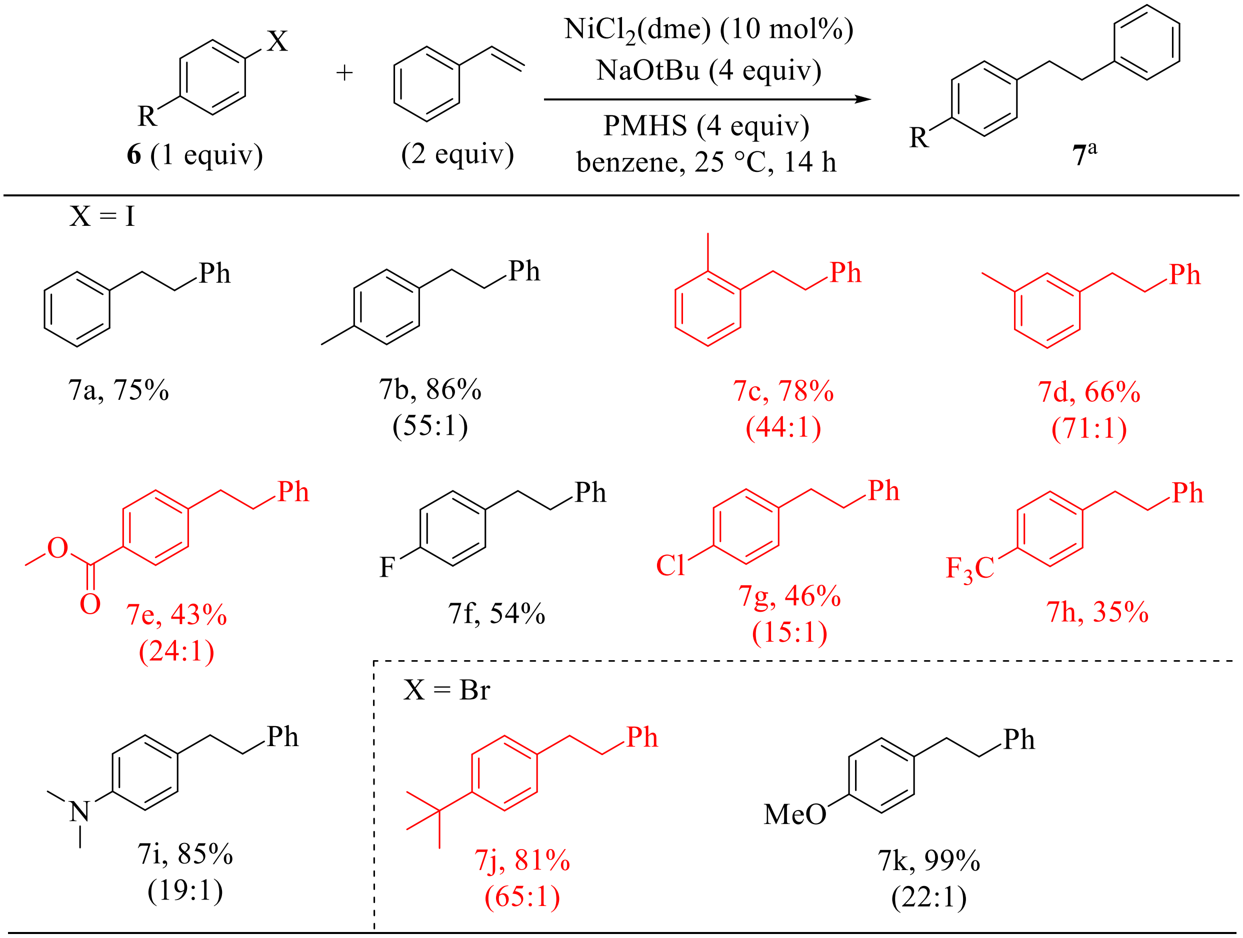
Table 1.4. Substrate scope of alkene coupling partners



[a] Yields of isolated products are reported. The ratios of linear to branched products were determined by GC analysis of the crude reaction mixture and are given in parenthesis.

Lastly, hydroarylation reactions of various aryl halides with styrene were performed. It was found that both aryl bromides and aryl iodides were competent coupling partners in this reaction. Electronic properties of arenes seem to affect the yield of the reaction, as electron-neutral and electron-rich aryl halides generally afforded higher yields while electron-poor aryl halides showed relatively diminished yields.

Table 1.5. Substrate scope of aryl halides



[a] Yields of isolated products are reported. The ratios of linear to branched products were determined by GC analysis of the crude reaction mixture and are given in parenthesis.

1.4 Conclusion

A single catalyst system for hydroarylation of alkenes and styrenes using nickel was developed, and this reaction shows good anti-Markovnikov regioselectivity. This method is compatible with a wide range of functional groups, such as ester, enol ethers and dienes. Further work can be performed to elucidate the mechanism of this reaction.

1.5 Experimental

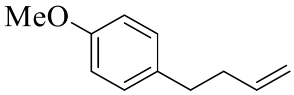
1.5.1 General Information

All reactions were performed by using standard Schlenk and glove box techniques under an atmosphere of nitrogen. Unless otherwise noted, all commercial materials were used without purification. All anhydrous solvents were obtained by running the solvent through a bed of alumina. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV- 300 MHz spectrometer or Bruker AV-500 MHz spectrometer.

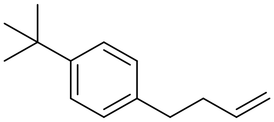
1.5.2 General procedure for cross coupling of alkenyl zinc halide and aryl bromide

A flame-dried and nitrogen flushed 50 mL Schlenk-tube is charged with the aryl bromide (5.0 mmol, 1 equiv), Pd_2dba_3 (0.5 mmol, 0.05 equiv), RuPhos (1.0 mmol, 0.1 equiv) and toluene (0.5 M). After stirring the reaction mixture for 5 min, alkenyl zinc chloride (10 mmol, 2 equiv, 1 M in THF) is added (mildly exothermic). The reaction mixture was heated to 75 °C and left overnight, during which time the color had progressed to dark brown/black. Then, the reaction mixture was cooled to room temperature and quenched with a saturated aqueous NH_4Cl solution and extracted with 1:1 v/v hexanes/ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and the solvent was removed by rotary evaporation under reduced pressure. The crude residue was purified by silica gel chromatography.

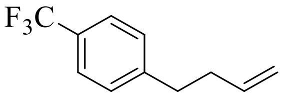
1.5.3 Characterization Data for Alkenes



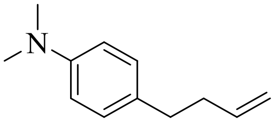
1-(but-3-en-1-yl)-4-methoxybenzene. Compound was isolated as a colorless oil. (608 mg, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.85 (ddt, J = 16.8, 10.2, 6.6 Hz, 1H), 5.14 – 4.87 (m, 2H), 3.79 (s, 3H), 2.79 – 2.55 (t, 2H), 2.34 (m, 2H). Spectral data match the reported literature values.[12]



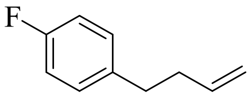
1-(but-3-en-1-yl)-4-(tert-butyl)benzene. Compound was isolated as a colorless oil. (800 mg, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 8.2 Hz, 2H), 6.00 – 5.76 (m, 1H), 5.15 – 4.91 (m, 2H), 2.78 – 2.60 (m, 2H), 2.46 – 2.29 (m, 2H), 1.31 (s, 9H). Spectral data match the reported literature values.[13]



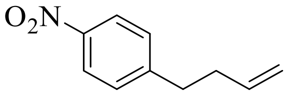
1-(but-3-en-1-yl)-4-(trifluoromethyl)benzene. Compound was isolated as a colorless oil. (510 mg, 51% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 5.83 (ddt, J = 16.8, 10.2, 6.5 Hz, 1H), 5.02 (m, 2H), 2.77 (t, J = 7.7 Hz, 2H), 2.39 (m, 2H). Spectral data match the reported literature values.[14]



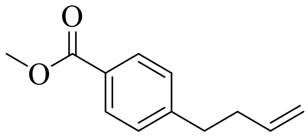
4-(but-3-en-1-yl)-N,N-dimethylaniline. Compound was isolated as a red oil. (788 mg, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 8.5 Hz, 2H), 5.87 (ddt, J = 16.8, 10.1, 6.5 Hz, 1H), 5.14 – 4.87 (m, 2H), 2.91 (s, 6H), 2.70 – 2.53 (m, 2H), 2.45 – 2.24 (m, 2H). Spectral data match the reported literature values.[15]



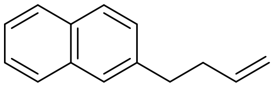
1-(but-3-en-1-yl)-4-fluorobenzene. Compound was isolated as a colorless oil. (436 mg, 58% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (dd, J = 8.4, 5.6 Hz, 2H), 6.96 (t, J = 8.7 Hz, 2H), 5.83 (ddt, J = 16.9, 10.3, 6.6 Hz, 1H), 5.01 (m, 2H), 2.78 – 2.61 (t, 2H), 2.45 – 2.23 (m, 2H). Spectral data match the reported literature values.[16]



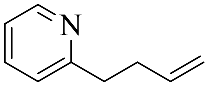
1-(but-3-en-1-yl)-4-nitrobenzene. Compound was isolated as a colorless oil. (532 mg, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 8.6 Hz, 2H), 5.81 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.03 (m, 2H), 2.82 (t, J = 7.7 Hz, 2H), 2.45 – 2.37 (m, 2H). Spectral data match the reported literature values.[17]



