Université de Montréal

Decarboxylative Generation of Carbenes for the Synthesis of *N*-Heterocyclic Carbene Copper(I) Complexes Applications in the Oxidative Coupling of 2-Naphthols

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Mémoire présenté à la Faculté des études supérieures
en vue de l'obtention du grade de maîtrise en sciences (M.Sc.)
en chimie

Octobre 2011

Université de Montréal
Faculté des études supérieures

Ce mémoire intitulé :

Decarboxylative Generation of Carbenes for the Synthesis of *N*-Heterocyclic Carbene Copper(I) Complexes
Applications in the Oxidative Coupling of 2-Naphthols

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Pr. Hélène Lebel, président-rapporteur
Pr. Shawn K. Collins, directeur de recherche
Pr. William Lubell, membre du jury

Résumé

Le présent mémoire décrit la synthèse et l'utilité de complexes Cu-NHC. En premier lieu, la synthèse de complexes de cuivre porteurs de ligand(s) de type carbène-*N*-hétérocyclique (NHC) *via* une génération décarboxylative de carbènes sera présentée. En effet, de précédents rapports font état de l'utilisation de carboxylates d'imidazol(in)ium en tant que précurseurs carbéniques sous conditions thermolytiques. Ainsi, la présente étude montre l'utilisation de ces espèces zwitterioniques pour la synthèse de complexes de cuivre(I) mono- et bis-NHC comportant divers substituants et contre-ions.

Une seconde partie du projet se concentrera sur l'évaluation de complexes Cu-NHC en tant que catalyseurs pour la synthèse de 2,2'-binaphtols *via* une réaction de couplage oxydatif de naphtols. L'objectif de ce projet de recherche est d'étudier les effets de variations structurales de différents complexes Cu-NHC afin de construire un processus catalytique plus efficace. Les effets de la structure du catalyseur sur la réaction de couplage ont été évalués en variant son contre-ion, le nombre de ligands NHC se coordonnant au cuivre, ainsi que la nature des substituants du ligand.

Mots clefs : carbène *N*-hétérocyclique, carboxylate d'imidazolium, carboxylate d'imidazolinium, complexe Cu-NHC, 2,2'-binaphtol, couplage oxydatif.

Abstract

The present thesis describes the synthesis and utility of NHC-Cu complexes. First, the synthesis of *N*-heterocyclic carbene (NHC) copper complexes *via* the decarboxylative generation of carbenes is presented. Indeed, literature precedents reported that imidazol(in)ium-2-carboxylates may be used as carbene precursors under thermolytic conditions. As such, the present study demonstrates how zwitterionic carboxylates may be utilized in the formation of both mono- and bis-NHC Cu complexes with various substitution patterns and counterions.

Secondly, the NHC-Cu complexes were evaluated for the synthesis of 2,2'-binaphthols *via* the oxidative coupling of naphthol derivatives. The objective of the study was to investigate how structural variations to various NHC-Cu catalysts may generate a more efficient catalytic process. Effects of the structure of the catalyst on the coupling reaction have been studied by varying the number of NHC ligands coordinating to Cu, as well as the nature of the NHC ligand substituents and the counterions.

Key words: *N*-heterocyclic carbene, imidazolium-2-carboxylate, imidazolinium-2-carboxylate, NHC-Cu complexes, 2,2'-binaphthol, oxidative coupling.

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List of Abbreviations

°C	Degree Celsius
Ac	Acetate
acac	Acetylacetonate
Ad	Adamantyl
BINAM	2,2′-Diamino-1,1′-binaphthyl
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	2,2′-Dihydroxy-1,1′-binaphthyl
Bn	Benzyl
Box	Bisoxazoline
cod	*cis,cis*-1,5-Cyclooctadiene
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
δ	Delta
DFT	Discrete Fourier transform
DIPP	2,6-Di-*iso*-propylphenyl
DMC	Dimethylcarbonate
DMF	Dimethylformamide
ee	Enantiomeric excess
Et	Ethyl
eq.	Equivalent
γ	Gamma
h	Hour
Hept.	Heptane
IAd	1,3-Diadamantylimidazolylidene
ICy	1,3-Dicyclohexylimidazolylidene
IMe	1,3-Dimethylimidazolylidene
IMe	1,3-Bis(2,4,6-trimethylphenyl)imidazolylidene
IPR	1,3-Bis(2,6-di-*iso*-propylphenyl)imidazolylidene
*i*Pr	*iso*-Propyl
I*t*Bu	1,3-Di-*tert*-butylimidazolylidene
HMDS	Hexamethyldisilylazide
M	Molar
mbar	Millibar
Me	Methyl
Mes	2,4,6-Trimethylphenyl
min	Minute
MS	Mass spectrometry
*n*Bu	*n*-Butyl
NHC	*N*-heterocyclic carbene

NMR	Nuclear magnetic resonance
*n*Pr	*n*-Propyl
Ph	Phenyl
RT	Room temperature
σ	Sigma
SIAd	1,3-Diadamantylimidazolinylidene
SICy	1,3-Dicyclohexylimidazolinylidene
SIMes	1,3-Bis(2,4,6-trimethylphenyl)imidazolinylidene
SIPR	1,3-Bis(2,6-di-*iso*-propylphenyl)imidazolinylidene
S_N2	Bimolecular nucleophilic substitution
*t*Bu	*tert*-Butyl
Tf	Trifluoromethanesulfonyl
TFE	1,1,1-Trifluoroethan-2-ol
TGA	Thermogravimetric analysis
THF	Tetrahydrofuran
TMEDA	N,N,N′,N′-Tetramethylethylenediamine
TMS	Trimethylsilyl

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Acknowledgements/Remerciements

Je voudrais remercier le professeur Shawn K. Collins de m'avoir accueillie au sein de son équipe de recherche. Il a su me donner à la fois un cadre et une liberté dans mon projet de recherche, me permettant ainsi d'épanouir mes compétences et ma passion pour la chimie. Je le remercie pour les discussions stimulantes que nous avons eues et les conseils éclairés qu'il m'a donnés.

Merci à ma famille qui m'a soutenue dans les hauts et les bas de mon projet de recherche. Merci surtout à ma mère de m'avoir toujours encouragée même lorsqu'elle était de l'autre côté de l'océan.

Je remercie tous les membres de mon groupe, anciens et présents, pour une ambiance de labo conviviale et surtout amicale. Merci à Anna et Anne-Catherine pour les moments karaoké du vendredi. Merci à Augusto, Marie-Eve et Mike pour leur bonne humeur et les moments de détente passés ensemble. Ça a été une chance pour moi de travailler avec vous tous.

Je tiens également à reconnaître tous les bons moments passés avec les membres du groupe du Pf. Andreea Schmitzer, notamment mon compagnon de thèse Vincent Gauchot, alias Végé. Je te remercie pour tes encouragements, pour les délicieux cafés et pour les "moments RMN". Les moments difficiles de ma thèse n'en étaient que plus faciles.

Merci aux équipes de RMN et de MS pour leur disponibilité et leur patience face à la caractérisation de mes molécules carbéniques. Je tiens également à remercier Mme Huguette Dinel du laboratoire d'enseignement pour m'avoir généreusement prêté de l'équipement. Vous avez indubitablement contribué à l'avancement de ma recherche.

Merci à tous.

Chapter 1. Introduction

1.1 Introduction to *N*-Heterocyclic Carbenes

Carbenes are neutral divalent carbons. They may be classified as Fischer, Schrock and persistent carbenes (Figure **1**). Fischer carbenes are electrophilic singlet carbenes whereas Schrock carbenes exhibit a triplet state and are strongly nucleophilic. Persistent carbenes differ from Fischer and Schrock carbenes in that they are particularly stable. Although persistent carbenes generally have a singlet state, the π-donation conferred by their adjacent heteroatoms protects them against nucleophilic attack, rendering them strongly nucleophilic.[1]

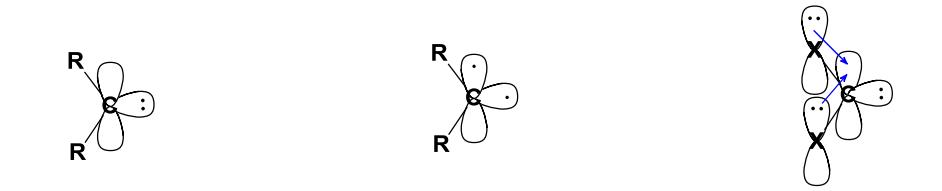


Figure 1. The three categories of carbenes encountered in synthesis.

N-Heterocyclic carbenes (NHCs) are heterocyclic persistent carbenes. Their design can be highly varied, exhibiting different ring sizes and substitution patterns, although the imidazole framework is the most encountered (Figure **2**).[1a,2] Substituents on both the heterocyclic skeleton and the *N*-substituent allow manipulation of their physical properties such as chirality, electronics and steric hindrance, thus influencing the reactivity of the NHC. The versatility and potential of *N*-heterocyclic carbenes and their metal complexes have been demonstrated in fields such as polymerization,

[1] (a) Kascatan-Nebioglu, A.; Panzner, M.; Tessier, C. A.; Cannon, C. L.; Youngs, W. J. *Coord. Chem. Rev*. **2007**, *251*, 884-895. (b) Kühl, O. *Functionalized N-Heterocyclic Carbene Complexes*, 1st Ed.; Wiley: United Kingdom, 2010; p7.
[2] (a) Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed*. **2010**, *49*, 2-15. (b) Poyatos, M.; Mata, J. A.; Peris, E. *Chem. Rev*. **2009**, *109*, 3677-3707.

photochemistry, supramolecular chemistry, but have had their greatest influence in catalysis.[2b,3]

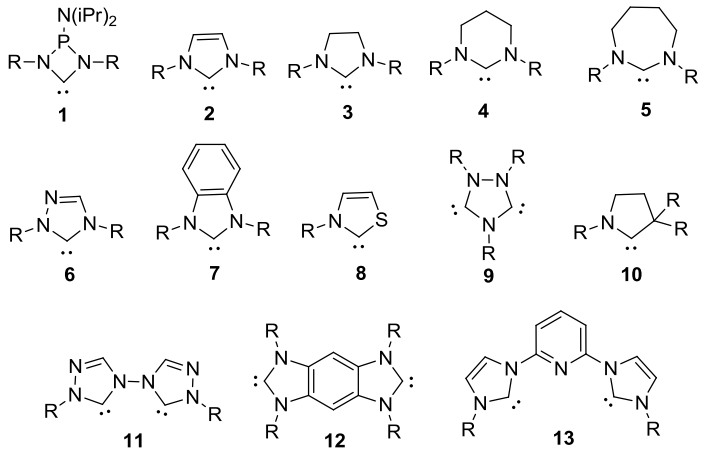


Figure 2. Common topologies of NHCs encountered in synthesis.

Due to the frequency of use of some common imidazolylidenes and imidazolinylidenes, some abbreviations have become commonplace (Figure **3**). The letter "I" is employed followed by the abbreviation of the *N*-substituents on the imidazole framework. For example, 1,3-bis(2,4,6-trimethylphenyl)imidazolylidene is an imidazolylidene (I) bearing two mesityl (Mes) ligands, and is commonly abbreviated as "IMes". In the case of imidazolinylidenes, the prefix "S" is added as the backbone of the heterocycle is saturated. As such, the carbene 1,3-bis(2,4,6-trimethylphenyl)imidazolinylidene is abbreviated "SIMes".

[3] Mercs, L.; Albrecht, M. *Chem. Soc. Rev.* **2010**, *39*, 1903-1912.

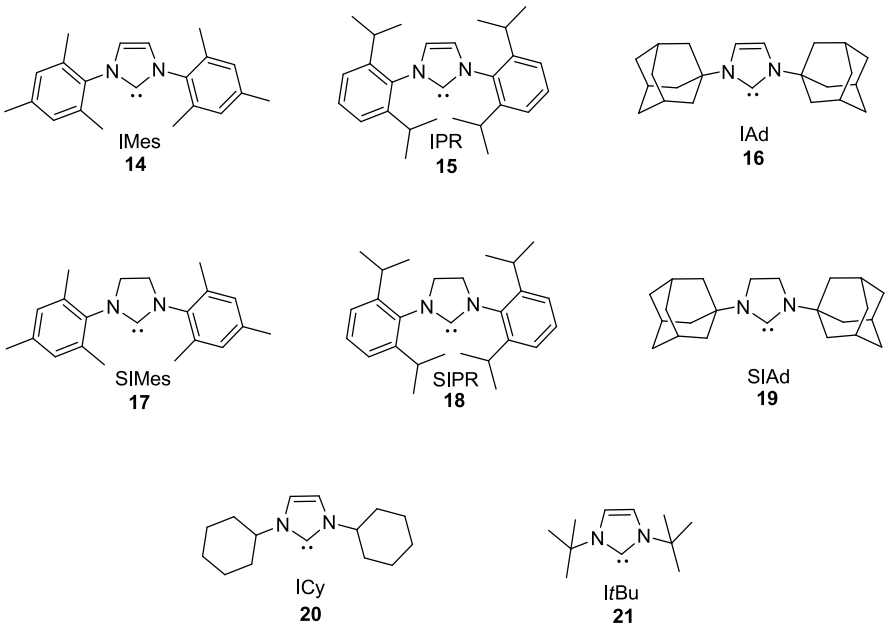


Figure 3. Common *N*-heterocyclic carbenes and their abbreviation.

In the 1960's, work by Wanzlick[4] and Öfele[5] pioneered the chemistry of NHCs, but it was the isolation of the first crystalline carbene by Arduengo in 1991[6] that brought to light their properties (Figure **4**).

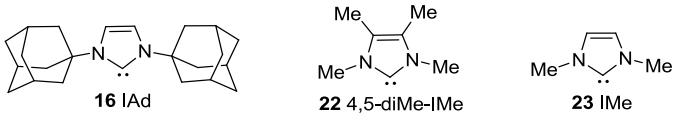


Figure 4. Stable carbenes isolated by Arduengo in the early 1990's.

It was first believed that the steric hindrance introduced by the *N*-substituents was the key factor in the stabilization of the carbene, but the isolation of the *N*-methyl substituted **22** and **23** proved otherwise (Figure **4**).[7] Indeed, bulky substituents protect the carbene from dimerization but in general, NHCs are stabilized to a greater degree by electronic factors. The electron donation of the nitrogen atom's lone pairs to the empty p orbitals of the sp^2-hybridized carbene contributes to the stabilization of the

[4] Wanzlick, H. W.; Kleiner, H.-J. *Angew. Chem*. **1961**, *73*, 493-494.
[5] Öfele, K. *J. Organomet. Chem*. **1968**, *12*, 42-43.
[6] Arduengo, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc*. **1991**, *113*, 361-363.
[7] Arduengo, A. J.; Rasika Dias, H. V.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc*. **1992**, *114*, 5530-5534.

singlet carbene. The electronegativity of the two nitrogen atoms stabilizes the σ electrons of the carbene through an inductive effect. The singlet carbene may also be stabilized by the overall aromaticity of the imidazolylidene core, although its contribution is minor (Figure **5**).[7]

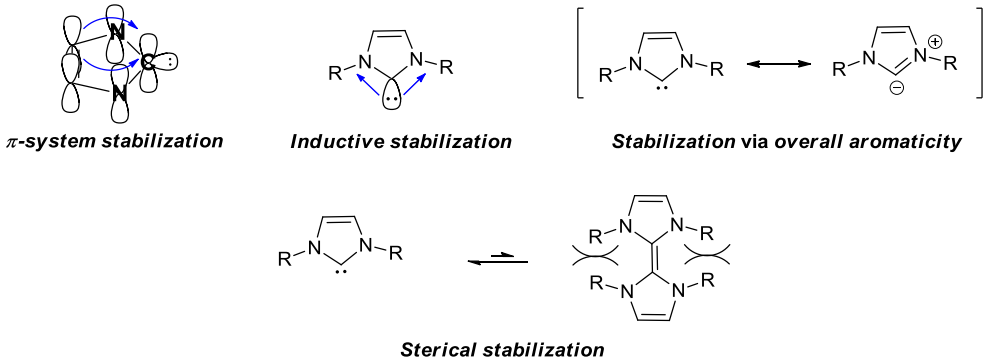


Figure 5. Stabilization of *N*-heterocyclic carbenes *via* electronic (top) and steric (bottom) effects.