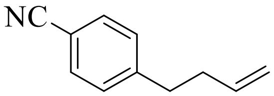
Methyl 4-(but-3-en-1-yl)benzoate. Compound was isolated as a colorless oil. (760 mg, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 6.9 Hz, 2H), 5.83 (ddt, J = 17.0, 10.4, 6.7 Hz, 1H), 5.01 (m, 2H), 3.90 (s, 3H), 2.85 – 2.68 (t, 2H), 2.39 (m, 2H). Spectral data match the reported literature values.[18]



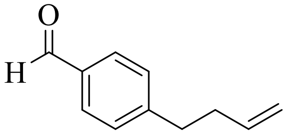
2-(but-3-en-1-yl)naphthalene. Compound was isolated as a colorless oil. (784 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 3H), 7.63 (s, 1H), 7.51 – 7.38 (m, 2H), 7.35 (d, J = 8.4 Hz, 1H), 5.90 (ddt, J = 16.9, 10.1, 6.6 Hz, 1H), 5.04 (m, 2H), 3.00 – 2.79 (t, 2H), 2.48 (m, 2H). Spectral data match the reported literature values.[19]



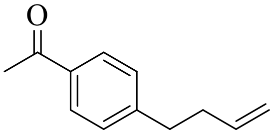
2-(but-3-en-1-yl)pyridine. Compound was isolated as a yellow oil. (86 mg, 13% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, J = 4.6 Hz, 1H), 7.60 (td, J = 7.7, 1.8 Hz, 1H), 7.17 – 7.07 (m, 2H), 5.88 (ddt, J = 16.9, 10.3, 6.6 Hz, 1H), 5.15 – 4.90 (m, 2H), 3.00 – 2.78 (m, 2H), 2.50 (m, 2H). Spectral data match the reported literature values.[20]



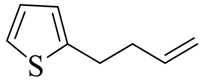
4-(but-3-en-1-yl)benzonitrile. Compound was isolated as a colorless oil. (630 mg, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 5.81 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.01 (m, 2H), 2.77 (t, J = 7.7 Hz, 2H), 2.38 (m, 2H). Spectral data match the reported literature values.[21]



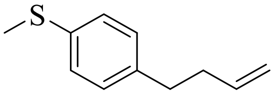
4-(but-3-en-1-yl)benzaldehyde. Compound was isolated as a colorless oil. (113 mg, 14% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.81 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 5.83 (ddt, J = 16.9, 10.3, 6.6 Hz, 1H), 5.18 – 4.89 (m, 2H), 2.95 – 2.68 (m, 2H), 2.41 (m, 2H). Spectral data match the reported literature values.[22]



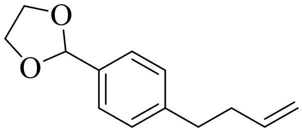
1-(4-(but-3-en-1-yl)phenyl)ethan-1-one. Compound was isolated as a colorless oil. (441 mg, 51% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 5.83 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.15 – 4.91 (m, 2H), 2.84 – 2.69 (m, 2H), 2.60 (t, 2H), 2.50 – 2.29 (m, 2H).



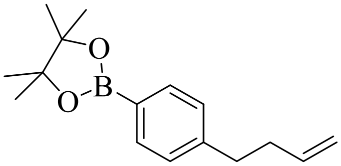
2-(but-3-en-1-yl)thiophene. Compound was isolated as a yellow oil. (383 mg, 43% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.12 (dt, J = 5.2, 1.2 Hz, 1H), 6.96 – 6.88 (m, 1H), 6.80 (m, 1H), 5.87 (ddt, J = 16.6, 10.1, 6.5 Hz, 1H), 5.20 – 4.92 (m, 2H), 3.05 – 2.85 (t, 2H), 2.44 (m, 2H). Spectral data match the reported literature values.[23]



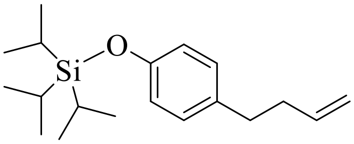
(4-(but-3-en-1-yl)phenyl)(methyl)sulfane. Compound was isolated as a yellow oil. (428 mg, 48% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.20 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 5.84 (ddt, J = 16.8, 10.1, 6.5 Hz, 1H), 5.13 – 4.88 (m, 2H), 2.76 – 2.56 (m, 2H), 2.47 (s, 3H), 2.42 – 2.26 (m, 2H).



2-(4-(but-3-en-1-yl)phenyl)-1,3-dioxolane. Compound was isolated as a colorless oil. (531 mg, 52% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.39 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 5.97 – 5.71 (m, 1H), 5.79 (s, 1H), 5.16 – 4.90 (m, 2H), 4.25 – 3.93 (m, 4H), 2.85 – 2.63 (t, 2H), 2.36 (m, 2H).



2-(4-(but-3-en-1-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Compound was isolated as a colorless oil. (633 mg, 49% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.74 (d, J = 7.8 Hz, 2H), 7.20 (d, J = 7.8 Hz, 2H), 5.85 (ddt, J = 16.8, 10.2, 6.6 Hz, 1H), 5.09 – 4.88 (m, 2H), 2.79 – 2.64 (t, 2H), 2.37 (m, 2H), 1.34 (s, 12H). Spectral data match the reported literature values.[24]

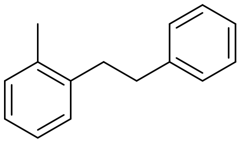


(4-(but-3-en-1-yl)phenoxy)triisopropylsilane. Compound was isolated as a colorless oil. (914 mg, 60% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.01 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 5.84 (ddt, J = 16.8, 10.1, 6.6 Hz, 1H), 5.07 – 4.86 (m, 2H), 2.70 – 2.55 (t, 2H), 2.33 (m, 2H), 1.36 – 1.15 (m, 3H), 1.09 (d, J = 6.9 Hz, 18H).

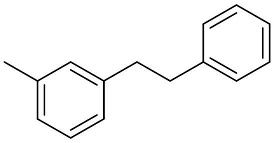
1.5.4 General procedure for hydroarylation of alkenes

Stock solutions of alkene, PMHS and aryl halide in benzene were prepared separately. To a dram vial charged with a stir bar, NiCl$_2$(dme) and sodium tert-butoxide were weighed and added. Then, alkene, PMHS and aryl halide were added in sequence. This reaction was stirred at room temperature for 14 hours. Upon completion, the reaction was quenched by addition of a minimal amount of methanol and stirred until reaction stopped bubbling. The solution was filtered through silica to remove nickel solid. The filtered solution was purified by silica gel chromatography using a toluene/hexane solution.

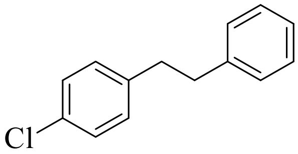
1.5.5 Characterization Data for products of hydroarylation reaction



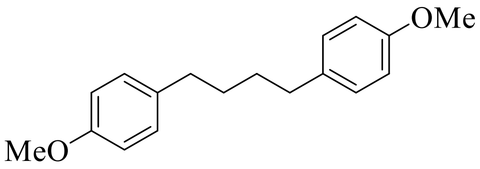
1-methyl-2-phenethylbenzene. Compound was isolated as a colorless oil (38.8 mg, 78% yield). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.47 (m, 2H), 7.38 (m, 3H), 7.31 (m, 4H), 3.07 (m, 4H), 2.48 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 142.09, 140.06, 135.99, 130.29, 128.92, 128.52, 128.49, 126.20, 126.11, 126.06, 36.88, 35.54, 19.35. GCMS (EI) calculated for [M]$^+$ 196.13, found 196.10. FTIR (neat, cm^{-1}): 3062.2 (s), 3025.9 (s), 2942.7 (s), 2865.2 (s), 1603.4 (m), 1494.8 (s), 1453.7 (s). Spectral data match the reported literature values.[25]



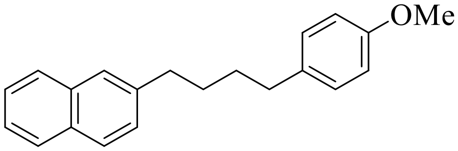
1-methyl-3-phenetylbenzene. Compound was isolated as a colorless oil (32.6 mg, 66% yield). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.38 (m, 2H), 7.32 – 7.27 (m, 4H), 7.13 – 7.07 (m, 3H), 3.05 – 2.94 (m, 4H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 142.00, 141.84, 137.91, 129.36, 128.53, 128.43, 128.35, 126.77, 126.00, 125.55, 38.12, 38.03, 21.51. GCMS (EI) calculated for [M]$^+$ 196.13, found 196.10. FTIR (neat, cm^{-1}): 3061.1 (s), 3026.4 (s), 2922.8 (s), 2858.5 (s), 1604.6 (s), 1495.8 (s), 1453.9 (s). Spectral data match the reported literature values.[26]



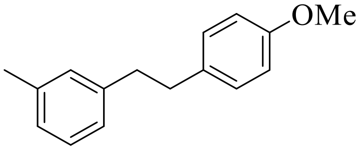
1-chloro-4-phenethylbenzene. Compound was isolated as a white solid (24.9 mg, 46% yield). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.32 (t, J = 7.3 Hz, 2H), 7.29 – 7.21 (m, 3H), 7.19 (d, J = 7.5 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 2.93 (m, 4H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.38, 140.22, 131.75, 129.96, 128.58, 128.51, 126.16, 37.86, 37.30. GCMS (EI) calculated for $[M]^+$ 216.07, found 216.10. FTIR (neat, cm^{-1}): 3028.1 (m), 2926.0 (m), 2859.4 (m), 1492.1 (s), 1454.2 (m), 812.7 (s). Spectral data match the reported literature values.[27]



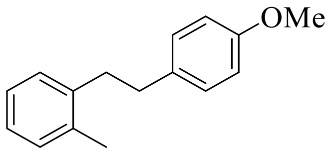
1,4-bis(4-methoxyphenyl)butane. Compound was isolated as a white solid (51.1 mg, 76% yield). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.14 (d, J = 7.6 Hz, 4H), 6.88 (d, J = 7.5 Hz, 4H), 3.83 (s, 6H), 2.63 (m, 4H), 1.68 (m, 4H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 157.78, 134.80, 129.36, 113.78, 55.31, 34.98, 31.37. GCMS (EI) calculated for $[M]^+$ 270.16, found 270.10. FTIR (neat, cm^{-1}): 3004.1 (m), 2931.9 (s), 2852.6 (s), 2834.2 (m), 1612.6 (s), 1582.8 (s), 1513.2 (s), 1454.3 (s) 1246.4 (s), 1034.8 (s). Spectral data match the reported literature values.[28]



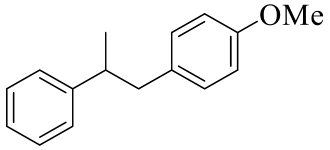
2-(4-(4-methoxyphenyl)butyl)naphthalene. Compound was isolated as a white solid (61.5 mg, 85% yield). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.80 (m, 3H), 7.61 (s, 1H), 7.50 – 7.38 (m, 2H), 7.34 (dd, J = 8.3, 1.7 Hz, 1H), 7.10 (d, J = 7.7 Hz, 2H), 6.84 (d, J = 7.8 Hz, 2H), 3.80 (s, 3H), 2.81 (t, J = 7.1 Hz, 2H), 2.62 (t, J = 7.2 Hz, 2H), 1.73 (m, 4H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 157.91, 140.27, 134.80, 133.83, 129.42, 127.92, 127.74, 127.55, 126.48, 125.96, 125.17, 113.91, 55.40, 36.11, 35.05, 31.44, 31.00. GCMS (EI) calculated for [M]$^+$ 290.17, found 290.10. FTIR (neat, cm^{-1}): 3052.3 (m), 2929.1 (s), 2853.6 (s), 1611.9 (m), 1511.7 (s) 1463.1 (m), 1245.6 (s), 1036.5 (s).



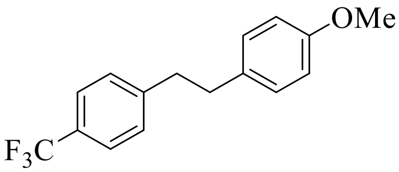
1-(4-methoxyphenethyl)-3-methylbenzene. Compound was isolated as a colorless oil (41.2 mg, 73% yield). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.28 (m, 1H), 7.24 – 7.15 (m, 2H), 7.15 – 7.02 (m, 3H), 7.02 – 6.85 (m, 2H), 3.87 (s, 3H), 2.97 (m, 4H), 2.44 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 157.94, 141.92, 137.89, 134.09, 129.40, 129.36, 128.31, 126.70, 125.55, 113.83, 55.26, 38.26, 37.18, 21.49. GCMS (EI) calculated for [M]$^+$ 226.14, found 226.10. FTIR (neat, cm^{-1}): 3007.0 (m), 2922.5 (s), 2856.9 (m), 2833.9 (m), 1610.7 (s), 1512.2 (s), 1440.6 (m), 1246.8 (s), 1037.7 (s).



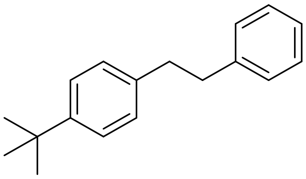
1-(4-methoxyphenethyl)-2-methylbenzene. Compound was isolated as a colorless oil (45.1 mg, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 6H), 6.97 (d, J = 6.7 Hz, 2H), 3.90 (s, 3H), 3.05 – 2.91 (m, 4H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.00, 140.13, 135.99, 134.18, 130.25, 129.40, 128.94, 126.13, 126.07, 113.89, 55.31, 35.94, 35.76, 19.35. GCMS (EI) calculated for $[M]^+$ 226.14, found 226.20. FTIR (neat, cm^{-1}): 3012.3 (s), 2934.5 (s), 2865.0 (s), 2834.4 (s), 1612.4 (s), 1512.6 (s), 1463.0 (s), 1246.6 (s), 1037.4 (s). Spectral data match the reported literature values.[29]



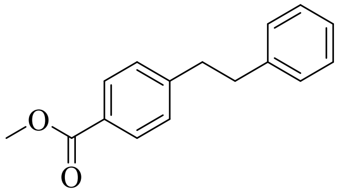
1-methoxy-4-(2-phenylpropyl)benzene. Compound was isolated as a white solid (31.6 mg, 56% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, J = 7.6 Hz, 2H), 7.28 – 7.22 (m, 3H), 7.06 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 3.82 (s, 3H), 3.00 (m, 2H), 2.79 (m, 1H), 1.32 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.90, 147.14, 132.98, 130.13, 128.37, 127.17, 126.06, 113.60, 55.23, 44.24, 42.13, 21.21. GCMS (EI) calculated for $[M]^+$ 226.14, found 226.10. FTIR (neat, cm^{-1}): 3027.6 (s), 2958.6 (s), 2927.8 (s), 2834.2 (s), 1611.9 (s), 1512.2 (s) 1452.9 (s), 1247.3 (s), 1037.4 (s). Spectral data match the reported literature values.[30]



1-methoxy-4-(4-(trifluoromethyl)phenethyl)benzene. Compound was isolated as a colorless oil (32.0 mg, 46% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 7.9 Hz, 2H), 7.27 (d, J = 7.3 Hz, 2H), 7.08 (d, J = 8.2 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 3.81 (s, 3H), 3.03 – 2.81 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.05, 145.91, 133.14, 129.40, 128.87, 128.66, 128.41, 128.02 (q, J = 32.2 Hz), 125.57, 125.39 (q, J = 3.8 Hz), 123.37 (q, J = 270.7 Hz), 113.86, 55.24, 37.95, 36.64. GCMS (EI) calculated for $[M]^+$ 280.11, found 280.10. FTIR (neat, cm^{-1}): 3006.3 (m), 2954.2 (s), 2928.3 (s), 2863.4 (s), 1613.0 (m), 1512.6 (s), 1327.0 (s), 1244.0 (s), 1165.5 (s), 1124.4 (s).



1-(tert-butyl)-4-phenethylbenzene. Compound was isolated as a white solid (48.5 mg, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 9H), 3.00 (m, 4H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.90, 142.19, 138.94, 128.56, 128.49, 128.20, 126.02, 125.38, 38.04, 37.52, 34.52, 31.58. GCMS (EI) calculated for $[M]^+$ 238.17, found 238.20. FTIR (neat, cm^{-1}): 3027.0 (m), 2963.2 (s), 2862.5 (m), 1604.7 (m), 1515.6 (m), 1496.5 (m), 1454.5 (m).



Methyl 4- phenethylbenzoate. Compound was isolated as a colorless oil (25.7 mg, 43% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (m, 2H), 7.34 – 7.31 (m, 2H), 7.28 – 7.23 (m, 3H), 7.21 - 7.19 (m, 2H), 3.94 (s, 3H), 3.10 – 2.84 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.20, 147.25, 141.22, 129.77, 128.63, 128.53, 128.48, 128.03, 126.17, 52.04, 37.96, 37.53. GCMS (EI) calculated for $[M]^+$ 240.12, found 240.10. FTIR (neat, cm^{-1}): 3028.3 (m), 2949.9 (s), 2924.7 (s), 2859.0 (s), 1723.9 (s), 1611.5 (s), 1454.3 (s), 1435.4 (s), 1280.3 (s).

1.6 References

(1) Rueping, M.; Nachtsheim, B. J.; Scheidt, T. *Org. Lett.* **2006**, *8* (17), 3717–3719.

(2) Chu, C. M.; Huang, W. J.; Liu, J. T.; Yao, C. F. *Tetrahedron Lett.* **2007**, *48* (39), 6881–6885.

(3) Lee, S. Y.; Villani-Gale, A.; Eichman, C. C. *Org. Lett.* **2016**, *18* (19), 5034–5037.

(4) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366* (6455), 529–531.

(5) Semba, K.; Ariyama, K.; Zheng, H.; Kameyama, R.; Sakaki, S.; Nakao, Y. *Angew. Chemie - Int. Ed.* **2016**, *55* (21), 6275–6279.

(6) Zhou, Q.-L.; Xiao, L.-J.; Cheng, L.; Feng, W.-M.; Li, M.-L.; Xie, J.-H. *Angew. Chemie Int. Ed.* **2017**, 1–5.

(7) Friis, S. D.; Pirnot, M. T.; Dupuis, L. N.; Buchwald, S. L. *Angew. Chemie - Int. Ed.* **2017**,

56 (25), 7242–7246.

(8) Friis, S. D.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138* (27), 8372–8375.

(9) Liang, L. C.; Chien, P. S.; Lee, P. Y. *Organometallics* **2008**, *27* (13), 3082–3093.

(10) Julia Nguyen (Member of Gojko Lalic's Lab).

(11) Manolikakes, G.; Muñoz Hernandez, C.; Schade, M. A.; Metzger, A.; Knochel, P. *J. Org. Chem.* **2008**, *73* (21), 8422–8436.

(12) Mahajani, N. S.; Chisholm, J. D. *Org. Biomol. Chem.* **2018**, *16* (21), 4008–4012.

(13) Lebleu, T.; Paquin, J. F. *Tetrahedron Lett.* **2017**, *58* (5), 442–444.

(14) Kohler, D. G.; Gockel, S. N.; Kennemur, J. L.; Waller, P. J.; Hull, K. L. *Nat. Chem.* **2018**, *10* (3), 333–340.