When comparing the stability of imidazolylidenes and imidazolinylidenes, the double-bond of the imidazole core provides increased stability to the carbene. The N-C=C-N π system of an imidazolylidene donates to the empty p orbital of the carbene, thus stabilizing the singlet state over the more unstable triplet state. In the case of imidazolinylidenes, the carbene p orbital is stabilized solely by the nitrogen electron pairs, making the carbene more prone to by-product formation such as carbene dimers (Figure **6**).[7,8]

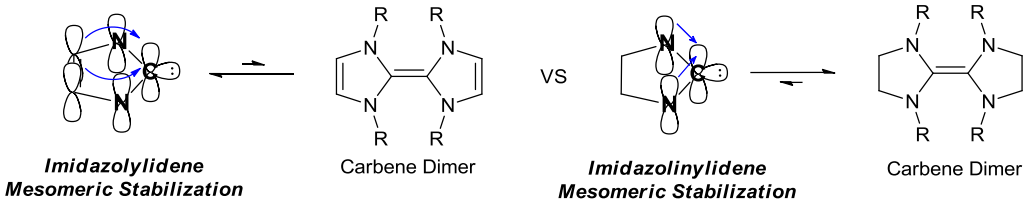


Figure 6. Comparison of the π stabilization of saturated and unsaturated *N*-heterocyclic carbenes.

[8]Arduengo, A. J.; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1995**, *55*, 14523-14535.

As ligands in organometallic complexes, NHCs allow for the generation of very stable complexes that are air and moisture stable, particularly with low-valence metals.[9] The carbenic ligands are often compared to phosphines although they are generally better σ donors and generate more reactive metal complexes.[10] Recent studies have shown that NHCs may exhibit π-backbonding when coordinated to a metal center, although these π-interactions are generally poor (Figure **7**).[9,10]

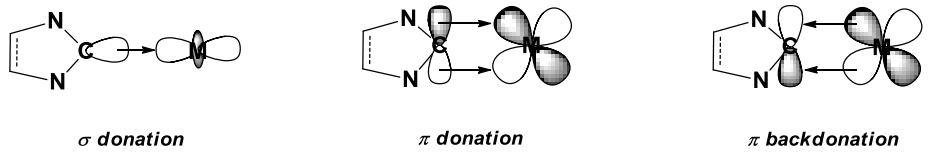
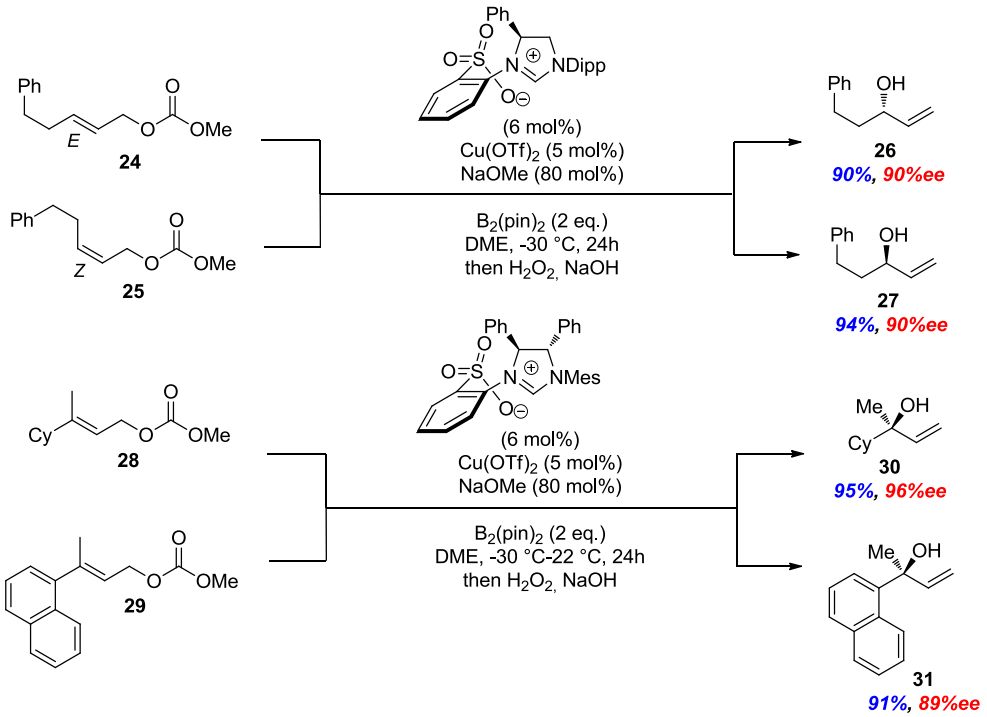


Figure 7. Possible orbital interactions between *N*-heterocyclic carbenes and metals.

[9] (a) Diez-Gonzalez, S.; Marion, N.; Nolan, S. *Chem. Rev.* **2009**, *109*, 3612-3676. (b) Jacobsen, H.; Correa, A.; Poater, A.; Costabile, C.; Cavallo, L. *Coord. Chem. Rev*. **2009**, *253*, 687-703.
[10] Radius, U.; Bickelhaupt, F. M. *Coord. Chem. Rev*. **2009**, *253*, 678-686.

1.2 *N*-Heterocyclic Carbene Copper(I) Complexes in Organic Synthesis

N-heterocyclic carbene metal complexes have become commonplace in organometallic catalysis.[9a,11] Among the transition metals, NHC-Cu complexes are one of the most utilized in catalysis as they are versatile reagents with extensive applications in organic synthesis. They catalyze reactions such as conjugate additions, [3+2] cycloadditions, allylic alkylations, cross-coupling reactions and many others.[9a,11] One of the attractive features of NHC-Cu complexes is their unique reactivity, which allows one to carry out normally challenging transformations. For example, Hoveyda and co-workers showed that an *in situ* generated bidentate NHC-Cu complex could catalyze a formal S_N2' reaction on allylic carbonates to form allylic boronates bearing tertiary or quaternary stereocenters (Scheme **1**).[12] Conversion of the allylboronate to its analogous allylalcohol was performed by a subsequent oxidative work-up.



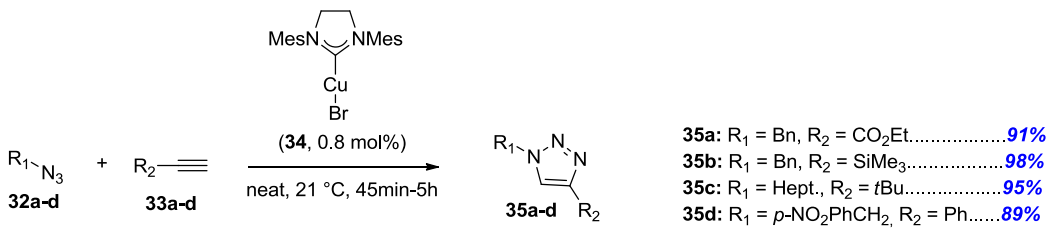
Scheme 1. Synthesis of allylic tertiary and quaternary stereocenters catalyzed by *in situ* generated NHC-Cu catalysts.

[11] Lin, J. C. Y.; Huang, R. T. W.; Lee, C. S.; Bhattacharyya, A.; Hwang, W. S.; Lin, I. J. B. *Chem. Rev.* **2009**, *109*, 3561-3598.
[12] Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2010**, *132*, 10634-10637.

When comparing the reactivity and selectivity of the *in situ* derived NHC-Cu catalysts with traditional phosphine-Cu catalysts, the former demonstrated a wider applicability. For example, when using phosphine-metal catalysts,[13] *Z*-allylic carbonates bearing linear alkyl groups yielded generally allylic boronates in excellent yield and enantioselectivity. However, *E*-allylic boronates were formed with low enantioselectivity. Moreover, sterically hindered alkyl and aryl substituted carbonates did not yield their corresponding allylic boronate. In the case of NHC-Cu catalyzed allylboronate formation, both *E* and *Z* isomers **24** and **25** were transformed in excellent yield and enantioselectivity (**26**, 90% yield, 90% *ee* and **27**, 94% yield, 90% *ee* respectively). Challenging quaternary stereocenters bearing allylic alcohols were also formed in high *ee* and isolated yield. The branched alkyl substituted alcohol **30** was formed in 95% yield and 96% *ee*. Even the sterically demanding naphthyl substituted **31** was formed in 91% yield and 89% *ee*.

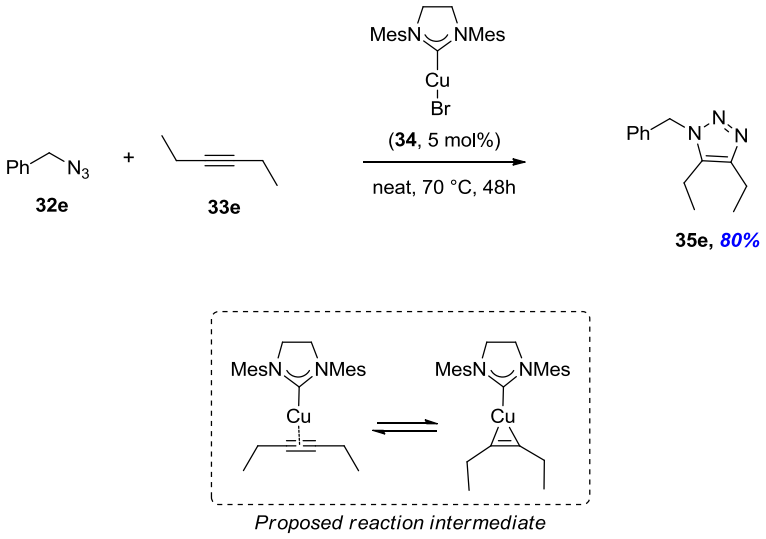
NHC-Cu complexes have also proven their efficiency in Huisgen cycloaddition reactions.[14] The [3+2] cycloaddition of azides with terminal alkynes to yield 1,4-disubstituted triazoles was carried out neat at 21 °C with a catalyst loading as low as 0.8 mol% of Cu(SIMes)Br **34** (Scheme **2**). The low catalyst loading and short reaction time illustrate the high reactivity of the catalyst. The cycloadducts **35a-d** were obtained in more than 89% yield, showing that the method is tolerant of various functional groups on the terminal alkyne (such as ester, TMS, aryl and alkyl groups) and tolerant of both alkyl and aryl substituted azides.

[13] (a) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856-14857. (b) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328-16329. (c) Gerdin, M.; Moberg, C. *Adv. Synth. Catal.* **2005**, *347*, 749-753.
[14] Diez-Gonzalez, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem. — Eur. J.* **2006**, *12*, 7558-7564.



Scheme 2. NHC-Cu catalyzed Huisgen cycloaddition from azides and terminal alkynes.

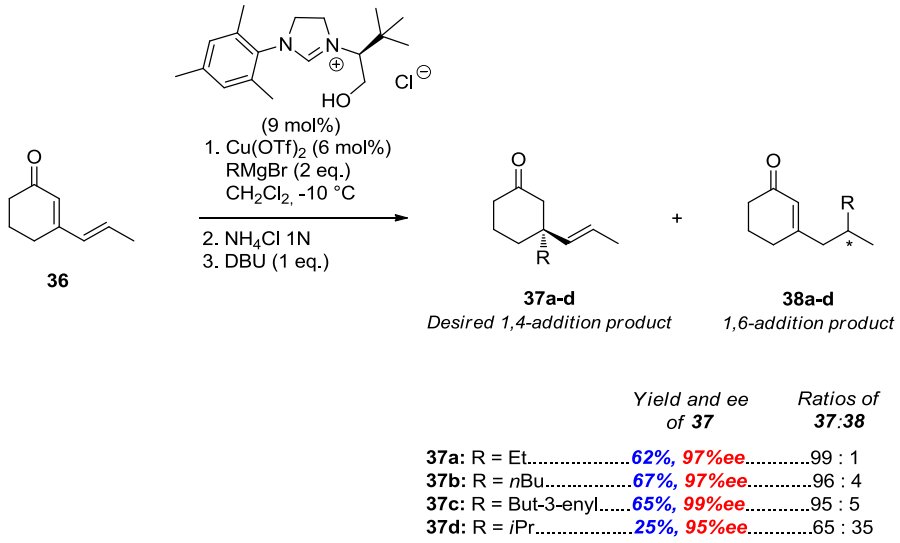
Although the addition of azides and terminal alkynes may be carried out with a simple cuprous halide salt in the presence of a base,[15] stoichiometric amounts of the metal are necessary and the Cu(I) oxidation state enables undesired alkyne-alkyne coupling. Stabilizing the Cu(I) salt with a phosphine,[16] a nitrogen-based,[17] or as shown in Scheme **2**, a NHC ligand[14] makes it possible to control the selectivity of the catalyst and to employ a much lower catalyst loading.



Scheme 3. NHC-Cu catalyzed Huisgen cycloaddition from azide **32e** and internal alkyne **33e**.

[15] Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem*. **2002**, *67*, 3057-3064.
[16] Pérez-Balderas, F.; Ortega-Munoz, M.; Morals-Sanfrutos, J.; Hernandez-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asin, J. A.; Isac-Garcia, J.; Santoyo-Gonzalez, F. *Org. Lett*. **2003**, *5*, 1951-1954.
[17] Chan, T. R.; Hilgraf, R.; Sharpless, B.; Fokin, V. V. *Org. Lett*. **2004**, *6*, 2853-2855.

Remarkably, Cu(SIMes)Br **34** promoted the cycloaddition of azide **32e** with internal alkyne **33e** while traditional Cu-complexes are completely ineffective (Scheme **3**). It is presumed that the presence of the NHC ligand confers properties to the copper center that promotes the formation of a Cu(π-alkyne) complex, thus activating the alkyne towards cycloaddition with azide **32e**.



Scheme 4. NHC-Cu catalyzed 1,4-addition to cyclic enones for the generation of quaternary stereocenters.

The conjugate addition of Grignard reagent nucleophiles to α,β-γ,δ-unsaturated carbonyls for the generation of quaternary stereocenters using NHC-Cu complexes was recently reported by Alexakis and co-workers.[18] Literature precedents for Cu catalyzed conjugate addition of carbon nucleophiles usually promote the formation of the 1,6-addition product in α,γ-substituted enones.[19] However, when the transformation was catalyzed by the *in situ* formed NHC-Cu complex, the nucleophilic attack occurs at the most hindered position of the cyclohexanone **36**, yielding the 1,4-addition product **37**, and a quaternary stereocenter (Scheme **4**). When linear alkyl substituted Grignard reagents are employed as nucleophiles,

[18] Henon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., Int. Ed*. **2008**, *47*, 9122-9124.
[19] Fillion, E.; Wilsily, A.; Liao, E.-T. *Tetrahedron: Asymmetry* **2006**, *17*, 2957-2959.

products **37a-c** are obtained in excellent regioselectivities (>95%), enantiomeric excesses (>97% *ee*) and >62% yields. However, when the branched Grignard reagent *i*PrMgBr was employed, the selectivity for the 1,4-addition product **37d** was diminished (65%) and its yield dropped significantly (25%); however its enantioselectivity remained excellent (95% *ee*). The preceding examples from the literature demonstrate that NHC-Cu complexes may exhibit a reactivity that is unique from other Cu catalysts.

1.3 Synthesis of *N*-Heterocyclic Carbene Copper(I) Complexes

Transition metal complexes of *N*-heterocyclic carbenes may be formed *via* three main synthetic routes: (i) the free carbene route or base method, (ii) the metal base route and (iii) the masked carbene route. Each of these methods will be presented along with their advantages and disadvantages.

1.3.1 Synthesis of NHC-Cu Complexes via *the Free Carbene Route*

The free carbene route, also known as the base method, consists in the deprotonation of a heterocyclic salt in the presence of a base under anhydrous conditions. The carbene generated then coordinates to the metal source in solution to generate the desired complex (Figure **8**). The base method has been extensively used by Nolan and co-workers to generate bis and mono-*N*-heterocyclic carbene copper complexes.[20]

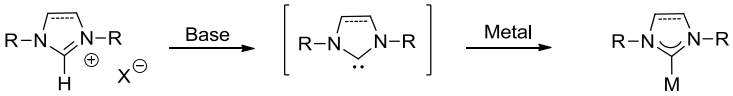
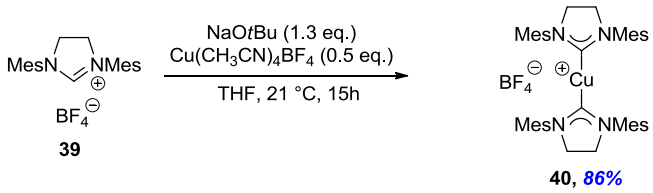


Figure 8. General synthesis of NHC metal complexes *via* the free carbene route.