(15) Lang, S. B.; O'Nele, K. M.; Tunge, J. A. *J. Am. Chem. Soc.* **2014**, *136* (39), 13606–13609.

(16) Lai, Y. L.; Huang, J. M. *Org. Lett.* **2017**, *19* (8), 2022–2025.

(17) Fernandez Reina, D.; Ruffoni, A.; Al-Faiyz, Y. S. S.; Douglas, J. J.; Sheikh, N. S.; Leonori, D. *ACS Catal.* **2017**, *7* (6), 4126–4130.

(18) Zhang, X.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138* (42), 13862–13865.

(19) Li, Y.; Hu, Y. Y.; Zhang, S. L. *Chem. Commun.* **2013**, *49* (90), 10635–10637.

(20) Stathakis, C. I.; Manolikakes, S. M.; Knochel, P. *Org. Lett.* **2013**, *15* (6), 1302–1305.

(21) Datta, S.; Chang, C. L.; Yeh, K. L.; Liu, R. S. *J. Am. Chem. Soc.* **2003**, *125* (31), 9294–9295.

(22) Mulholland, A. R.; Woodward, C. P.; Langford, S. J. *Chem. Commun.* **2011**, *47* (5), 1494–1496.

(23) Green, S. A.; Matos, J. L. M.; Yagi, A.; Shenvi, R. A. *J. Am. Chem. Soc.* **2016**, *138* (39), 12779–12782.

(24) Shimada, Y.; Haraguchi, R.; Matsubara, S. *Synlett* **2015**, *26* (17), 2395–2398.

(25) Wang, Y.; Huang, Z.; Leng, X.; Zhu, H.; Liu, G.; Huang, Z. *J. Am. Chem. Soc.* **2018**, *140* (12), 4417–4429.

(26) Gieshoff, T. N.; Villa, M.; Welther, A.; Plois, M.; Chakraborty, U.; Wolf, R.; Jacobi Von Wangelin, A. *Green Chem.* **2015**, *17* (3), 1408–1413.

(27) Bergmann, A. M.; Oldham, A. M.; You, W.; Brown, M. K. *Chem. Commun.* **2018**, *54* (42), 5381–5384.

(28) McLane, R. D.; Le Cozannet-Laidin, L.; Boyle, M. S.; Lanzillotta, L.; Taylor, Z. L.; Anthony, S. R.; Tranter, M.; Onorato, A. J. *Bioorganic Med. Chem. Lett.* **2018**, *28* (3), 334–338.

(29) Sandrock, D. L.; Molander, G. A. *J. Org. Chem.* **2009**, *11* (11), 2369–2372.

(30) Basnet, P.; Thapa, S.; Dickie, D. A.; Giri, R. *Chem. Commun.* **2016**, *52* (74), 11072–11075.

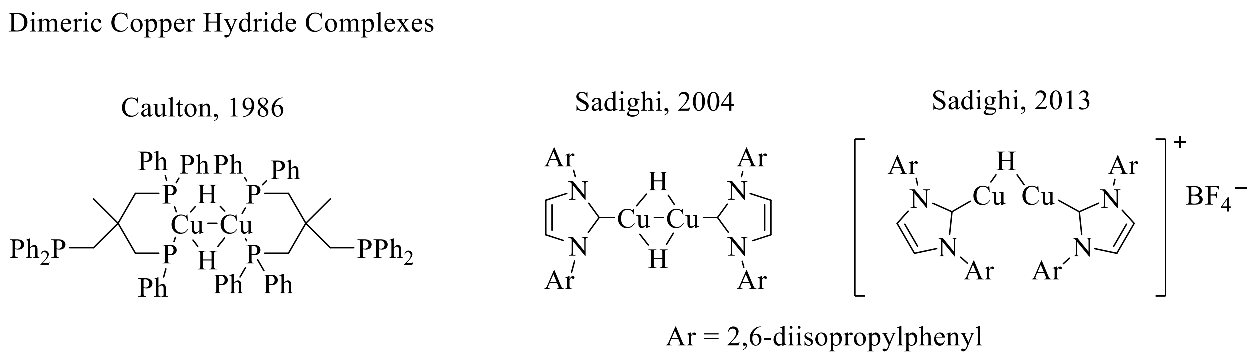
Chapter 2: Synthesis and characterization of a monomeric copper hydride complex

2.1 Introduction

Copper hydride (CuH) complexes have shown great potential as versatile intermediates in various copper-catalyzed reductions,[31,32] and as selective reducing reagents in stoichiometric reactions.[33,34] In 1844, Wurtz et al. prepared copper hydride by reduction of aqueous cupric sulfate with hypophosphorus acid.[35] Then, the synthesis of thermally stable phosphine-stabilized hexamer, $[(Ph_3P)CuH]_6$ was reported by Osborn and Churchill in 1971, and this is known as the first isolated pure copper hydride.[36] Since then, extensive studies have explored different analogues of the $[(Ph_3P)CuH]_6$ complex such as pentameric[37] or octanuclear clusters[38] and hexamers supported by other phosphine ligands.[38,39]

To date, research of low-nuclearity copper hydride complexes is still underdeveloped. Some exploration of lower nuclearity copper hydrides have been done using phosphines and *N*-heterocyclic carbenes as supporting ligands. These works can be traced back to 1986, where Caulton and co-workers reported the synthesis of bis(phosphine)copper(I) μ-hydride dimer, supported by triphosphine ligand (Figure 2.1).[40] The study of phosphine-stabilized copper hydride was expanded by Lipshutz as he described a chiral copper hydride species bearing biaryl bis-phosphine ligand (DTBM-segphos),[41] which appears to be highly stable and can be easily stored in a solution under argon atmosphere. However, the nuclearity of this complex was not characterized.

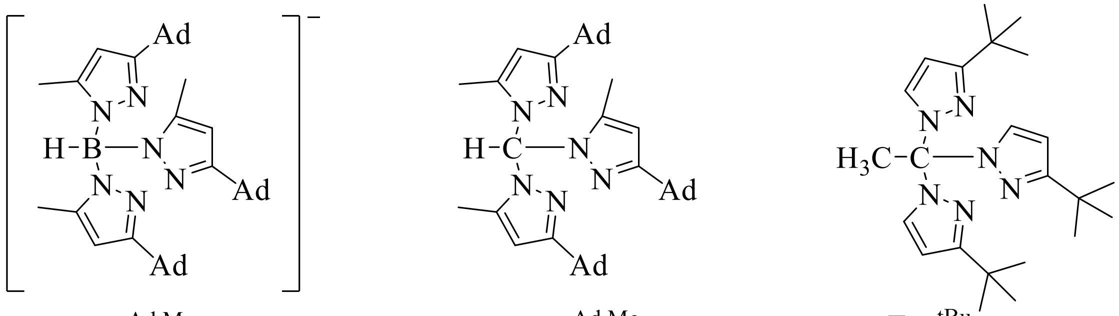
Soon after, as *N*-heterocyclic carbene (NHC) ligand favors low coordination number in metal complexes, Sadighi et al. showed the ability of NHC ligands to stabilize copper(I) complexes with low nuclearity. His group reported the reaction of carbene-ligated copper (I) *tert*-butoxide with triethoxysilane to produce (NHC)copper (I) hydride,[42] which upon characterization was revealed to be dimeric structure (Figure 2.1). They later synthesized singly-hydrido bridged dicopper cation with BF_4^- counteranion by a reaction of siloxide-bridged dicopper cation with HBpin,[43] which is also characterized as dimer.



Ar = 2,6-diisopropylphenyl

Figure 2.1. Previous reports of low-nuclearity copper hydride complexes

In addition to phosphine- and *NHC*-based ligands, tris(pyrazolyl)borate is also extensively studied in organometallic chemistry, as a prevalent class of tridentate ligand. Tris(pyrazolyl)borate ligand (Tp) is a monoanionic, borate-centered ligand which consists of three pyrazolyl arms, and the nitrogen atom from each pyrazole coordinates with metal to form a tripod structure (Figure 2.2, left). In 2000, Fujisawa et al. reported the prominent role of steric bulk of substituents on third position of pyrazolyl rings to enable formation of copper complexes with low coordination number. They synthesized and characterized mononuclear copper (II) hydroxo complex using more-hindered $[HB(3\text{-tBu-5-iPrpz})_3]^-$ compared to $[HB(3,5\text{-iPr}_2\text{pz})_3]^-$ (Scheme 2.1).[44]



$Tp^{Ad,Me}$ $Tpm^{Ad,Me}$ Tpe^{tBu}

Figure 2.2. Tris(pyrazolyl)borate ligands and its neutral analogues synthesized

$$[Cu(NO_3)\{HB(3,5\text{ -}iPr_2pz)_3\}] + NaOH\ (aq) \longrightarrow [\{Cu[HB(3,5\text{ -}iPr_2pz)_3]\}_2(\mu\text{-}OH)_2$$

Dinuclear mode

$$[Cu(NO_3)\{HB(3\text{ -}tBu\text{-}5\text{ -}iPrpz)_3\}] + NaOH\ (aq) \longrightarrow [Cu(OH)\{HB(3\text{ -}tBu\text{-}5\text{ -}iPrpz)_3\}]$$

Mononuclear mode

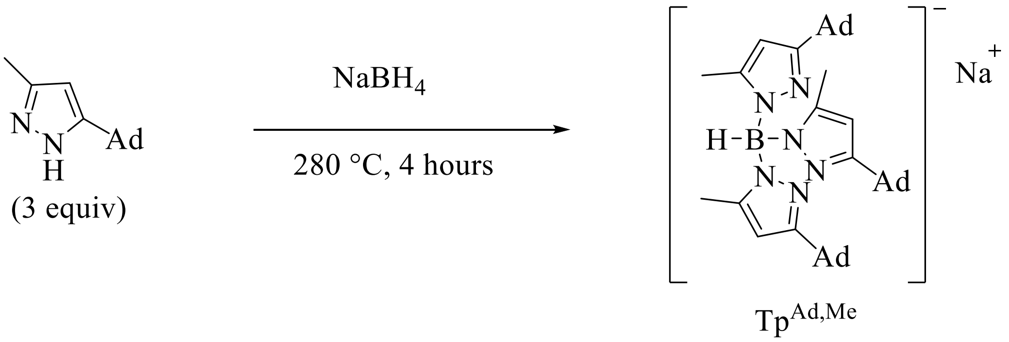
Scheme 2.1. Synthesis of copper (II) hydroxo complexes with Tp ligands (Fujisawa, 2000)

In view of the ability of tris(pyrazolyl)phosphine ligand to enable low-coordinate complexes of copper, it will be interesting to expand the study of this ligand to synthesize many other copper complexes especially monomeric copper hydride complex. This work will encourage the exploration of low-nuclearity copper complexes stabilized by tris(pyrazolyl)phosphine ligand. In addition, the synthesis of mononuclear copper hydride complex will also allow a more extensive study of the reactivity of terminal hydride as compared to bridging hydride of other dimeric copper hydride complexes. This study can later proceed to investigate if the terminal hydride will display different reactivity pattern towards copper-catalyzed reactions.

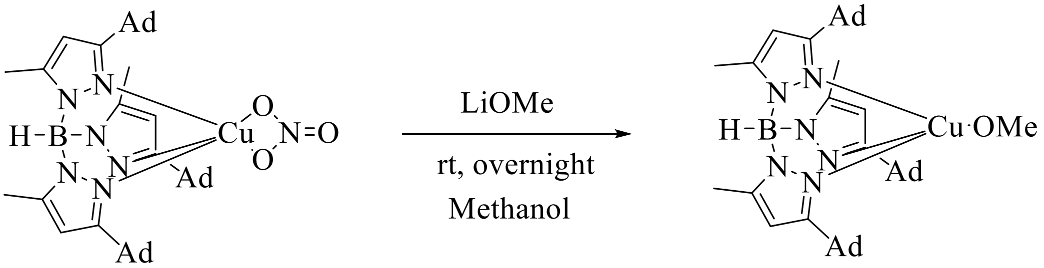
Inspired by Fujisawa’s work, it is hypothesized that the three nitrogen atoms from hydrotris(pyrazolyl)borate ligands could bind to copper center as a facially coordinating structure, and bulkiness of these pyrazoles could significantly influence the coordination environment around the metal center. Synthesis of mononuclear copper hydride complex can be envisioned by introducing sterically demanding substituent groups on pyrazolyl rings of hydro(tris)pyrazolyl borate ligand.

2.2 Results and Discussion

To probe this hypothesis, an extremely bulky analog of tris(pyrazolyl)borate ligand was synthesized (Scheme 2.2).[45] Employing this ligand, various copper complexes were also produced, such as acetonitrile, chloro and nitrato, to determine their competency to access copper hydride. Results showed that the reaction of copper (II) nitrato complex with alkoxide enables conversion to copper (II) alkoxide complexes, a prevalent precursor for the in situ generation of copper hydride as reported by Sadighi.[42] In the attempt to generate copper alkoxide complex, several alkoxides of lithium and sodium were explored such as methoxide, ethoxide, isopropoxide and tert-butoxide. Results showed that only lithium methoxide gives clean conversion of copper (II) nitrato to copper (II) alkoxide (Scheme 2.3). Single crystal X-ray diffraction of the copper (II) methoxide reveals a monomeric structure (Figure 2.3).



Scheme 2.2. Synthesis of hydrotris(pyrazolyl) ligand



Scheme 2.3. Synthesis of copper (II) methoxide, [Cu(OMe){HB(3-Ad-5-Mepz)$_3$}]

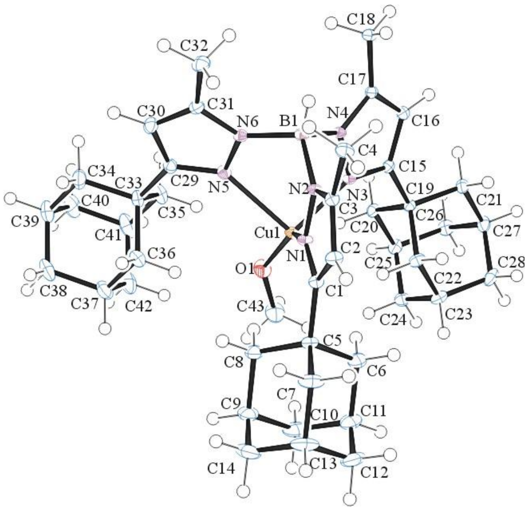
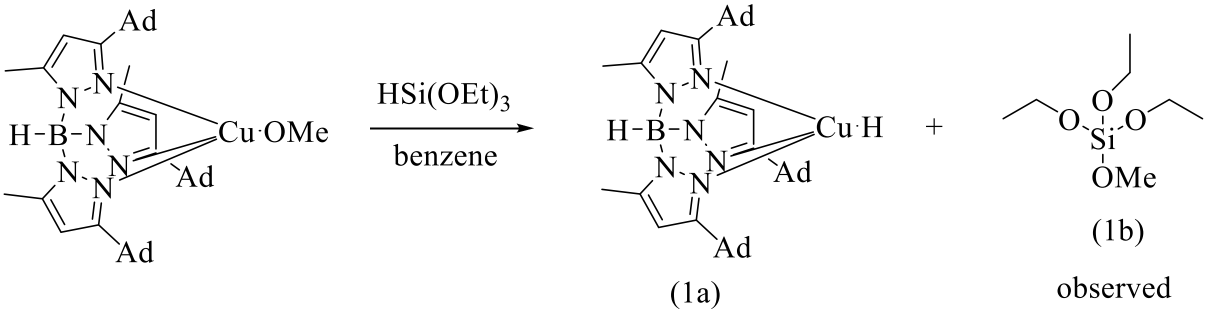


Figure 2.3. An ORTEP of [Cu(OMe){HB(3-Ad-5-Mepz)$_3$}]. Hydrogen atoms are not labelled for clarity.

Sadighi's work showed that the transmetallation reaction of carbene-ligated copper(I) tert-butoxide with triethoxysilane in benzene led to the formation of (NHC) copper(I) hydride,[42] with the immediate appearance of an intense yellow color. Using these reaction conditions, a promising result was observed, in which the red solid of isolated copper (II) methoxide complex promptly turn to bright yellow upon addition of triethoxysilane. While the copper (II) complex is paramagnetic, (MeO)Si(OEt)$_3$ (1b), the byproduct of transmetallation reaction with copper (II) methoxide, is observed by ^{1}H NMR when the reaction is performed in C_6D_6 solution (Scheme 2.4). These implies that transmetallation occurred between the copper complex and the silane, and by the extension suggests existence of copper (II) hydride complex in the solution.



Scheme 2.4. Synthesis of copper (II) hydride complex, [HCu{HB(3-Ad-5-Mepz)$_3$}]

Interestingly, after 3 hours of reaction with silane, a white solid precipitated from solution, and was later characterized as a dimeric copper-ligand complex (Figure 2.4). This can be explained by Warren's proposal of bimolecular coupling between tris(pyrazolyl)borate ligand-based copper (II) hydride to generate H_2 gas and 2 equivalents of copper (I) fragments, as evidenced by their DFT calculation data.[46]

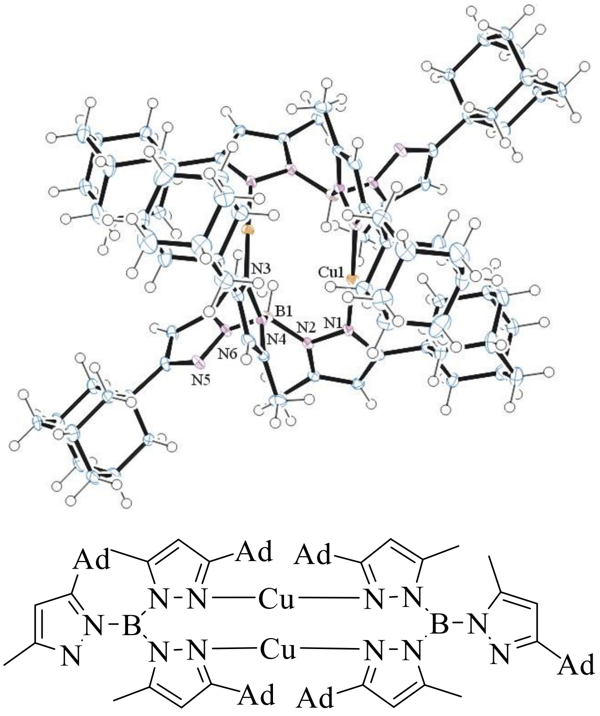
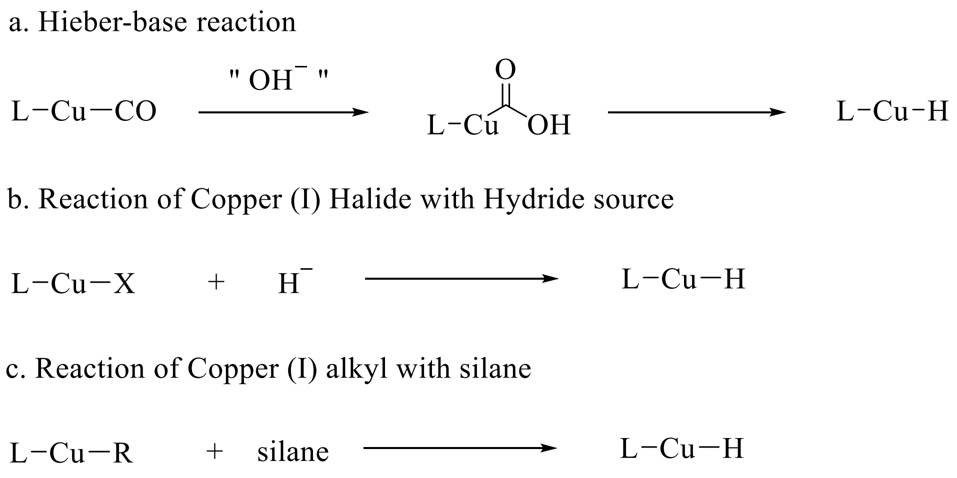


Figure 2.4. (Top) An ORTEP of $[Cu\{HB(3\text{-}Ad\text{-}5\text{-}Mepz)_3\}]_2$. Hydrogen atoms are not labelled for clarity. **(Bottom)** Structure of $[Cu\{HB(3\text{-}Ad\text{-}5\text{-}Mepz)_3\}]_2$.