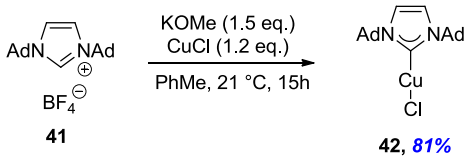
The base method has been used to prepare both mono- and bis-NHC Cu complexes. When synthesizing bis-NHC Cu complex **40**, the imidazolium salt SIMes·HBF_4 **39** was deprotonated in the presence of NaO*t*Bu in THF at 21 °C to form the desired carbene (Scheme **5**).[20a] Reaction of the carbene with the copper source $Cu(CH_3CN)_4BF_4$ generated the bis-*N*-heterocyclic complex **40** in 86% yield.

[20] (a) Diez-Gonzalez, S.; Stevens, E. D.; Scott, N. M.; Petersen, J. L.; Nolan, S. P. *Chem. — Eur. J.* **2008**, *14*, 158-168. (b) Díez-González, S.; Escudero-Adán, E. C.; Benet-Buchholz, J.; Stevens, E. D.; Slawin, A. M. Z.; Nolan, S. P. *Dalton Trans*. **2010**, *39*, 7595-7606.



Scheme 5. Synthesis of $Cu(SIMes)_2BF_4$ **40** *via* the deprotonation of imidazolinium salt **39** with a strong base.

Similarly, for the synthesis of a mono-NHC complex **42**, the imidazolium salt **41** could be deprotonated with KOMe in toluene at 21 °C to form the necessary carbene (Scheme **6**).[20b] In the presence of CuCl, the carbene reacted to form the mono-*N*-heterocyclic carbene copper complex **42** in 81% yield.



Scheme 6. Synthesis of Cu(IAd)Cl **42** *via* the deprotonation of imidazolium salt **41** with a soft base.

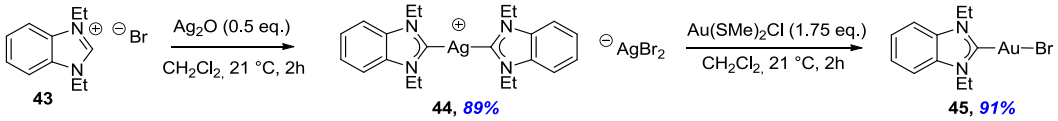
The base method for the synthesis of NHC-Cu complexes can employ both strong and mild bases for the deprotonation of imidazol(in)ium salts under the appropriate conditions. The base method generally shows versatility and high yields. Although it is widely used to synthesize NHC metal complexes, the free carbene route is not suitable for the generation of *N*-heterocyclic carbenes when starting from base sensitive precursors.

1.3.2 Synthesis of NHC-Cu Complexes via *the Metal Base Route*

In cases where milder conditions are necessary, basic metal complexes are often used. In 1998, Lin and co-workers pioneered the use of Ag_2O as a basic metal for the generation of Ag(NHC)X complexes.[21] It was found that *N*-heterocyclic

[21] Wang, H. M.; Lin, J. B. *Organometallics* **1998**, *17*, 972-975.

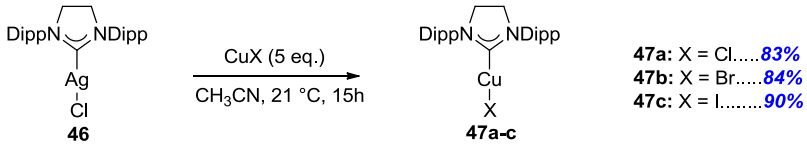
carbene silver complexes may serve as carbene transfer agents (Scheme **7**). The method does not require dry solvents and the reactions may be run under an air atmosphere.



Scheme 7. Synthesis of Au complex **45** *via* the generation of NHC transfer agent **44**.

Lin and co-workers showed that reacting benzimidazolium salt **43** with Ag_2O in CH_2Cl_2 at 21 °C for 2h afforded bis(benzimidazolylidene)silver salt **44** in 89% yield. When the silver complex **44** was reacted with $Au(SMe)_2Cl$, the *N*-heterocyclic carbene underwent transmetalation from the silver cation to the gold cation to generate the mono(benzimidazolylidene)gold(I) species **45** in 91% yield. Consequently, NHC-Ag species have frequently been used as NHC transfer agents for the synthesis of NHC-Cu complexes.[22]

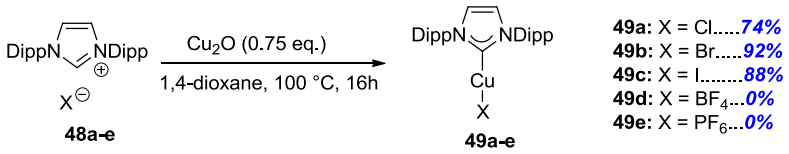
Nolan and co-workers have shown that using the free carbene route to form NHC-Cu complexes **47a-c** leads to a mixture of mono- and bis-NHC Cu complexes.[16b] However, when using the silver NHC salt **46** in the presence of 5 equivalents of the appropriate Cu halide source, a transmetalation reaction occurs with the exclusive formation of mono-NHC Cu salts **47a-c** in more than 83% yield (Scheme **8**).



Scheme 8. Synthesis of Cu(SIPR)X complexes from transmetalation of silver complex **46**.

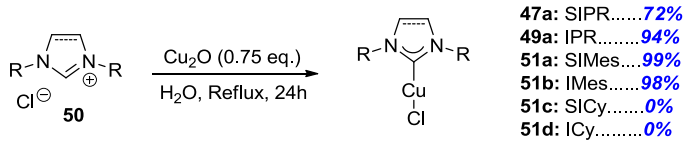
[22] (a) Pytkowicz, J.; Roland, S.; Mangeney, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2087-2089. (b) Dabrowski, J. A.; Gao, F.; Hoveyda, A. *J. Am. Chem. Soc*. **2011**, *133*, 4778-4781.

NHC-Cu complexes can be prepared through the metal base route without the use of a transmetalating agent. The use of silver salts may be avoided if a basic metal copper source such as Cu_2O is employed. Son and co-workers reported that 1,6-di-*iso*-propylphenyl substituted imidazolium salts **48a-c** could be reacted with Cu_2O to afford mono-NHC Cu complexes **49a-c** in yields ranging from 74% to 92% (Scheme **9**).[23] The method is successful with imidazolium halide precursors **48a-c**; however, there is no reactivity with imidazolium salts **48d-e** bearing the non-coordinating tetrafluoroborate and hexafluorophosphate counterions.



Scheme 9. Synthesis of Cu(IPR)X complexes using Cu_2O as a metal base.

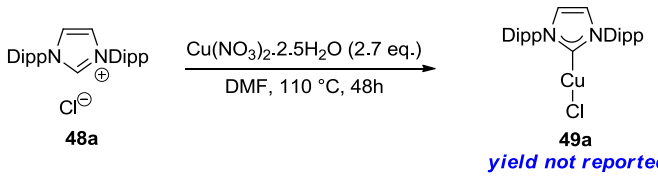
Cazin and co-workers also demonstrated that Cu_2O was a suitable metal base for the formation of mesityl and 1,6-di-*iso*-propylphenyl substituted imidazol(in)ilydene copper(I) chloride complexes **47a**, **49a**, **51a** and **51b** in aqueous media with yields ranging from 72% to 99% (Scheme **10**).[24] However, the method was not successful for 1,3-dicyclohexylimidazol(in)ilydene copper chloride complexes **51c** and **51d**.



Scheme 10. Synthesis of various Cu(NHC)X complexes using Cu_2O in aqueous media.

[23] Chun, J.; Lee, H. S.; Jung, I. G.; Lee, S. W.; Kim, H. J.; Son, S. U. *Organometallics* **2010**, *29*, 1518-1521.
[24] Citadelle, C. A.; Le Nouy, E.; Bisaro, F.; Slawin, A. M. Z.; Cazin, C. S. J. *Dalton Trans*. **2010**, *39*, 4489-4491.

Other copper salts can be used for the synthesis of NHC-Cu complexes *via* the metal base route. Indeed, it was shown that the Cu(II) salt $Cu(NO_3)_2{\cdot}2.5H_2O$ could serve as a metal base for the generation of NHC-Cu complexes.[25] Treating the nitrate salt with IPR·HCl **48a** in DMF at 110 °C resulted in the formation of complex **49a**, albeit no yield was reported (Scheme **11**). Interestingly, Cu(II) is reduced to Cu(I) during the reaction.



Scheme 11. Synthesis of Cu(IPR)Cl **49a** using $Cu(NO_3)_2{\cdot}2.5H_2O$ as a copper source.

1.3.3 Synthesis of NHC-Metal Complexes via *the Masked Carbene Route*

1.3.3.1 Application of Masked Carbenes in the Synthesis of NHC-Metal Complexes

Masked carbenes are precursors that, upon decomposition, generate the desired NHC. They may be found under the form of alkoxy,[26] pentafluoroaryl[27] and haloformyl[28] precursors (respectively **52**, **53** and **54**) but also under the form of thioureas[29] (**55**) and zwitterionic carboxylates[30] (**56**, Figure **9**). Masked carbenes are generally air and moisture stable and may be prepared and stored in large quantities.

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[25] Chun, J.; Jung, G.; Kim, H. J.; Park, M.; Lan, M. S.; Son, S. U. *Inorg. Chem*. **2009**, *48*, 6353-6355.
[26] Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.-P.; Ebel, K.; Brode, S. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1021–1023.
[27] Nyce, G. W.; Csihony, S.; Waymouth, R. M.; Hedrick, J. L. *Chem. — Eur. J.* **2004**, *10*, 4073-4079.
[28] Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc*. **2003**, *125*, 2546–2558.
[29] (a) Kuhn, N.; Kratz, T. *Synthesis* **1993**, *6*, 561–562. (b) Hahn, F. E.; Wittenbecher, L.; Boese, R.; Blaser, D. *Chem. — Eur. J.* **1999**, *5*, 1931–1935.
[30] (a) Tudose, A.; Demonceau, A.; Delaude, L. *J. Organomet. Chem*. **2006**, *691*, 5356-5365. (b) Holbrey, J. D.; Reichert, W. M.; Tkatchenko, I.; Bouajila, E.; Walter, O.; Tommasi, I.; Rogers, R. D. *Chem. Commun.* **2003**, 28-29. (c) Voutchkova, A. M.; Appelhans, L. N.; Chianese, A. R.; Crabtree, R. H. *J. Am. Chem. Soc*. **2005**, *127*, 17624-17625.

Their decomposition is commonly induced through heating, making them suitable carbene transfer agents under thermolytic conditions.

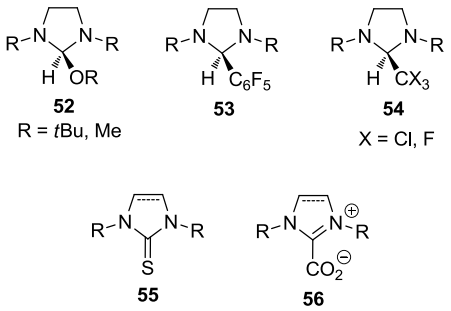
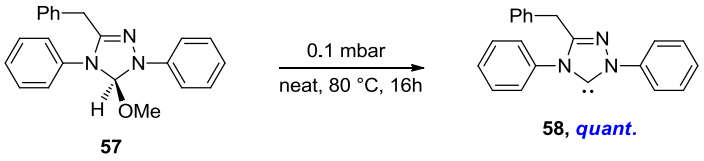


Figure 9. Common masked carbenes used for the *in situ* generation of NHCs.

The use of masked carbenes for the *in situ* generation of NHCs was first introduced by Enders and co-workers who found that thermal decomposition of methoxy adduct **57** under reduced pressure induced the formation of the *N*-heterocyclic carbene **58** by extrusion of methanol (Scheme **12**).[26]



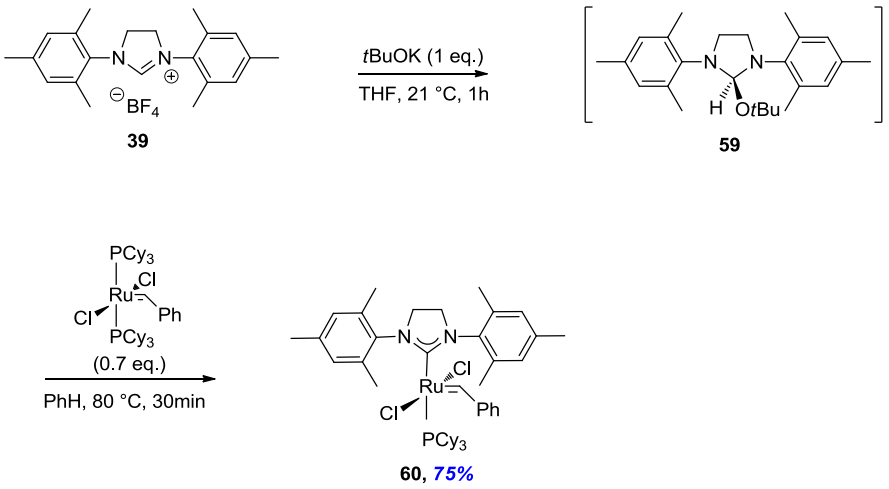
Scheme 12. Thermal decomposition of methoxy NHC adduct **57** to its analogous carbene **58**.

Accordingly, masked carbenes have been thermally decomposed in the presence of a metal source to generate the corresponding NHC metal complex. Although a multitude of NHC metal complexes have been formed using the masked carbene route,[31] there is only one report of a NHC-Cu complex synthesized *via* the

[31] de Frémont, P.; Marion, N.; Nolan, S. P. *Coord. Chem. Rev*. **2009**, *253*, 862-892.

use of such adducts.[32] To illustrate the use of masked carbenes for the synthesis of NHC complexes, several examples will be presented with diverse metal sources.

Following Enders' study of alkoxy NHC adducts, Grubbs and co-workers employed masked carbenes for the generation of NHC-Ru complexes (Scheme **13**). The mesityl substituted salt **39** was reacted with *t*BuOK to generate the *t*butoxy adduct **59** *in situ*. When submitting **59** to the reaction conditions, thermal decomposition of the *t*butoxy adduct formed the desired carbene by elimination of *t*butanol. Upon reaction with Grubbs I catalyst, the metathesis catalyst **60** was formed in 75% yield.[33]



Scheme 13. Generation of Grubbs' second generation catalyst from the decomposition of alkoxy NHC adduct **59**.

Carmichael and co-workers employed a similar strategy to generate the NHC-Yttrium complex **62** (Scheme **14)**.[34] Upon decomposition of the bicyclic alkoxy precursor **61** in the presence of $Y(N(SiMe_3)_3)_2$, the NHC-Yttrium complex **62** was formed in 51% yield.

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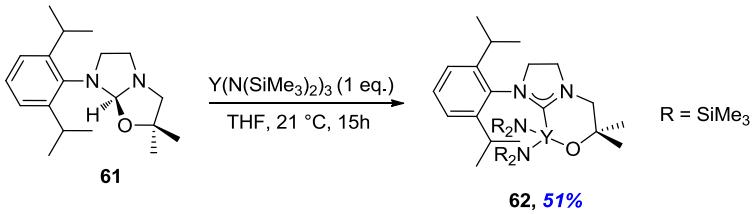
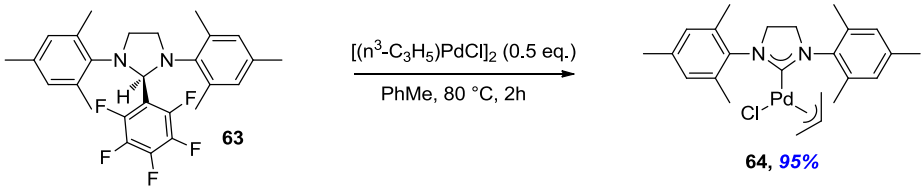
[32] Grandbois, A.; Mayer, M.-E.; Bédard, M.; Collins, S. K.; Michel, T. *Chem. — Eur. J.* **2009**, *15*, 9655-9659.
[33] Scholl, M.; Ding, S.; Choon Woo, L.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.
[34] Arnold, P. L.; Caseley, I. J.; Turner, Z. R.; Carmichael, C. D. *Chem. — Eur. J.* **2008**, *14*, 10415-10422.



Scheme 14. Generation of NHC-Y complex **62** from the decomposition of alkoxy NHC adduct **61**.