Confirmation of the monomeric structure of copper (II) methoxide demonstrated that the hypothesis of steric influence is viable, even though the isolation of copper (II) hydride was not successful. To overcome the issue of unstable copper (II) hydride, neutral analogues of tris(pyrazolyl)borate ligand was exploited to synthesize copper (I) hydride complex. The synthesis of tris(pyrazolyl)methane ligands was done by reaction of sodium carbonate with pyrazole in a biphasic solvent system of water and chloroform, facilitated by phase-transfer catalyst.[47] In addition, the methylated analog of tris(pyrazolyl)methane ligand, Tpe^{tBu} was also synthesized (Figure 2.2), as the methine proton of tris(pyrazolyl)methane is acidic and can possibly be removed in basic reaction conditions.

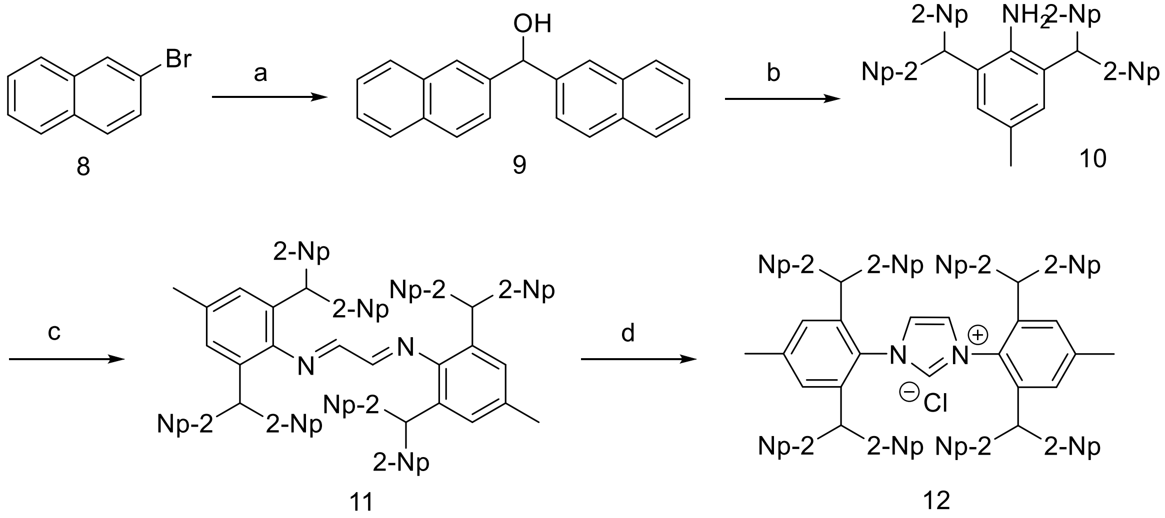
While screening various reaction conditions to obtain a precursor of copper(I) hydride, synthesis of copper (I) alkoxide was attempted, to obtain a known precursor to copper (I) hydride. However, it was observed that tris(pyrazolyl)-methane or -ethane ligands underwent ligand dissociation from copper complex during the reaction to introduce alkoxide ligand. This condition is likely to be caused by the change in overall charge from borate ligand to methane/ethane ligand, which probably leads to weaker ligand binding.

Thus, many alternative reactions were explored to obtain access to copper (I) hydride with other non-alkoxide based copper precursor, such as copper (I) carbonyl, halide and alkyl complexes. copper (I) carbonyl complexes was prepared by reaction of copper (I) acetonitrile in CO atmosphere. Meanwhile, copper (I) methyl complex was formed by reacting copper(I) chloride with dimethyl magnesium as methyl source. Utilizing these copper complexes, several conventional organometallic reactions were investigated to synthesize metal hydride complex, such as Hieber base reaction condition,[48] reaction of copper halide with hydride sources[49] and transmetallation reactions of copper alkyls with silane (Figure 2.5). Unfortunately, none of these reactions showed successful conversion to Copper (I) hydride complexes.



Scheme 2.5. General scheme to synthesize copper (I) hydride

Although it is unknown why the synthesis of copper (I) hydride complexes with tris(pyrazolyl)methane and -ethane ligands were unsuccessful, the steric effect of ligand still seemed to play a dominant influence in supporting monomeric copper hydride complexes. Therefore, this study then focused on synthesis of copper hydride utilizing *N*-heterocyclic carbene ligand, which has been recognized to be involve in many reported formations of dimeric copper (I) hydride complexes. In particular, IPr*$^{(2\text{-Np})}$ ligand appears to be the most sterically demanding N-heterocyclic carbene reported to date.[50] Thus, the imidazolium salt IPr*$^{(2\text{-Np})}$ · HCl was synthesized through a four steps synthesis (Scheme 2.5), and then was used successfully to be engaged in preparation of exceptionally bulky copper (I) chloride complex.



(a) Mg, THF, reflux, then HCO_2Et, 0C; (b) p- toluidine, $ZnCl_2$, HCl (36%), 160C; (c) glyoxal, AcOH, AcOEt, reflux; (d) $ZnCl_2$, HCl (4 M dioxane), $(CH_2O)_n$, THF, 70C

Scheme 2.6. Synthesis of imidazolium salt, IPr*$^{(2\text{-Np})}$ · HCl.

2.3 Conclusion

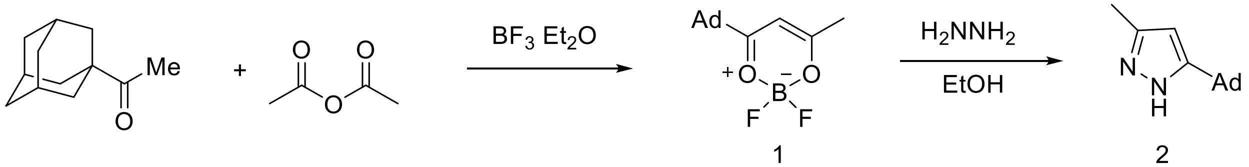
In summary, the existence of copper (II) hydride in solution was observed. The copper (II) hydride was shown to undergo bimolecular coupling, and thus has low stability. The synthesis of copper complexes with tris(pyrazolyl)borate ligand as well as its neutral analogues were performed. Due to poor results of accessing these copper complexes to copper hydride, this study later switched to synthesize *N*-heterocyclic carbene ligand and produced a very bulky copper (I) chloride compound. Further work needs to be done to synthesize and isolate copper alkoxide complexes engaging IPr*$^{(2\text{-Np})}$ ligand and investigate their reaction with various hydride sources to form monomeric copper (I) hydride complex.

2.4 Experimental

2.4.1 General information

All reactions were performed by using standard Schlenk and glove box techniques under an atmosphere of nitrogen. Unless otherwise noted, all commercial materials were used without purification. All anhydrous solvents were obtained commercially. 1H and 13C NMR spectra were recorded on a Bruker AV- 300 MHz spectrometer or Bruker AV-500 MHz spectrometer.

2.4.2 Procedures for synthesis of Hydrotris(pyrazolyl)borate ligand



4-(1-Adamantyl)-2,2-difluoro-6-methyl-1,3,2-di-oxaborium-2-uide. (1) To a mixture of 1 g (5.6 mmol, 1 equiv) of 1-(1-adamantyl)ethanone with 1.06 mL (11.2 mmol, 2 equiv) of acetic anhydride was added 2.08 mL (16.8 mmol, 3 equiv) of boron trifluoride etherate (vacuum distilled from $CaCl_2$). The reaction mixture was refluxed for 5 h and cooled. The separated precipitate was filtered off, washed with water, and dried under high vacuum to yield reddish orange solid (1.05 g, 70% yield). Characterization matched as reported in literature.[51]

3-(1-Adamantyl)-5-methyl-1H-pyrazole. (2) To a solution of 1 g (3.73 mmol, 1 equiv) of compound 1 in 10 mL of ethanol was added 3 equivalent of hydrazine hydrate (11.2 mmol, 3 equiv), the mixture was refluxed for 5 h and cooled. The separated precipitate was filtered off and purified by column chromatography using silica gel with 50% Ethyl Acetate/Hexane solution to yield light yellow solid (484 mg, 60% yield). Characterization matched as reported in literature.[52]

$NaTp^{Ad,Me}$. (3) Pyrazole 2 (9.8 mmol, 3 equiv) and $NaBH_4$ (3.27 mmol, 1 equiv) were combined in Schlenk flask equipped with a condenser. The mixture was heated at 280 °C with stirring for 4 hours. The melt was cooled slowly, and while still hot, acetronitrile (16 mL) was added. The mixture was refluxed overnight where white precipitate deposited. The white solid was collected by filtration while still hot and washed with several portions of hot acetronitrile, then drying at 100 °C in vacuo overnight to afford $NaTp^{Ad,Me}$ (1.68 g , 78% yield). Characterization matched as reported in literature.[53]

2.4.2 Procedures for synthesis of tris(pyrazolyl)methane and tris(pyrazolyl)ethane ligand

$Tpm^{Ad,Me}$. (4) Sodium carbonate (62 mmol) was added in portions at 0 °C to a mixture of pyrazole 2 (10 mmol, 1 equiv), tetrabutylammonium bromide (0.5 mmol, 0.05 equiv) in water (20 mL) with vigorous stirring. Chloroform (6.5 mL) was then added to the mixture and the suspension was subsequently heated at 80 °C for 3 days to yield a red-brown suspension. Then, the mixture was cooled to room temperature, and dichloromethane was added with vigorous stirring. The organic phase was then separated, and the aqueous phase was washed with dichloromethane (3 x 20 mL).