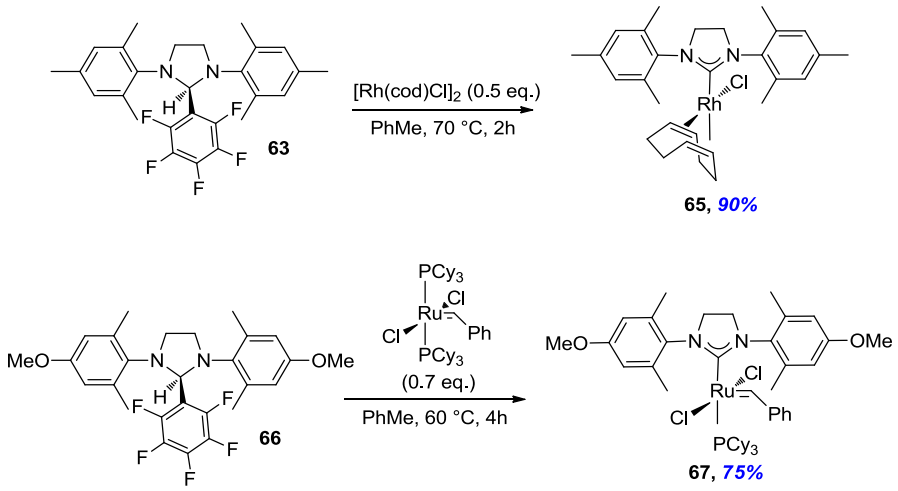
In 2004, Hedrick and co-workers reported the synthesis of pentafluorophenyl adduct **63** and its use as a NHC precursor in the polymerization of lactides (Scheme **15**).[27] It was also shown that heating **63** in the presence of the dimeric complex $[Pd(\eta^3\text{-allyl})Cl]_2$ in PhMe yielded 95% of the NHC-Pd complex **64**, with concomittant extrusion of HC_6F_5.



Scheme 15. Generation of NHC-Pd complex **64** from pentafluorophenylimidazoline adduct **63**.

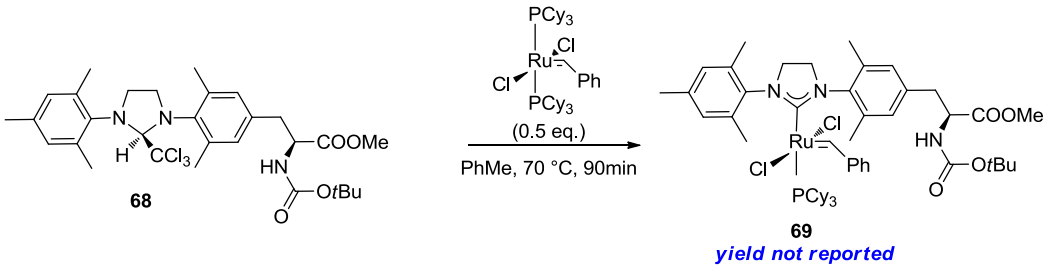
Extrusion of pentafluorobenzene to generate carbenes has been used by Grubbs and co-workers for the generation of Rh and Ru based catalysts (Scheme **16**).[35] Submitting adducts **63** and **66** to thermolysis induced the elimination of HC_6F_5 to form the corresponding carbenes, which coordinated to the metal source. Complexes **65** and **67** were formed in 90% and 75% yields, respectively.

[35] Blum, A. P.; Ritter, T.; Grubbs, R. H. *Organometallics* **2007**, *26*, 2122-2124.



Scheme 16. Generation of NHC-Rh and Ru complexes **65** and **67** from pentafluorophenyl adducts.

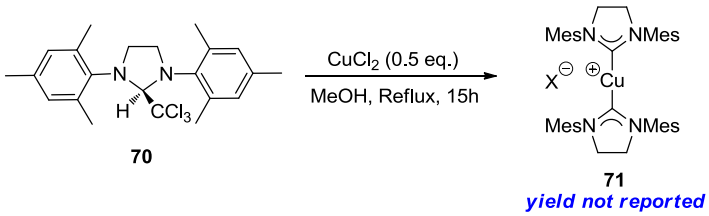
Grubbs and co-workers have also shown that chloroform NHC adducts were suitable carbene precursors for the formation of Grubbs' second generation catalyst.[28,35] Gilbertson and co-workers later employed a similar strategy for the generation of amino acid substituted *N*-heterocyclic carbene ruthenium complexes (Scheme **17**).[36] Upon heating, thermal decomposition of the highly functionalized chloroform adduct **68** yielded the desired carbene by elimination of chloroform. The carbene then reacted with Grubbs I to generate **69**. No yield was reported for the transformation.



Scheme 17. Generation of the highly functionalized NHC-Ru complex **69** from the thermal decomposition of chloroform adduct **68**.

[36] Gilbertson, S. R.; Xu, G. *Org. Lett*. **2005**, *7*, 4605-4608.

Collins and co-workers employed the chloroformylimidazoline adduct **70** as a carbene precursor under thermal conditions (Scheme **18**).[32] When **70** decomposed to its carbene analog, it reacted with $CuCl_2$ to yield the bis-NHC Cu complex **71**. Although the reaction involves a Cu(II) salt, the Cu(I) species **71** is obtained. The cationic structure of **71** was identified by MS; however, the poor solubility of the complex hampered the characterization of its anion X^-, which remains unidentified. Since the complex formed is ill-defined, no yield was reported for the transformation. This is the only report of the use of masked carbene for the synthesis of NHC-Cu salts.



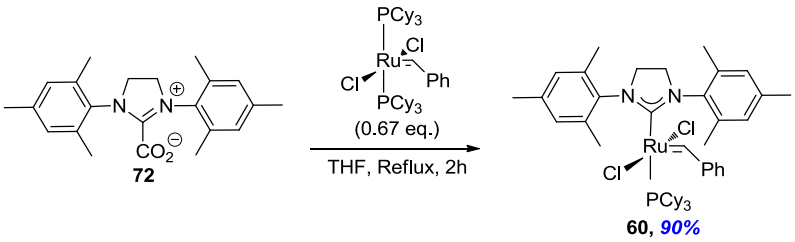
70 **71**

yield not reported

Scheme 18. Synthesis of the bis-NHC Cu complex **71** from the thermal decomposition of chloroform adduct **70**.

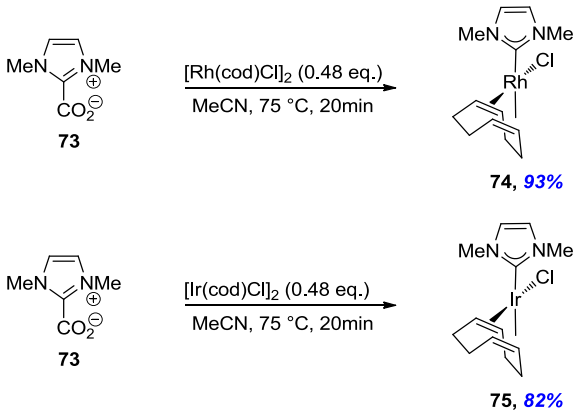
The thermal decomposition of masked carbenes results in the extrusion of a small molecule. Zwitterionic carboxylates have been studied as masked carbene precursors, because thermal decomposition affords only CO_2 gas. Such masked carbenes have been used in the synthesis of NHC-Ru complexes.[30a] The synthesis of Grubbs' second generation catalyst can be achieved with alkoxy,[33] chloroform[28,35] and pentafluorophenyl[35] imidazoline adducts of *N*-heterocyclic carbenes as well as the zwitterionic carboxylate adduct **72** (Scheme **19**).[30a,37] 1,3-Dimesitylimidazolinium-2-carboxylate **72** generated its analogous carbene by extrusion of CO_2 gas under thermolytic conditions. When the carbene reacted with Grubbs' first generation catalyst, Grubbs' second generation catalyst was formed in 90% yield.

[37] Sauvage, X.; Demonceau, A.; Delaude, L. *Adv. Synth. Catal.* **2009**, *351*, 2031-2038.



Scheme 19. Generation of Grubbs' second generation catalyst **60** from imidazolinium-2-carboxylate **72**.

Crabtree and co-workers also showed that 1,3-dimethylimidazolium-2-carboxylate **73** reacted with $[Rh(cod)Cl]_2$ under thermolytic conditions to form the NHC-Rh complex **74** in 93% yield (Scheme **20**).[30c] Similarly, using $[Ir(cod)Cl]_2$ as a metal source allowed for the generation of NHC-Ir complex **75** in 82% yield.[30c]



Scheme 20. Generation of NHC-Rh and Ir complexes **74** and **75** from an imidazolium-2-carboxylate.

Imidazol(in)ium-2-carboxylates with different substitution patterns do not have the same stability towards decarboxylation. Louie and co-workers have studied the stability of the zwitterionic species by evaluating diverse imidazol(in)ium carboxylates by thermogravimetric analysis (TGA, Figure **10**).[38] Increase in steric bulk near the C_2 carbon center resulted in a decrease in the decarboxylation temperature of imidazolium-2-carboxylates. For example, the methyl substituted

[38] Van Ausdall, B. R.; Glass, J. L.; Wiggins, K. M.; Aarif, A. M.; Louie, J. *J. Org. Chem*. **2009**, *75*, 7935-7942.

IMe·CO_2 **73** decomposes at 162 °C. In comparison, the steric hindrance conferred by the two *t*butyl substituents of I*t*Bu·CO_2 **79** eases the decarboxylation process, which occurs at 71 °C.

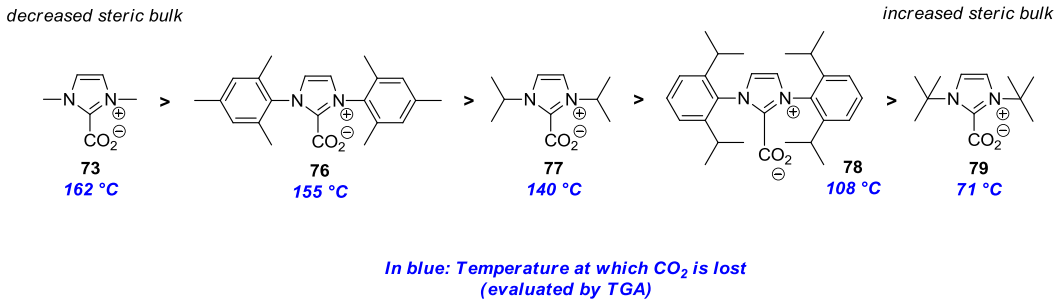
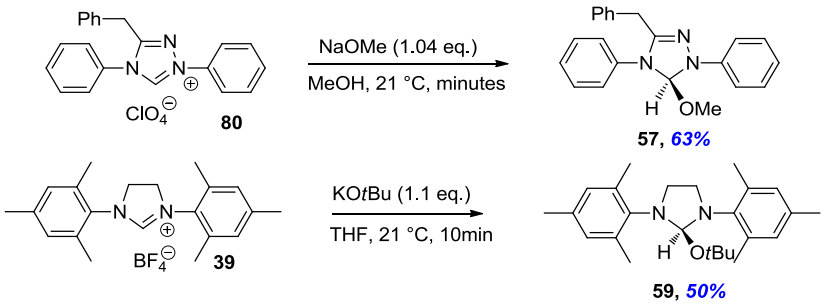


Figure 10. Correlation between the decarboxylation temperature of imidazolium-2-carboxylates and the size of their *N*-substituents.

1.3.3.2 Synthesis of Masked Carbenes

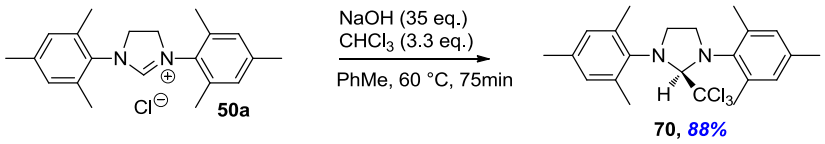
Various methods have been developed for the synthesis of masked carbenes, but they are commonly formed from their analogous azolium salt. Indeed, when Enders and co-workers generated the first alkoxy adduct, triazolium perchlorate salt **80** was reacted with NaOMe (Scheme **21**, top).[26] Addition of the methoxide anion to the electrophilic azolium salt yielded the methoxy adduct **57** in 63% yield. In a similar manner, Grubbs and co-workers generated *t*butoxy adduct **59** by reacting imidazolinium salt **39** with a slight excess of KO*t*Bu (Scheme **21**, bottom).[28] The desired masked carbene was recovered in a low 50% yield and readily decomposed by extruding *t*BuOH at room temperature. As a result, the product was generally formed *in situ* when employed as a carbene precursor.



Scheme 21. Generation of alkoxy adducts **57** and **59** from their analogous azolium salt.

Interestingly, when Nolan and co-workers reacted SIMes·HBF_4 **39** with NaO*t*Bu in the presence of $Cu(MeCN)_4BF_4$ (Scheme **5**), it was assumed that the *t*butoxide anion deprotonated the imidazolinium precursor to form the free carbene. At the time, it seems unclear what would favor the addition of $tBuO^-$ to form the masked carbene **59** over the deprotonation reaction to form the free carbene **17**.

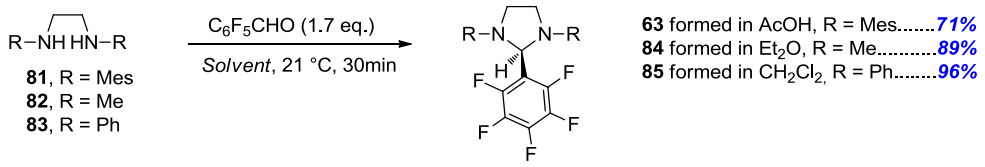
When forming the chloroform adduct **70**, the mesityl substituted imidazolinium salt **50a** was reacted with a large excess of NaOH (Scheme **22**).[28] Upon deprotonation, the carbene generated inserted into the chloroform C-H bond to form the desired haloformyl imidazoline **70** in 88% yield.



Scheme 22. Generation of chloroform adduct **70** from imidazolinium salt **50a**.

Unlike other masked carbenes, pentafluorophenyl adducts are formed from diamines.[27] Condensation of pentafluorobenzaldehyde with the corresponding ethylene diamine species **81**-**83** generated the desired imidazolidines **63**, **84** and **85** in

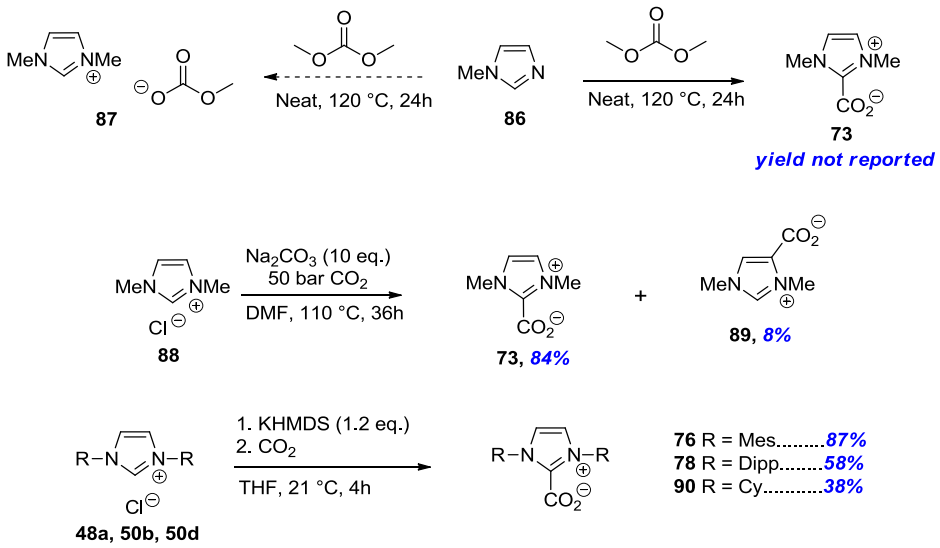
71% to 96% yields (Scheme **23**). This approach provided imidazoline adducts without the *in situ* generation of a carbene.



Scheme 23. Generation of pentafluorophenyl adducts **63**, **84** and **85** from their corresponding ethylene diamine precursors.