The combined dichloromethane extract was washed with water. The extract was then dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was then washed with diethyl ether to yield 4 as a white powder (1.17 g, 52% yield). Characterization matched as reported in literature.[47]

Tpm^{tBu}. (5) 5 was prepared in the same manner as 1 using chloroform (2.0 M), 3-tert-butyl-pyrazole (8 mmol, 1 equiv), sodium carbonate (48 mmol), and tetrabutylammonium bromide (0.4 mmol, 0.05 equiv). The filtrate was evaporated under vacuum, and a brown oil was obtained. Pre-dried p-toluenesulfonic acid (10 mol%) in toluene was then added to the remaining brown oil. The solution was heated and gently reflux for 1 day. The solution was cooled to room temperature and evaporated under high vacuum. The remaining brown oil was purified by column chromatography using silica gel with 20% Ether/Hexane solution to give yellow oil (586 mg, 57% yield). Characterization matched as reported in literature.[54]

Tpe^{tBu}. (6) Compound 5 (1 mmol, 1 equiv) was dissolved in schlenk flask containing THF (25 mL) at -78 °C. n-butyllithium (2.5 M in hexanes, 1 mmol, 1 equiv) was then added dropwise via syringe into reaction mixture. The mixture was gradually warmed to room temperature and then returned to -78 °C, to which iodomethane (1.7 mmol, 1.5 equiv) was added dropwise via syringe. The reaction mixture was warmed slowly to room temperature and stirred overnight. Water (20 mL) was added and the mixture was extracted with diethyl ether (3 x 30 mL). The organic extracts were combined, dried over Sodium Sulfate and filtered. The solvent was removed under vacuum to yield oily yellow solid (68.4 mg, 53% yield). Characterization matched as reported in literature.[55]

2.4.3 Procedures for synthesis of very bulky N-heterocyclic carbene ligand

Alcohol 8. A schlenk flask containing stir bar and magnesium turning (180 mmol, 2.1 equiv) was flame-dried under nitrogen atmospehere. One crystal of iodine and 60 mL of dry THF were introduced and heated to reflux. After 10 mins, a few mL of 2-bromonaphthalene (180 mmol, 2.1 equiv), dissolved in 90 mL of dry THF, were added in one portion. After decolorization (10-15 min), the remaining 2-bromonaphthalene was added dropwise over 3 hours. The resulting black mixture was stirred for 90 min under reflux and then cooled with an ice bath. Ethyl Formate (85.8 mmol, 1 equiv) was added over 1 hour using syringe pump. The resulting suspension was warmed slowly to room temperature overnight and then cooled with an ice bath before carefully adding 150 mL of 1 M HCl. The aqueous layer was acidified to pH ∼2 with concentrated HCl (36%). The reaction mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a beige solid. The crude product was triturated with a minimum amount of hexane overnight, filtered, washed with hexane, and dried under high vacuum to afford alcohol 7 as a white solid (23 g, 94% yield). Characterization matched as reported in literature.[50]

Aniline 9. Alcohol 8 (82.17 mmol, 2 equiv) and p- toluidine (41.1 mmol, 1 equiv) were mixed and finely powdered together in a mortar. This solid blend was introduced in a 250 mL Schlenk round-bottomed flask equipped and heated in an oil bath (110 °C, external temperature) until liquefaction. Separately, zinc chloride (20.6 mmol, 0.5 equiv) was dissolved in concentrated HCl (36% in water, 3.60 mL, 41.1 mmol, 1 equiv) and then added over 1 min under vigorous stirring (This addition is accompanied by vigorous gas evolution!). The Schlenk flask was sealed with a septum immediately after the end of the addition. The reaction mixture solidified rapidly and was heated to 160 °C (external temperature). After 2 h, the solid was cooled slowly to room temperature and then dissolved in dichloromethane (120 mL). The organic layer was washed with saturated ammonium chloride (100 mL) and brine (100 mL) and dried over potassium carbonate. Silica gel was added (10 g), and the suspension was stirred and filtered after 10 min. Evaporation of the solvent under reduced pressure afforded the crude product as a brown solid, which was purified by trituration with 1-butanol (350 mL) under reflux for 4 h. The suspension was cooled with an ice bath, filtered, washed with cold 1-butanol (3 × 20 mL), and dried under high vacuum at 50 °C, to obtain aniline 9 as beige solid (19.45 g, 74% yield). Characterization matched as reported in literature.[50]

Diaza Diene 10. In a 50 mL round-bottomed flask was equipped with condenser, aniline 9 (15.63 mmol, 2 equiv), 20 mL of ethyl acetate, and 5 drops of acetic acid were added. The white suspension was stirred vigorously under reflux, and glyoxal (40% in water, 0.89 mL, 7.8 mmol, 1 equiv) was added in one portion. A yellow precipitate appeared immediately, and the reaction mixture was stirred overnight under reflux. The suspension was cooled with an ice bath, filtered, and washed with cold ethyl acetate (3 × 15 mL), and dried under high vacuum to give diaza diene 10 as bright yellow solid (5.43 g, 53% yield). Characterization matched as reported in literature.[50]

Imidazolium Salt, IPr*$^{(2\text{-}Np)}\cdot$ HCl (11). In a flame-dried Schlenk flask equipped with condenser, diazadiene 10 (4.17 mmol, 1 equiv) and 400 mL of dry tetrahydrofuran were added and heated with an oil bath (70 °C, external temperature). Zinc chloride (4.17 mmol, 1 equiv), 4 M HCl in 1,4-dioxane (1.3 mL, 5.21 mmol, 1.25 equiv), and paraformaldehyde (14.1 mmol, 1.1 equiv) were added successively and rapidly. The homogeneous solution evolved from yellow to deep red immediately. The progress of the reaction was monitered by TLC. After 1 day, the black homogeneous mixture was cooled to room temperature and concentrated to dryness under reduced pressure. The solid residue was dissolved in ethyl acetate (50 mL) and water (25 mL). The organic layer was washed with water (2 × 50 mL) and brine (50 mL), dried over magnesium sulfate, filtered, and evaporated under reduced pressure to afford a brown solid. The crude product was purified by column chromatography (100% Toluene) to remove impurities and flushed with methanol, dried under high vacuum to obtain imidazolium salt, IPr*(2-Np)·HCl (11) as light brown solid (1.5 g, 27% yield). Characterization matched as reported in literature.[50]

2.4.4 Procedures for preparation of Copper complexes

[Cu(L)Cl]. Acetone (40 mL) was added to a mixture of ligand (1.4 mmol, 1 equiv) and copper (I) chloride (1.55 mmol, 1.1 equiv). After the mixture was stirred for 24 hours, the solvent was evaporated under vacuum. The resulting solid was extracted with dichloromethane. The filtrate was evaporated under vacuum and a yellowish white powder was obtained. Recrystallization from dichloromethane/ether at -30 °C to yield colorless crystals.

[Cu(L)NCMe](PF$_6$). Ligand (1.35 mmol, 1 equiv) was dissolved in dichloromethane (15 mL) and added to tetrakis(acetonitrile) copper (I) hexafluorophosphate (1.49 mmol, 1.1 equiv) in acetonitrile (23 mL). After the mixture was stirred for 24 hours, the solvent was evaporated under vacuum. The resulting solid was extracted with dichloromethane. The filtrate was evaporated under vacuum and a white powder was obtained. Recrystallization from dichloromethane/ether at -30 °C to yield colorless crystals.

[Cu(L)NO$_3$]. Ligand (0.915 mmol, 1 equiv) was dissolved in dichloromethane (60 mL) and added to Cooper (II) Nitrate Trihydrate (1.01 mmol, 1.1 equiv) in acetone (20 mL). The color of solution gradually turned to green, while white solid precipitated. After stirring for 24 hours, the solvent was removed under vacuum. The residue was extracted with dichloromethane and filtered. The filtrate was evaporated under vacuum to give green solid. Recrystallization from dichloromethane/acetonitrile at -30 °C to yield yellow powder.

[Cu(OMe)Tp^{Ad,Me}]. Lithium Methoxide (0.85 mmol, 1 equiv) was added to a solution of Cu(NO$_3$)Tp^{Ad,Me} (0.85 mmol, 1 equiv) in methanol (0.1 M). The color of solution gradually turned to red. After stirring overnight, the solvent was removed under vacuum. The residue was extracted with toluene and filtered. The filtrate was evaporated under vacuum to give red solid (450 mg, 70% yield). Single Crystals of Cu(OMe)Tp^{Ad,Me} suitable for X-ray diffraction was obtained by slow diffusion from pentane into tetrahydrofuran solution.