The general interest for imidazol(in)ium-2-carboxylates has led to the elaboration of various synthetic methods for their generation. Three methods have been reported for the synthesis of imidazol(in)ium-2-carboxylates (Scheme **24**). Rogers and co-workers reported the reaction of methyl imidazole **86** with dimethyl carbonate (DMC) (Scheme **24**, top).[30b] The expected ionic liquid 1,3-dimethylimidazolium methylcarbonate **87** was not generated; instead, the zwitterionic imidazolium-2-carboxylate **73** was isolated. The method is limited to the generation of **73**. Reacting DMC with mono-alkylated imidazoles yields imidazolium carbonates. Tommasi and co-workers also demonstrated that IMe·CO_2 **73** formed from treating an imidazolium chloride salt **88** with a high pressure of CO_2 gas under basic conditions (Scheme **24**, middle).[39] However, carboxylation of imidazolium salt **88** occurred at both the C_2 and C_4 positions, and the lack of selectivity resulted in an inseparable mixture of two carboxylate isomers. The desired zwitterion **73** was formed in 84% yield, along with its isomer **89** in 8% yield. Delaude and co-workers developed a more general methodology for the synthesis of zwitterionic carbene precursors.[30a] Imidazolium salts **48a**, **50b** and **50d** were deprotonated with KHMDS (Scheme **24**, bottom). The *in situ* generated carbenes were then trapped by CO_2 gas to form the carboxylate adducts **76**, **78** and **90** in 38% to 87% yields.

[39] Tommasi, I.; Sorrentino, F. *Tetrahedron Lett*. **2006**, *47*, 6453-6456.



Scheme 24. Synthetic routes developed for the generation of zwitterionic carboxylates.

1.4 The Oxidative Coupling of Naphthol Derivatives

1.4.1 Introduction to 2,2'-Binaphthols

2,2'-Binaphthols (BINOLs) are molecules exhibiting a biaryl motif frequently occurring in nature (Figure **11**).[40] The lack of rotation upon the C_1-C_1' bond results in axial chirality in the binaphthyl skeleton, making binaphthol derivatives powerful ligands in asymmetric catalysis.[41] The synthesis of BINOLs is usually carried out *via* the oxidative coupling of naphthols. A stoichiometric method was first performed by Pummerer in 1926 using $FeCl_3$.[42] Stoechiometric methods were later developed for biaryl coupling using K_3FeCN_6,[43] $Mn(acac)_3$[44] as well as Cu(II)-amine complexes.[45] Further discussion will concentrate on advances in the catalytic formation of the binaphthyl skeleton. Synthetic methods and their respective advantages and disadvantages in both the homocoupling and heterocoupling of naphthol derivatives will be discussed.

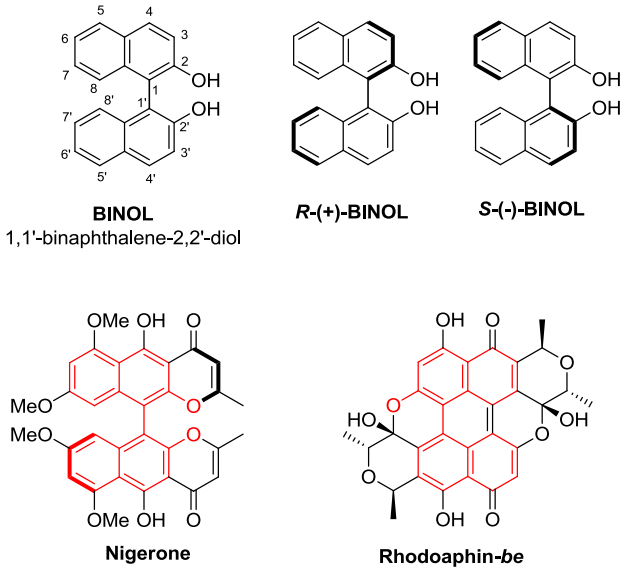


Figure 11. Enantiomers of BINOL and its motif in natural products.

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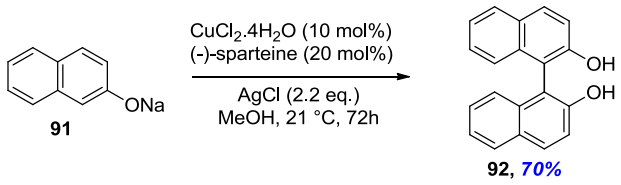
[40] (a) DiVirgilio, E. S.; Dugan, E. C.; Mulrooney, C. A.; Kozlowski, M. C. *Org. Lett*. **2007**, *9*, 385-388. (b) Mulrooney, C. A.; Morgan, B. J.; Li, X.; Kozlowski, M. C. *J. Org. Chem*. **2010**, *75*, 16-19.
[41] Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev*. **2003**, *103*, 3155-3211.
[42] Pummerer R.; Prell, E.; Rieche, A. *Chem. Ber.* **1926**, *59*, 2159-2161.
[43] Feringa, B.; Wynberg, H. *J. Org. Chem*. **1981**, *46*, 2547-2557.
[44] Yamamoto, K.; Fukushima, H.; Okamoto, Y.; Hatada, K.; Nakazaki, M. *J. Chem. Soc. Chem. Commun*. **1984**, 1111-1112.
[45] (a) Feringa, B.;Wynberg, H. *Tetrahedron Lett*. **1977**, *18*, 4447-4450. (b) Smrcina, M.; Polakova, J.; Vyskocil, S.; Kocovsky, P. *J. Org. Chem.* **1993**, *58*, 4534-4538.

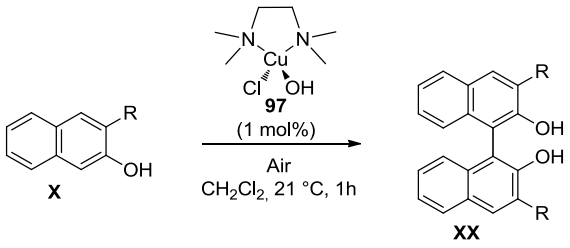
1.4.2 Oxidative Homocoupling of Naphthols Catalyzed by Amine-Cu Complexes

The first catalytic process for oxidative naphthol coupling involved $CuCl_2$ and (-)-sparteine as well as a stoichiometric amount of AgCl which served as a silver based oxidant (Scheme **25**).[45b] Significant advancement was later achieved in the catalytic oxidative coupling reaction by employing air and O_2 as oxidants in the amine-Cu catalytic systems.



Scheme 25. First catalytic process for the oxidative coupling of 2-naphthol.

In 1999, Nakajima and co-workers reported the use of a diamine-Cu system for the coupling of naphthol derivatives (Scheme **26**).[46] Only 1 mol% of the commercially available organometallic complex Cu(OH)Cl·TMEDA **97** was necessary to catalyze carbon-carbon bond formation under very mild conditions. Under air at 21 °C, greater than 90% yield of electron-rich BINOLs **92**, **98** and **99** were obtained in only 1h. When the more electron poor **96** was subjected to the reaction conditions, a higher catalyst loading and longer reaction time were necessary, to obtain an excellent yield (90% yield).



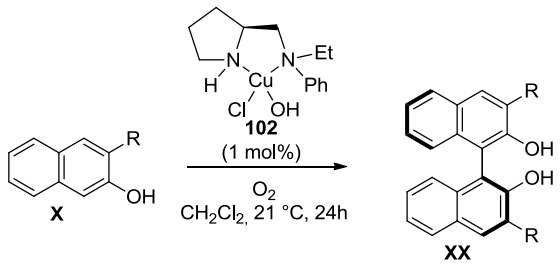
Entry	X	Coupling product XX Yield (%)	
1	**93** R = H	**92**	***92***
2	**94** R = Me	**98**	***95***
3	**95** R = OMe	**99**	***95***
4	**96** R = CO_2Me	**100**[a]	***90***

[a](Carried out with 10 mol% **97**, 48h)

Scheme 26. Catalysis of the oxidative coupling of naphthol derivatives **93-96** with Cu(OH)Cl·TMEDA complex **97**.

[46] Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.-I. *J. Org. Chem*. **1999**, *64*, 2264-2271.

Nakajima and co-workers also demonstrated that the proline-diamine derived complex **102** catalyzed the enantioselective coupling of 2-naphthols **93** and **94** to generate the corresponding BINOLs **92** and **98** in 89% and 93% yields, albeit with 17% *ee* and 12% *ee* respectively (Scheme **27**). The reaction of ester substrates **96** and **101** afforded **100** and **103** with increased enantiomeric excesses of 78% *ee* and 76% *ee*. An ester substituent at C_3 may allow for chelation of the substrate to the copper catalyst, in order to induce enantioselectivity (Figure **12**).



		Coupling product		
Entry	**X**	**XX**	*Yield (%)*	*ee (%)*
1	**93** R = H	**92**	***89***	***17***
2	**94** R = Me	**98**	***93***	***12***
3	**96** R = CO_2Me	**100**	***85***	***78***
4	**101** R = CO_2Bn	**103**	***77***	***76***

Scheme 27. Catalyzed enantioselective oxidative coupling of naphthol derivatives **93**, **94**, **96** and **101** with chiral catalyst **102**.

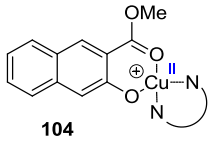


Figure 12. Postulated intermediate formed in the homocoupling of ester substituted naphthol derivatives with amine-Cu complexes.

Kozlowski and co-workers developed another amine-Cu system for the enantioselective homocoupling of naphthol derivatives by using the commercially available (*R,R*)-1,5-diazadecalin **105** as a ligand.[47] Mechanistic studies supported (*R,R*)-1,5-diazadecalin-CuI(OH) **106** as the active catalyst in the coupling reaction (Figure **13**). In the presence of substrate **96**, ligand exchange occurs on the catalyst

[47] (a) Li, X.; Hewgley, J. B.; Mulrooney, C. A.; Yang, J.; Kozlowski, M. C. *J. Org. Chem*. **2003**, *68*, 5500-5511. (b) Hewgley, J. B.; Stahl, S.; Kozlowski, M. C. *J. Am. Chem. Soc*. **2008**, *130*, 12232-12233.

via chelation of the carbonyl functionality at C_3. The chelate **107** is a fixed stereochemical environment for induction of enantioselectivity. Upon electron-transfer, the Cu(II) species **107** gets reduced to Cu(I) and the naphthyl moiety undergoes a radical-radical combination leading to carbon-carbon bond formation. Upon tautomerization, BINOL product **100** is released and O_2 regenerates the Cu(II) species **106**.

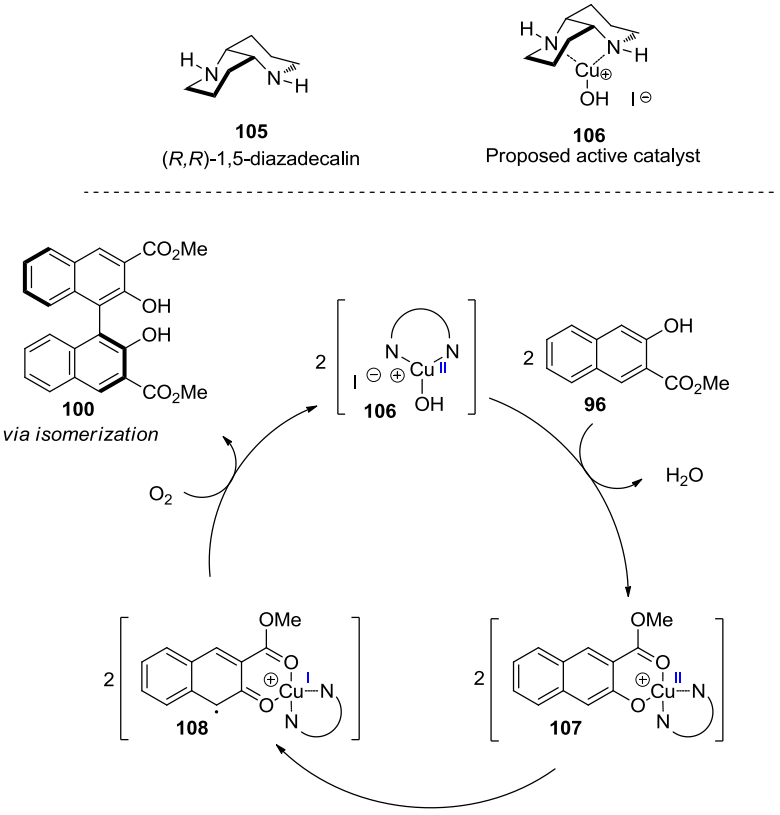
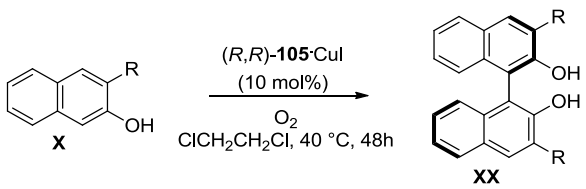


Figure 13. Proposed catalytic cycle for the homocoupling of naphthol ester **96**.

Kozlowski and co-workers reasoned that, under the oxidizing conditions of the coupling reaction, the slow step of the catalytic cycle would be the reduction of the Cu(II) species **107** to the Cu(I) species **108**.[47] To improve the reaction efficiency Kozlowski strategically looked to stabilize the Cu(I) oxidation state. Coordinating solvents such as acetone or MeOH were avoided, because they are known to stabilize

the Cu(II) species.[48] Optimization showed that DCE was the most suitable solvent. With respect to the catalyst, softer copper ligands such as iodide were favored over the tighter coordinating chloride.



		Coupling product		
Entry	**X**	**XX**	*Yield (%)*	*ee (%)*
1	**93**: R = H	**92**[a]	*81*	*16*
2	**96**: R = CO_2Me	**100**	*85*	*91-93*
3	**109**: R = $CONEt_2$	**110**	*27*	*92*

[a](Carried out with CuCl, DCM, 21°C)

Scheme 28. Enantioselective coupling of naphthols **93**, **96** and **109** with the CuI·(*R,R*)-1,5-diazadecalin catalytic system.

The catalytic system **105**·CuI was investigated in the coupling reaction (Scheme **28**). Although oxidative coupling of **93**, bearing no C_3 substituent, afforded product **92** in 81% yield and 16% *ee*, the oxidative coupling of **96** gave 2-hydroxy-3-methylnaphthoate **100** in 85% yield and 91-93% *ee*. As previously explained, substrates bearing a C_3 substituent having the ability to chelate to the metal center of the catalyst provide better enantiomeric selectivities likely because they create a rigid stereochemical environment for the coupling reaction. However, the yield of the reaction was diminished to 27% when the amide substrate **109** was used, likely because the chelation between the substrate and the metal center hampered substrate release. Enantioselectivity for the coupling of amide **109** remained high (92% *ee*).

1.4.3 Oxidative Homocoupling of Naphthols Catalyzed by Other Metals

In addition to amine-Cu complexes for the chiral and achiral oxidative coupling of naphthols, catalytic systems with other transition metals have been developed. Particular interest has been given to oxovanadium complexes (Figure **14**)

[48] Rayner-Canham, G.; Overton, T. *Descriptive Inorganic Chemistry*, 3rd Ed.; Freeman: New York, 2002, pp.511-513.

which have proven their efficiency in the enantioselective formation of BINOL derivatives having no chelating substituents in the C_3 position. [49]

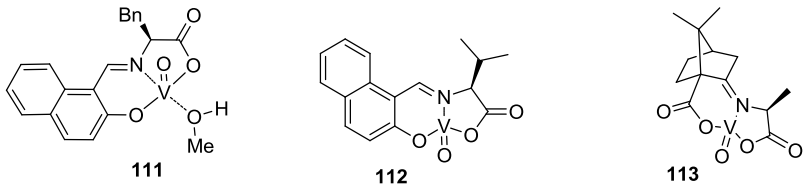
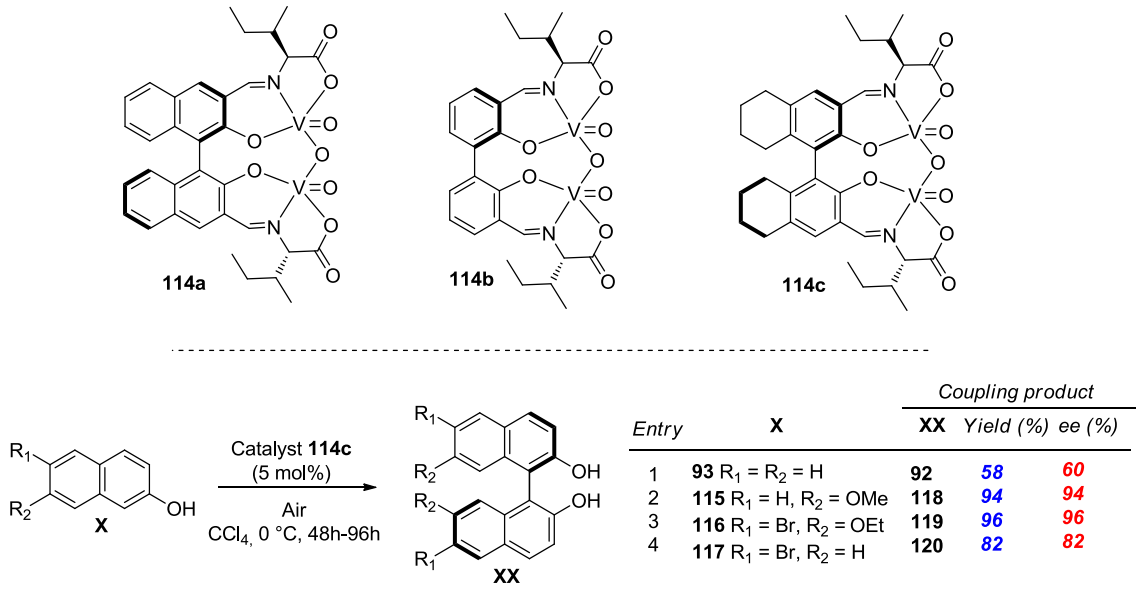


Figure 14. Oxovanadium complexes employed for the enantioselective synthesis of BINOL derivatives.

Gong and co-workers developed various chiral bimetallic oxovanadium(IV) catalysts (Scheme **29**).[50] Biaryl complex **114c** proved to be the most efficient in the enantioselective coupling of naphthol derivatives. The oxidative coupling reaction was carried out under air at 0 °C and proceeded smoothly with C_6 and C_7 substituted naphthols. Unlike amine-Cu complexes, oxovanadium complex **114c** coupled naphthols without a chelating functional group in the C_3 position in good enantioselectivities. The oxidative coupling to give 2,2'-binaphthol **92** afforded the product in low enantiomeric excess (60% *ee*), which shows that functional groups at C_6 and C_7 are important for the induction of enantioselectivity.

[49] (a) Theriot, L. J.; Carlisle, G. O.; Hu, H. J. *J. Inorg. Nucl. Chem.* **1969**, *31*, 2841-2844. (b) Frausto da Silva, J. J. R.; Wootton, R.; Gillard, R. D. *J. Chem. Soc. A* **1970**, 3369-3372. (c) Chu, C.-Y.; Hwang, D.-R.; Wang, S.-K.; Uang, B.-J. *Chem. Commun.* **2001**, *11*, 980-981. (d) Hon, S.; Li, C.; Kuo, J.; Barhate, N. B.; Liu, Y.; Wang, Y.; Chen, C. *Org. Lett.* **2001**, *3*, 869-872. (e) Barhate, N. B.; Chen, C. *Org. Lett.* **2002**, *4*, 2529-2532.

[50] Guo, Q.-X.; Wu, Z.-J.; Luo, Z.-B.; Liu, Q.-Z.; Ye, J.-L.; Luo, S. W.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc*. **2007**, *129*, 13927-13938.



Scheme 29. Biaryl bisoxovanadium complexes evaluated in the enantioselective homocoupling of naphthol derivatives (top) and enantioselective synthesis of BINOLs **92**, **118-120** with chiral oxovanadium catalyst **114c** (bottom).

Mechanistic studies and DFT calculations suggest the reaction occurs *via* a radical-radical coupling and the two metallic centers are essential for C-C bond formation (Figure **15**). The enantioselectivity of the coupling is controlled by the stereochemical environment conferred by the ligands about the two metallic centers. The presence of C_6 and C_7 substituents on the substrate increases selectivity.

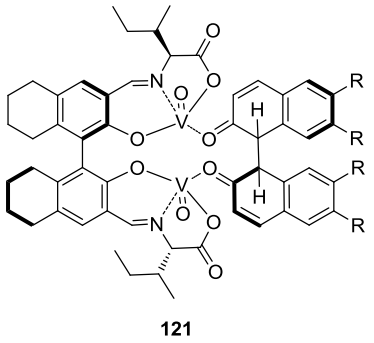
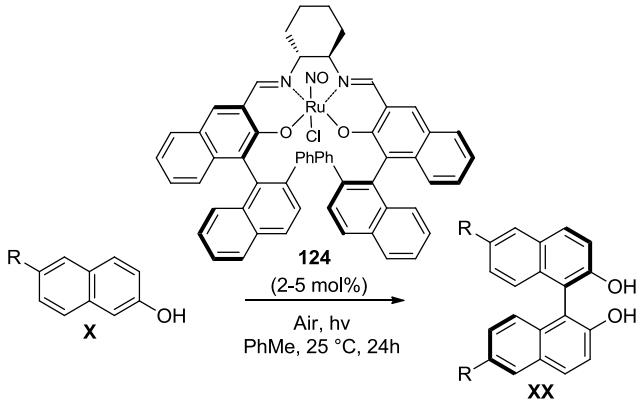


Figure 15. Postulated intermediate in the enantioselective homocoupling of C_6 and C_7 substituted naphthol derivatives.

Although amine-Cu and vanadium complexes remain the most studied systems in the homocoupling of naphthol derivatives, methods involving other transition metals have been reported. Katsuki and co-workers showed the process may also be photopromoted.[51] The Ru(Salen) complex **124** catalyzes the oxidative coupling of 2-naphthols under air and with exposure to light using a halogen lamp (Scheme **30**). Light is presumed to activate catalyst **124** by promoting the disassociation of either the chloride or nitro ligand to allow both substrate binding and eventual oxidation by oxygen.



Entry	X	Coupling product XX	Yield (%)	ee (%)
1	**93** R = H	**92**[a]	*72*	*65*
2	**117** R = Br	**120**[b]	*77*	*69*
3	**122** R = PhCC	**125**[b]	*93*	*68*
4	**123** R = OMe	**126**[a]	*73*	*33*

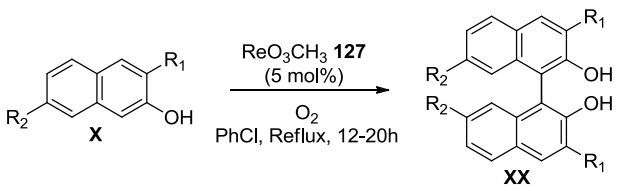
[a](Carried out with 2 mol% **124**), [b](Carried out with 5 mol% **124**)

Scheme 30. Oxidative coupling of naphthols **93**, **117**, **122**, and **123** catalyzed by Ru(Salen) complex **124**.

The oxidative coupling of electron poor naphthols using Ru(Salen) complex **124** provided good yields and moderate enantioselectivities (Scheme **30**). When 2-naphthol **93** was submitted to the reaction conditions, the BINOL **92** was isolated in 72% yield and 65% *ee*. When the 2-naphthol substrate was substituted with a Br or PhCC group at C_6 (**117** and **122**), the coupled products **120** and **125** were formed with sensibly the same enantioselectivity (69% *ee* and 68% *ee* respectively), although a slower reaction rate was observed and 5 mol% of catalyst was necessary to obtain complete conversion. When an electron-donating OMe was introduced at the C_6

[51] Irie, R.; Masutani, K.; Katsuki, T. *Synlett.* **2000**, *10*, 1433-1436.

position (**123**), the reaction rate was increased but the enantioselectivity of BINOL product **126** dropped significantly (33% *ee*).



Entry	X	Coupling product XX Yield (%)	
1	**93** $R_1 = R_2 = H$	**92**	***92***
2	**96** $R_1 = CO_2Me$, $R_2 = H$	**100**	***40***
3	**115** $R_1 = H$, $R_2 = OMe$	**118**	***90***

Scheme 31. Generation of BINOL derivatives *via* catalysis with methylrhenium(VII) trioxide **127**.

Sain and co-workers reported the aerobic coupling of naphthols catalyzed by methylrhenium(VII) trioxide (Scheme **31**).[52] The method proved efficient with electron rich naphthols such as **93** and **115**, obtaining >90% yields for the BINOL products. However, naphthol **96** bearing a C_3 ester functional group afforded BINOL **100** in 40% yield even when the reaction was carried out at elevated temperature. In general, methylrhenium trioxide coupled electron rich naphthols more successfully than electron poor substrates.

1.4.4 Oxidative Heterocoupling of Naphthol Derivatives

Although a wide variety of methods promoting the oxidative homocoupling of naphthol derivatives are known, few examples have been reported for the formation of C_1-symmetric BINOLs *via* oxidative cross-coupling. One difficulty in promoting formation of cross-coupled BINOLs lies in the preference of most catalytic systems to operate *via* a radical-radical mechanism producing a mixture of products often favoring the formation of homocoupled products.[47] When Kozlowski and co-workers attempted to couple two electronically different naphthols, a mixture of products was obtained (Figure **16**). The desired heterocoupled product **131** was formed along with a significant amount of homocoupled products **130** and **132**.

[52] Sharma, V. B.; Jain, S. L.; Sain B. *Tetrahedron Lett*. **2003**, *44*, 2655-2656.

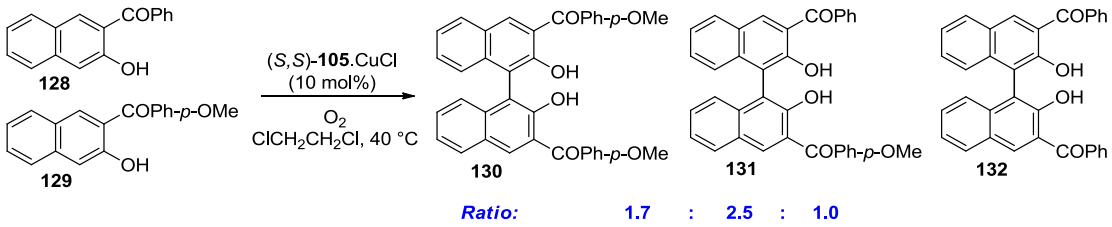
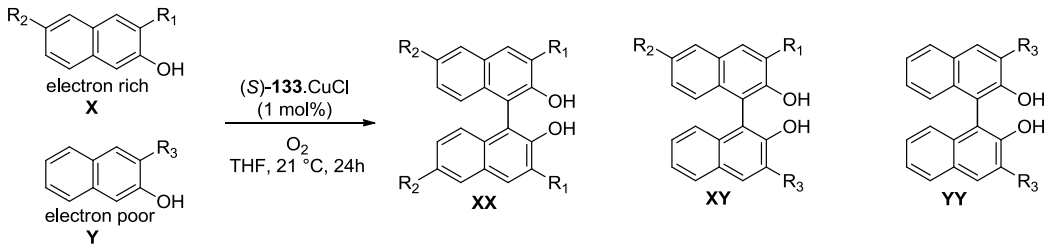
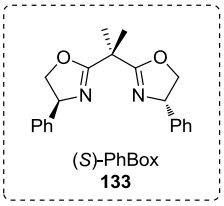


Figure 16. Mixture of products obtained in the coupling of naphthols **128** and **129** with (*S,S*)-**105**·CuCl.

In 2006, Habaue developed an aerobic cross-coupling of C_5 substituted 2-naphthols with C_3 substituted naphthoates.[53] The process was catalyzed by a complex of a chiral bis-oxazoline ligand (*S*)-PhBox **133** and CuCl (Scheme **32**).





Entry	X	Y	Cross-coupling product XY	Yield (%)	ee (%)	Coupling Ratio XX:XY:YY
1	**93** R_1 = R_2 = H	**96** R_3 = CO_2Me	**137**	*79*	*8 (S)*	0 : 99.6 : 0.4
2	**134** R_1 = H, R_2 = OAc	**96** R_3 = CO_2Me	**138**	*94*	*10 (S)*	0 : 99.7 : 0.3
3	**134** R_1 = H, R_2 = OAc	**136** R_3 = CO_2Ph	**139**	*76*	*46 (R)*	0 : 97.3 : 2.7
4	**135** R_1 = OBn, R_2 = H	**136** R_3 = CO_2Ph	**140**[a]	*70*	*70 (R)*	11.1 : 87 : 1.9

[a](Carried out with 5 mol% CuCl and 6 mol% **100**)

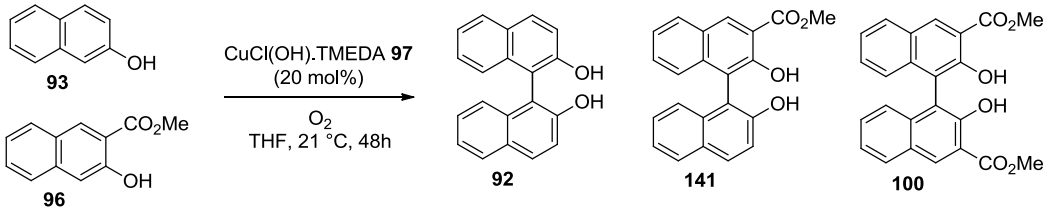
Scheme 32. Synthesis of C_1-symmetric BINOLs catalyzed by oxazoline-Cu complex **133**·CuCl.

High selectivity for the cross-coupled products **137** and **138** was observed (>99%) in the coupling of 2-naphthols **93** and **134** with naphthoate **96**, albeit with poor enantiomeric excess (8-10% *ee*). Like other amine-Cu catalyzed systems, enantioselectivity was favored using a chelating substituent at the C_3 position of the

[53] Temma, T.; Hatano, B.; Habaue, S. *Tetrahedron* **2006**, *62*, 8559-8563.

electron rich and the electron poor naphthol, (*i.e.,* Entry **4** with substrates **135** and **136**). However the introduction of such a group promoted the formation of homocoupled product **XX** with a chemoselectivity of 11.1%. Although no reaction mechanism was proposed, it is presumed that electron rich naphthols **93, 134** and **135** undergo oxidation by the copper catalyst to yield a radical species that may attack the electron poor naphthoates **96** and **136**. Electron poor naphthoates **96** and **136** are less likely to undergo homocoupling and more likely to act as radical acceptors, due to their higher oxidation potential.

Habaue and co-workers further improved the coupling process with the use of a Lewis acid additive. Adding $Yb(OTf)_3$ to the reaction mixture favored the heterocoupling of naphthol derivatives **93** and **96** using 20 mol% of the achiral CuCl(OH)·TMEDA **97** to catalyze the reaction (Scheme **33**).[54] With no additive, a mixture of homocoupled **92** and heterocoupled **141** was formed, and **141** was isolated in only 47% yield after 48h. When 10 mol% $Yb(OTf)_3$ was added to the reaction, a significant increase to 91% yield of heterocoupled **141** was observed with >99% selectivity, and no homocoupled product was formed.



Scheme 33. CuCl(OH)·TMEDA catalyzed heterocoupling of **93** and **96** assisted by $Yb(OTf)_3$.

[54] Habaue, S.; Temma, T.; Sugiyama, Y.; Yan, P. *Tetrahedron Lett*. **2007**, *48*, 8595-8598.

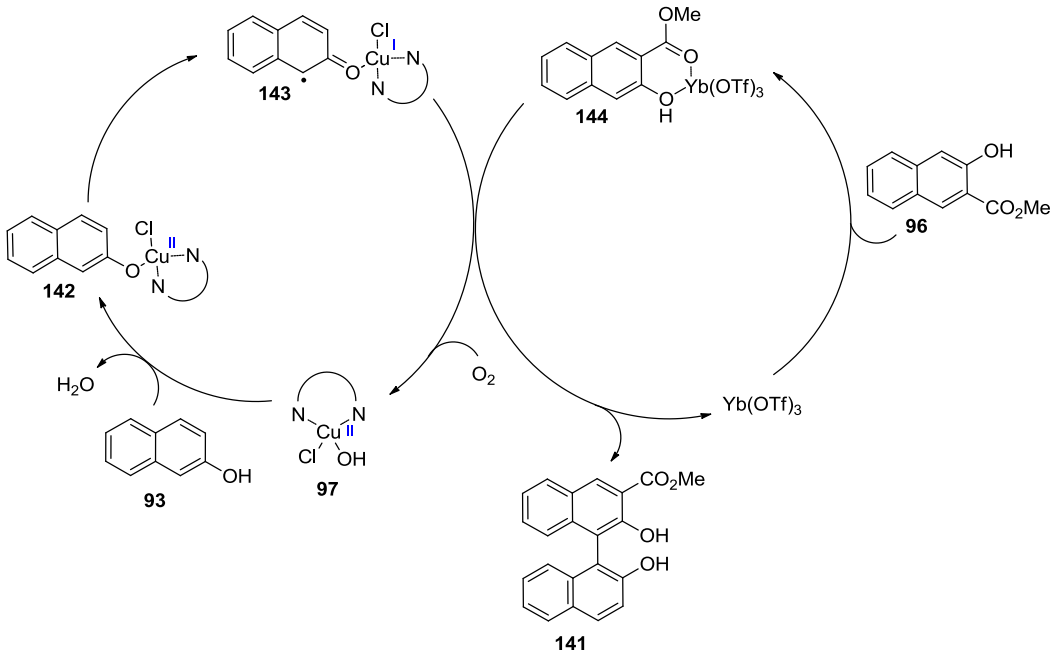
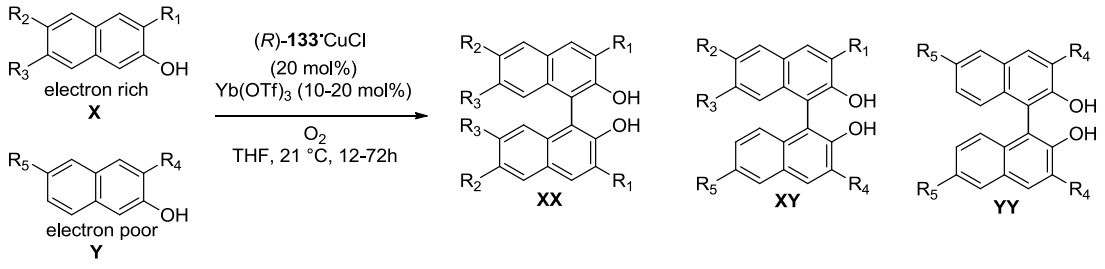


Figure 17. Proposed catalytic cycle for the $Yb(OTf)_3$ assisted heterocoupling of **93** and **96**.