Cu(H)Tp^{Ad,Me}. To a stirring suspension of Cu(OMe)Tp^{Ad,Me} (0.025 mmol, 1 equiv) in d^6-benzene, triethoxysilane (0.025 mmol, 1 equiv) added and the reaction mixture immediately became bright yellow in color. 1H NMR spectrum was taken as soon as possible thereafter.

[CuTp^{Ad,Me}]$_2$ dimer. Reaction was performed in the same manner as Cu(Tp^{Ad,Me})H. After 3 hours of reaction, white precipitate formed and was collected through filtration. Single Crystals of [CuTp^{Ad,Me}]$_2$ suitable for X-ray diffraction was obtained by slow diffusion from pentane into tetrahydrofuran solution.

[Cu(L)CO](PF$_6$). [Cu(L)NCMe](PF$_6$) (0.5 mmol)was dissolved in dichloromethane (0.01 M) using schlenk technique. The solution was cooled to -78°C in nitrogen atmosphere, the nitrogen was then replaced by CO. The solution was warmed to room temperature and stirred for 36 hours. After that, the solvent was evaporated under vacuum. The resulted solid was extracted with degassed chloroform (0.02 M). The filtrate was evaporated under vacuum to yield white powder. Colorless crystals were obtained from recrystallization with chloroform/pentane at -30°C.

[IPr*$^{(2\text{-Np})}$CuCl]. In glovebox, a flame-dried 10 mL round-bottomed flask was added with imidazolium salt 11 (0.125 mmol, 1 equiv), Copper (I) chloride (0.13 mmol, 1 equiv) and 4.2 mL of dry dichloromethane. Sodium tert-butoxide (0.19 mmol, 1.5 equiv) was introduced, and the resulting homogenous brown solution was stirred overnight. The reaction mixture was filtered through silica with dichloromethane as eluent and concentrated under high vacuum to afford white solid (79.2 mg, 45% yield). Characterization matched as reported in literature.[50]

2.4.4 Characterization Data for Copper complexes

[Cu$^{(I)}${HB(3-Ad-5-Mepz)$_3$)}(NCMe)]. Compound was isolated and recrystallized as colorless crystal (648 mg, 63% yield). ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 5.71 (s, 3H, pyr-*H*), 2.33 (s, 9H, pyr-Me), 2.23 (s, 3H, MeCN), 2.06 (s, br, 18H, pyr-Ad(C*H*$_2$)), 2.03 – 1.97 (m, br, 9H, pyr-Ad(C*H*)), 1.76 (s, br, 18H, pyr-Ad(C*H*$_2$)).

[Cu$^{(I)}${HC(3-Ad-5-Mepz)$_3$)}(NCMe)](PF$_6$). Compound was isolated and recrystallized as colorless crystal (721 mg , 70% yield). ^{1}H NMR (CDCl3, 300 MHz): δ 7.91 (s, 1H, *H*C), 5.99 (s, 3H, pyr-*H*), 2.56 (s, 9H, pyr-Me), 2.29 (s, 3H, MeCN), 2.09 (s, br, 9H, pyr-Ad(C*H*)), 2.03 (s, br, 18H, pyr-Ad(C*H*$_2$)), 1.78 (m, 18H, pyr-Ad(C*H*$_2$)).

[Cu$^{(I)}${Me-C(3-tBupz)$_3$}(NCMe)](PF$_6$). Compound was isolated and recrystallized as colorless crystal (170 mg, 66% yield). ^{1}H NMR (CDCl3, 300 MHz): δ 7.82 (s, 3H, Me-C), 6.28 (s, 3H, pyr-H), 3.07 (s, 3H, pyr-H), 2.33 (s, 3H, MeCN), 1.40 (s, 27H, $C(CH_3)_3$).

[Cu$^{(I)}${HC(3-Ad-5-Mepz)$_3$)}(Cl)]. Compound was isolated and recrystallized as colorless crystal (849 mg, 80% yield). ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 7.85 (s, 1H, *H*C), 5.96 (s, 3H, pyr-*H*), 2.32 (s, br, 9H, pyr-Me), 2.09 (s, br, 18H, pyr-Ad(C*H*$_2$)), 2.02 (s, br, 9H, pyr-Ad(C*H*)), 1.79 (m, 18H, pyr-Ad(C*H*$_2$)).

[Cu$^{(II)}${Me-C(3-tBupz)$_3$}(NO$_3$)]•[Cu(NO$_3$)$_4$]$^{1/2}$. Compound was isolated and recrystallized as yellow crystal (79.6 mg, 61% yield). ^{1}H NMR (CD$_2$Cl$_2$, 300 MHz):): δ 1.72, 1.33, 1.27, 0.88.

[Cu$^{(II)}${HB(3-Ad-5-Mepz)$_3$)}(OMe)]. Compound was isolated and recrystallized as orange crystal (450 mg , 70% yield). ^{1}H NMR (C$_6$D$_6$, 500 MHz): δ 2.87, 2.71, 2.30, 2.11, 1.22.

[Cu$^{(I)}${HB(3-Ad-5-Mepz)$_3$)}(CO)](PF$_6$). Compound was isolated and recrystallized as colorless crystal (250 mg, 56% yield). ^{1}H NMR (CDCl3, 300 MHz): δ 5.71 (s, 3H, pyr-*H*), 2.33 (s, br, 9H, pyr-Me), 2.04 (m, 27H, pyr-Ad(C*H* and C*H*$_2$)), 1.78 (m, 18H, pyr-Ad(C*H*$_2$)). FTIR (neat, cm^{-1}): 2805.8 (s), 2851.0 (s), 2345.7 (m), 2058.4 (vs), 1543.1 (m), 1421.1 (m).

[CuTpAd,Me]2 dimer. Compound was isolated as white solid. 1H NMR (300 MHz, CDCl3) δ 5.80 (s, 2H), 5.71 (s, 2H), 5.63 (s, 2H), 1.92 (m, 36H), 1.85 (m, 9H), 1.76 (m, 18H), 1.70 (m, 18H), 1.64 (m, 9H), 1.58 (m, 9H), 1.41 (m, 9H).

2.5 References

(31) Dang, H.; Cox, N.; Lalic, G. *Angew. Chemie - Int. Ed.* **2014**, *53* (3), 752–756.

(32) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125* (37), 11253–11258.

(33) Koenig, T. M.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31* (23), 3237–3240.

(34) Daeuble, J. F.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *13* (17), 2397–2400.

(35) Jordan, A. J.; Lalic, G.; Sadighi, J. P. *Chem. Rev.* **2016**, *116* (15), 8318–8372.

(36) Bezman, S. A.; Churchill, M. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1971**, *93* (8), 2063–2065.

(37) Albert, C. F.; Healy, P. C.; Kildea, J. D.; White, A. H.; Skelton, B. W. *Inorg. Chem.* **1989**, *28* (7), 1300–1306.

(38) Lemmen, T. H.; Folting, K.; Huffman, J. C.; Caulton, K. G. *J. Am. Chem. Soc.* **1985**, *107* (25), 7774–7775.

(39) Stevens, R. C.; McLean, M. R.; Bau, R.; Koetzle, T. F. *J. Am. Chem. Soc.* **1989**, *111* (9), 3472–3473.

(40) Goeden, G. V.; Huffman, J. C.; Caulton, K. G. A *Inorg. Chem.* **1986**, *25* (15), 2484–2485.

(41) Lipshutz, B. H.; Frieman, B. A. *Angew. Chemie - Int. Ed.* **2005**, *44* (39), 6345–6348.

(42) Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23* (14), 3369–3371.

(43) Wyss, C. M.; Tate, B. K.; Bacsa, J.; Gray, T. G.; Sadighi, J. P. *Angew. Chemie - Int. Ed.* **2013**, *52* (49), 12920–12923.

(44) Fujisawa, K.; Fujita, K.; Miyashita, Y.; Yamada, Y. *Bull. Chem. soc. Jpn.* **2000**, *73*, 1797–1804.

(45) Goodman, M. A.; Demarco, M. J.; Tarasek, S. E.; Nazarenko, A. Y.; Brennessel, W.; Goodman, M. S. *Inorganica Chim. Acta* **2014**, *423* (PA), 358–368.

(46) Zhang, S.; Fallah, H.; Gardner, E. J.; Kundu, S.; Bertke, J. A.; Cundari, T. R.; Warren, T. H. *Angew. Chemie - Int. Ed.* **2016**, *55* (34), 9927–9931.

(47) Lalrempuia, R.; Stasch, A.; Jones, C. *Chem. - An Asian J.* **2015**, *10* (2), 447–454.

(48) W. Hieber, F. L. Zur Kenntnis. *Naturwissenschaften* **1931**, *19*, 360–361.

(49) E. Wiberg, W. H. . *Z. Naturforsch* **1952**, No. 7b, 250.

(50) Dierick, S.; Dewez, D. F.; Markó, I. E. *Organometallics* **2014**, *33* (3), 677–683.

(51) Kon'kov, S. A.; Krylov, K. S.; Bormasheva, K. M.; Moiseev, I. K. *Russ. J. Org. Chem.* **2014**, *50* (11), 1636–1638.

(52) Kon'kov, S. A.; Moiseev, I. K. *Russ. J. Org. Chem.* **2009**, *45* (12), 1824–1828.

(53) Mcskimming, A.; Harman, W. H. *J. Am. Chem. Soc.* **2015**, *137* (28), 8940–8943.

(54) Collins, J. E.; Jameson, D. L.; Castellano, R. K.; Jin, H. 9. **1998**, *32*, 63–65.

(55) Reger, Daniel L.; Grattan, T. C. *Synthesis (Stuttg).* **2003**, *3*, 350–356.