Habaue proposed that electron rich naphthol **93** undergoes proton abstraction to form the naphthoxy-Cu(II) species **142**, followed by formation of the Cu(I) radical species **143** upon electron transfer (Figure **17**). The Lewis acid $Yb(OTf)_3$ chelates to the electron poor naphthol ester **96**, raising its oxidation potential and restraining the generation of a radical-like intermediate. The deactivated ester **144** then reacts with the radical species **143** to form the desired cross-coupled product **141**. The copper catalyst is regenerated upon oxidation by O_2.



Entry	X	Y	Cross-coupling product XY	Yield (%)	ee (%)	Coupling Ratio XX:XY:YY
1	**93** $R_1 = R_2 = R_3 = H$	**146** $R_4 = H$, $R_5 = CO_2Me$	**147**	*13*	*27 (R)*	52 : 35 : 13
2	**93** $R_1 = R_2 = R_3 = H$	**136** $R_4 = CO_2Ph$, $R_5 = H$	**148**	*36*	*59 (S)*	0: 99+ : 0
3	**123** $R_1 = R_3 = H$, $R_2 = OMe$	**136** $R_4 = CO_2Ph$, $R_5 = H$	**149**	*99*	*45 (S)*	0: 99+ : 0
4	**145** $R_1 = R_2 = H$, $R_3 = OBn$	**136** $R_4 = CO_2Ph$, $R_5 = H$	**150**	*74*	*67 (S)*	0: 96 : 4

Scheme 34. (*R*)-PhBox·CuCl catalyzed heterocoupling of **X** and **Y** assisted by $Yb(OTf)_3$.

The use of $Yb(OTf)_3$ in the enantioselective heterocoupling of naphthols was also evaluated using a (*R*)-PhBox·CuCl-catalyzed process (Scheme **34**). When coupling 2-naphthol **93** with C_6 naphthol ester **146**, poor selectivity was obtained and a significant amount of homocoupled product was formed. However, reacting 2-naphthol **93** with C_3 naphthol ester **136** gave excellent selectivity for the cross-coupled product **148** (>99%), albeit in poor yield (36%). Introduction of an ester substituent at C_3 of the electron poor naphthol allowed for the chelation of the substrate to the Yb Lewis acid, which may favor the formation of the heterocoupled **148**. Both C_6- and C_7-substituted electron rich naphthols **123** and **145** underwent oxidative coupling with high selectivity for the desired cross-coupled products **149** and **150** (>99% and 96% respectively) in good to excellent yields (99% and 74% respectively). Overall, the heterocoupling reaction of naphthols **93, 123** and **145** presented in Scheme **34** exhibited poor to moderate enantioselectivity. Although $Yb(OTf)_3$ increased the selectivity for the heterocoupled product, it did not increase enantioselectivity in the reaction.

The C_1-symmetric binaphthyl skeleton may also be constructed by an iron catalyzed heterocoupling reaction. Recently, Katsuki and co-workers reported the enantioselective heterocoupling of C_3-substituted 2-naphthols with less electron rich

2-naphthols catalyzed by a dimeric Fe(Salan) complex **151**, which reacted with the substrate to yield a monomeric naphthoxo-iron species **152** prior to oxidative coupling (Figure **18**).[55]

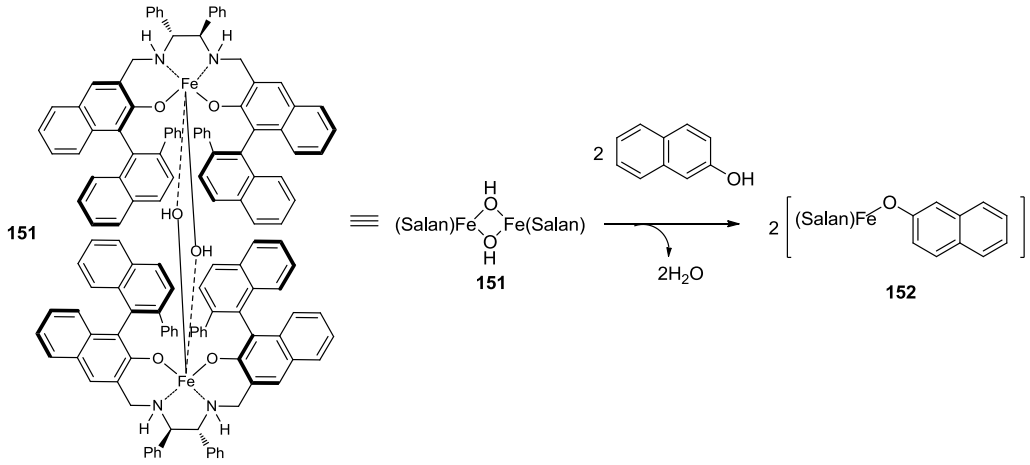
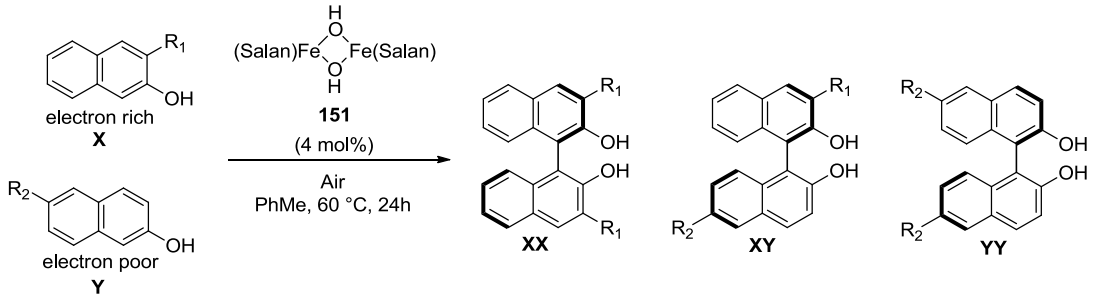


Figure 18. Intermediate formed upon reaction of catalyst **151** with 2-naphthol.

The coupling reaction was presumed to occur *via* a radical-anion mechanism,[56] because a mixture of products was obtained from the attempted cross-coupling. Although a mixture of products was obtained, the cross-coupled product was always the major one. For example, when coupling **153** (Entries **1** and **2**) and **154** (Entry **3**) with **134, 156** and **146**, no homocoupled products **YY** were observed; however, the heterocoupled products **157-159** were formed in 50-65% yield (Scheme **35**). Although **134**, **146** and **156** were too electron poor to be oxidized under the reaction conditions, they reacted with the oxidized **153** (Entries **1** and **2**) and **154** (Entry **3**) likely *via* a radical-anion mechanism. In the case of **155** and **117** (Entry **4**), both substrates were oxidized under the reaction conditions, resulting in a mixture of homo- and heterocoupled products with the desired **160** as the major product. Although the general yields of the heterocoupled products varied from poor to

[55] Egami, H.; Matsumoto, K.; Oguma, T.; Kunisu, T.; Katsuki, T. *J. Am. Chem. Soc*. **2010**, *132*, 13633-13635.
[56] For details on radical-anion mechanisms, see reference 55.

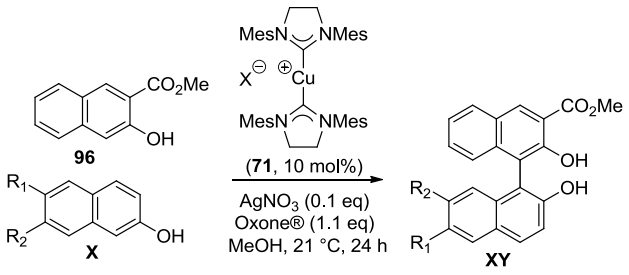
moderate, enantioselectivity was high (>88% *ee*) in spite of the absence of a coordinating substituent at C_3 of the naphthol substrates.



Entry	X	Y	Cross-coupling product XY Yield (%)	ee (%)	Coupling Ratio XX:XY:YY
1	**153** R_1 = Ph	**134** R_2 = Ac	**157**	*65*	*89*	2 : 15 : 0
2	**153** R_1 = Ph	**156** R_2 = CHO	**158**	*60*	*88*	1 : 6 : 0
3	**154** R_1 = I	**146** R_2 = CO_2Me	**159**	*50*	*95*	1 : 20 : 0
4	**155** R_1 = PhCC	**117** R_2 = Br	**160**	*44*	*88*	4 : 9 : 3

Scheme 35. [Fe(OH)Salan]$_2$ catalyzed aerobic heterocoupling of **X** and **Y**.

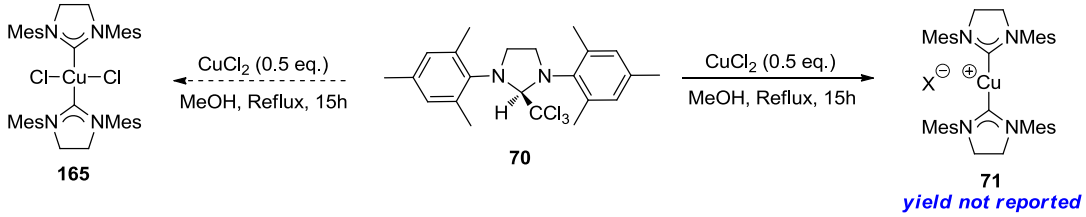
Collins and co-workers reported the achiral cross-coupling of naphthoate **96** with diverse electron rich naphthol derivatives (Scheme **36**).[32] The bis-NHC Cu catalyzed oxidative coupling reaction was selective for the heterocoupled product and no formation of homocoupled products was observed.



Entry	X	Coupling product XY Yield (%)	
1	**93:** R_1 = R_2 = H	**141**	*80*
2	**115:** R_1 = H, R_2 = OMe	**162**	*90*
3	**117:** R_1 = Br, R_2 = H	**163**	*65*
4	**161:** R_1 = Me, R_2 = H	**164**	*81*

Scheme 36. Heterocoupling of naphthoate **96** and naphthols **93**, **115**, **117** and **161** catalyzed by the bis-NHC Cu catalyst **71**.

As mentioned in the introduction (Chapter 1, Section 1.3.3.1), the ill-defined bis-NHC Cu catalyst **71** was formed *via* the masked carbene route (Scheme **37**). When the chloroform adduct **70** was reacted with $CuCl_2$, the expected NHC-Cu(II) salt **165** was not formed. The solid obtained was characterized by mass spectrometry, revealing the formation of a bis-NHC Cu(I) cationic species **71**. The poor solubility of complex **71** did not allow to characterize its anion X^- which remains unidentified.



Scheme 37. Synthesis of bis-NHC Cu complex **71** from chloroform adduct **70**.

When the ill-defined bis-NHC Cu(I) complex **71** was evaluated as a catalyst for the coupling of electron rich naphthols **93**, **115** and **161** with naphthoate **96**, the corresponding heterocoupled products were formed in more than 80% yield (Scheme **36**). Bromide substituted naphthol **117** afforded a lower yield of the heterocoupled product **162** (65% yield). The selective formation of cross-coupled binaphthols suggests a radical addition mechanism,[57] in contrast to the radical-radical mechanism observed typically with amine-Cu complexes, which promote the formation of homocoupled products.

A catalytic cycle for the heterocoupling of 2-naphthol **93** and naphthoate **96** was proposed based on established literature precedents (Figure **19**).[45b,58] The NHC-Cu(I) complex **71** would first undergo an oxidation by Oxone®, forming a Cu(II) species that coordinates to the electron rich naphthol **93** yielding **166**. Upon reduction

[57] For details on radical addition mechanisms, see: (a) Temma, T.; Habaue, S. *Tetrahedron Lett*. **2005**, *46*, 5655‑5657; (b) Temma, T.; Hatano, B.; Habaue, S. *Tetrahedron* **2006**, *62*, 8559‑8563; (c) Habaue, S.; Takahashi, Y.; Temma, T. *Tetrahedron Lett*. **2007**, *48*, 7301‑7304. (d) Habaue, S.; Temma, T.; Sugiyama, Y.; Yan, P. *Tetrahedron Lett*. **2007**, *48*, 8595-8598.

[58] (a) Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1137-1140. (b) Kozlowski, M. C.; Li, X.; Carroll, P. J.; Xu, Z. *Organometallics* **2002**, *21*, 4513-4522.

of **166**, the Cu(I) radical species **168** would form. Carbon-carbon bond formation would then occur *via* a radical-addition mechanism with the electron poor naphthoxy-Cu species **167**. Upon tautomerization, **169** would release the desired heterocoupled product **141**, regenerating the Cu(I) catalyst.

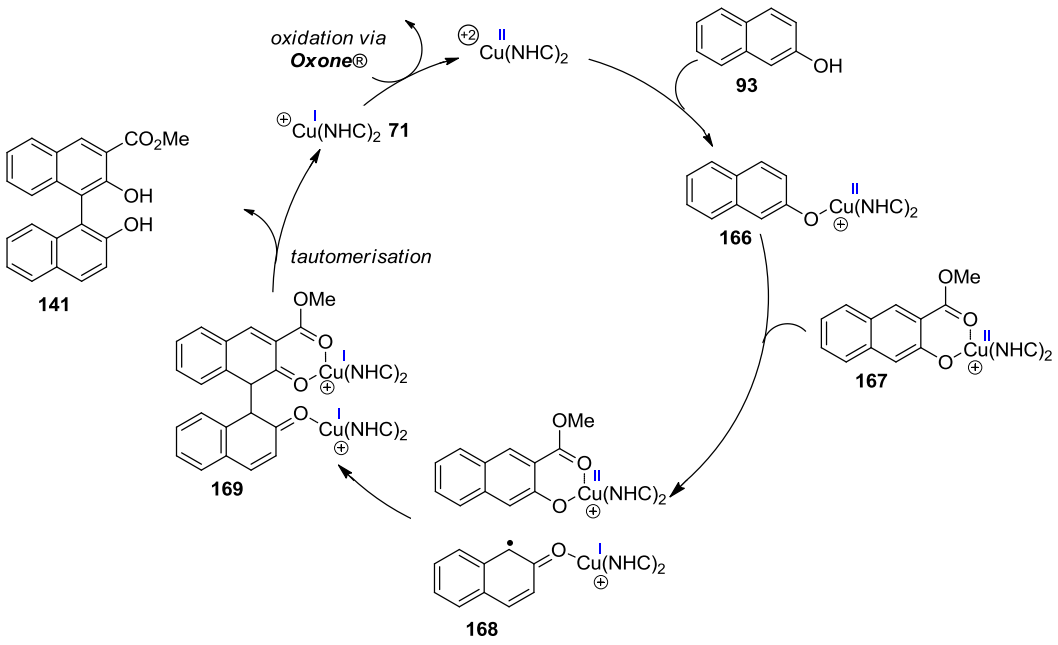


Figure 19. Proposed reaction mechanism for the oxidative heterocoupling of electron rich naphthol **93** and electron poor naphthol **96**.

While the $AgNO_3$ additive was shown to be essential for high yields, its role in the reaction mechanism is still unknown. It should also be noted that recent studies have suggested that radical intermediates may not be implicated in the C-C bond forming process.[59]

[59] Roithova, J.; Milko, P. *J. Am. Chem. Soc*. **2010**, *132*, 281-288.

1.5 Research Goals

Collins and co-workers developed a synthesis of C_1-symmetric BINOLs *via* the copper catalyzed heterocoupling of naphthol derivatives.[32] The method promoted the selective formation of cross-coupled binaphthol products. However, the NHC-Cu complex **71** developed to carry out the catalytic transformation was ill-defined, in part due to the poor solubility of the catalyst hampering characterization such that its counterion X^- remains unidentified. Aiming to further investigate the oxidative homo- and heterocoupling of naphthol derivatives with a well-defined catalyst, the objective of the current study is to evaluate the structural effects of the catalyst on the coupling process. Mono- and bis-NHC Cu complexes with different counterions and *N*-substituents were evaluated in the coupling reaction in order to study and improve the catalytic process (Figure **20**, top). Optimization was performed on the homocoupling of naphthoate **96** (Figure **20**, bottom).

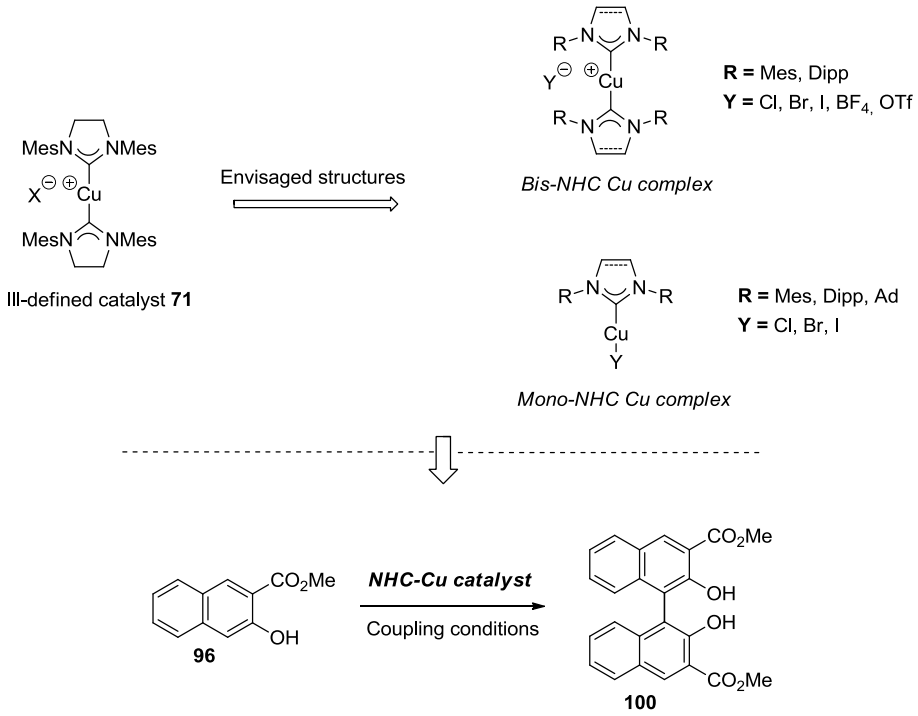


Figure 20. Different catalytic structures envisaged for the oxidative coupling of naphthol derivatives (top) and their application in the NHC-Cu catalyzed coupling of naphthoate **96** (bottom).

To synthesize an array of NHC-Cu complexes, a method was pursued for the formation of both mono- and bis-NHC Cu complexes with different substitution patterns and different counterions. The synthesis of NHC-Cu complexes has typically involved deprotonation with organic bases such as NaO*t*Bu, or basic metals such as Ag_2O. To avoid the use of strong bases and expensive silver salts, we explored masked carbenes. Crabtree[30c] and Delaude[30a] demonstrated that imidazol(in)ium-2-carboxylates were suitable NHC transfer agents. We thus envisaged a synthesis of mono- and bis-NHC Cu complexes *via* the decarboxylative generation of carbenes (Figure **21**).

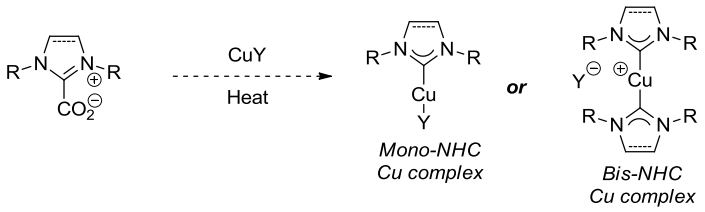


Figure 21. Decarboxylative generation of carbene for the synthesis of $Cu(NHC)_2Y$ and Cu(NHC)Y complexes.

The development of a synthesis of NHC-Cu complexes *via* zwitterionic carboxylates and the evaluation of the NHC-Cu complexes in the oxidative coupling of naphthol ester **96** will be discussed.

Chapter 2. Synthesis of Aryl and Alkyl Substituted Imidazol(in)ium Tetrafluoroborate Salts and Their Respective Imidazol(in)ium Carboxylates

2.1 Synthesis of Aryl and Alkyl Substituted Imidazol(in)ium Tetrafluoroborate Salts

Since the isolation of the first crystalline carbene by Arduengo,[6] interest in *N*-heterocyclic carbenes has greatly increased, due to their use as organocatalysts[60] and as ligands in organometallic complexes.[33,61] The extensive use of the NHCs presented in Figure **22** made them the ligands of choice for our study.

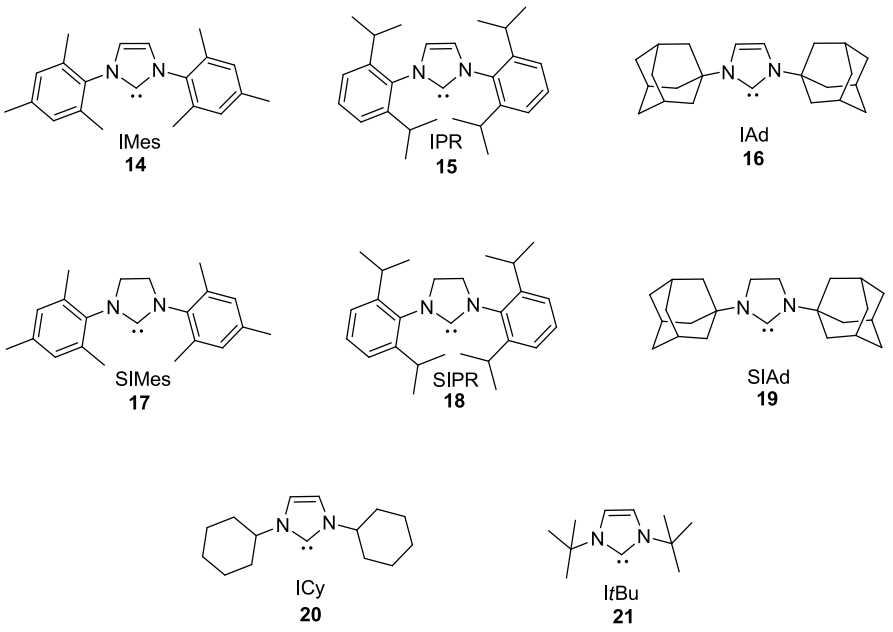


Figure 22. Common *N*-heterocyclic carbenes used in organic synthesis.

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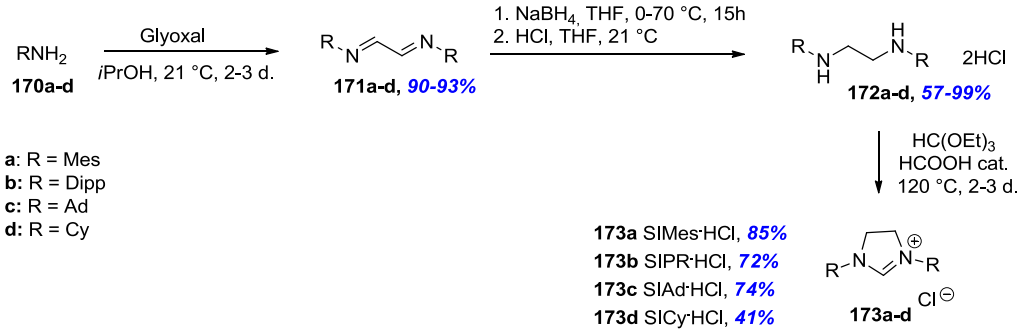
[60] (a) Duong, H. A.; Cross, M. J.; Louie, J. *Org. Lett.* **2004**, *6*, 4679-4681 (b) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371-374. (c) Reynolds, N. T.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518-9519. (d) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284-6289.

[61] (a) Dash, C.; Shaikh, M. M.; Butcher, R. J.; Ghosh, P. *Inorg. Chem*. **2010**, *49*, 4972–4983. (b) Zhang, K.; Conda-Sheridan, M.; Cooke, S. R.; Louie, J. *Organometallics* **2011**, *30*, 2546-2552. (c) Keitz, B. K.; Grubbs, R. H. *Organometallics* **2010**, *29*, 403–408. (d) Liu, R.; Herron, S. R.; Fleming, S. A. *J. Org. Chem.* **2007**, *72*, 5587-5591. (e) Trost, B. M.; Dong, G. *J. Am. Chem. Soc*. **2006**, *128*, 6054-6055.

In order to prepare the imidazol(in)ium-2-carboxylates correponding to the imidazol(in)ylidenes targeted, imidazol(in)ium precursors were pursued. The synthesis of imidazolinium salts **173a-d** was accomplished following literature precedents (Scheme **38**).[8] First, condensation of glyoxal with appropriately substituted amines generated the diimines **171a-d**, which underwent reduction with $NaBH_4$ to furnish diamines isolated as dihydrochloride salts **172a-d**. The diamine salts **172a-d** were then cyclized in neat triethyl orthoformate using a catalytic amount of formic acid, forming the desired imidazolinium chlorides **173a-d** possessing respectively 2,4,6-trimethylphenyl (Mes), 2,6-di-*iso*-propylphenyl (DIPP), adamantyl (Ad) and cyclohexyl (Cy) amine substituents.



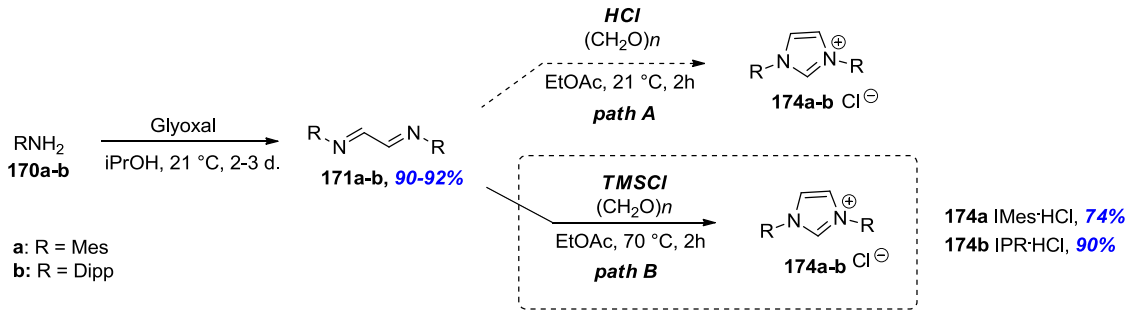
Scheme 38. General synthesis of imidazolinium chloride salts.

For the synthesis of aryl substituted imidazolium salts, the appropriate aniline was reacted with glyoxal to form the diimines **171a-b** (Scheme **39**). Ring closure was investigated using two different routes to yield the desired imidazolium salts (paths A and B, Scheme **39**). Following path A, diimines **171a-b** were cyclized with paraformaldehyde under acidic conditions to generate the desired aryl substituted imidazolium salts IMes·HCl **174a** and IPR·HCl **174b**. Crude **174a** and **174b** were isolated as brown powders, which were purified by flash chromatography[62] followed by recrystallization to yield white crystals. However, the white crystals became

[62] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923-2925.

slightly brown after 24h on the bench. Subsequent reactions using brown crystals of **174a** and **174b** always gave low yields.

An alternative synthesis of the desired salts developed by Hintermann was investigated (path B, Scheme **39**).[63] Diimines **171a-b** were reacted with paraformaldehyde and TMSCl. The cyclized products **174a-b** precipitated out of solution and were purified by filtration. The purity of **174a-b** was assessed by ^{1}H NMR spectroscopy. The white crystalline salts did not exhibit any decomposition over time and were used without further purification for subsequent synthesis.

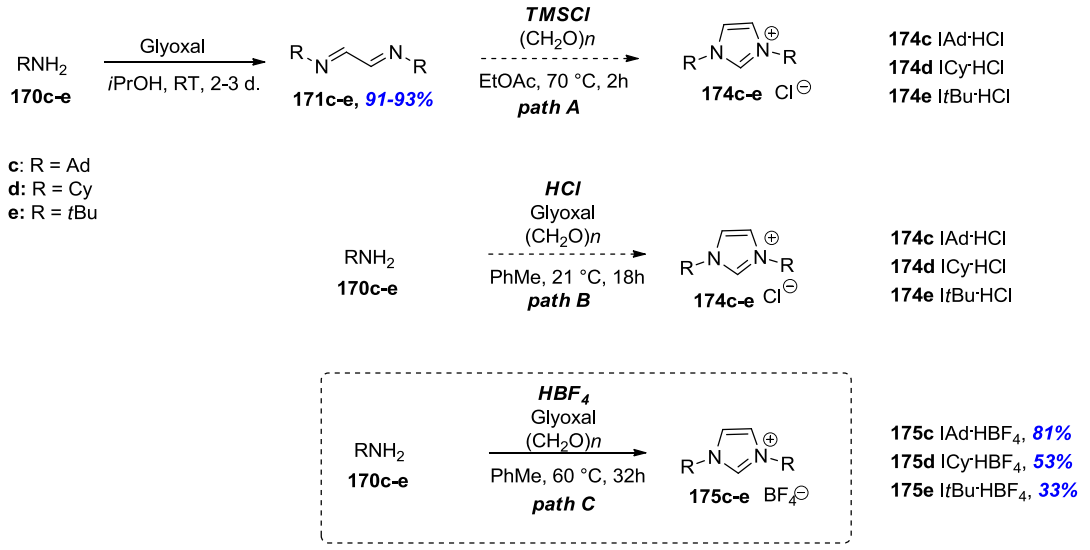


Scheme 39. Synthesis of aryl substituted imidazolium chloride salts.

Given the successful synthesis of **174a-b** *via* path B (Scheme **39**), expanding the method to alkyl substituted imidazolium salts IAd·HCl **174c**, ICy·HCl **174d** and I*t*Bu·HCl **174e** was attempted. However, the method developed by Hintermann proved inadequate for the synthesis of salts **174c-e** (path A, Scheme **40**). Indeed, reacting the diimines **171c-e** with paraformaldehyde and TMSCl yielded brown oils. The isolation of the desired cyclized salts **174c-e** by flash chromatography was inefficient as coloured by-products co-eluted with the desired imidazolium salts. Two alternate synthetic routes were examined (paths B and C, Scheme **40**). Along path B, a one pot procedure was employed in which the appropriate amine was reacted first with paraformaldehyde followed by the addition of hydrochloric acid and glyoxal.[64]

[63] Hintermann, L. *Beilstein J. Org. Chem*. **2007**, *3*, No. 22.
[64] Pévère, V. *Adduits de Carbène et de CO_2 pour le Stockage de Carbène et/ou de CO_2*, France Patent [07 58106], 2007**.**

Although ^{1}H NMR spectroscopy assessed the formation of imidazolium chloride salts **174c-e**, they were isolated as dark oils which could not be efficiently purified by flash chromatography or recrystallization.



Scheme 40. Synthesis of alkyl substituted imidazolium salts.

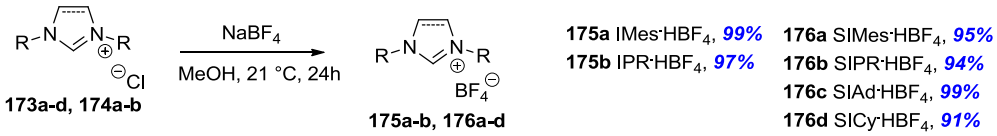
Glorius and co-workers have shown that a similar one-pot synthesis using tetrafluoroboric acid in the place of hydrochloric acid allows for the successful formation and facile purification of IAd·HBF_4 **175c**.[65] Using this method (path C, Scheme **40**), stirring adamantylamine **170c** with paraformaldehyde followed by glyoxal and HBF_4 in toluene at 60 °C for 32h afforded the desired imidazolium tetrafluoroborate salt. Purification by flash chromatography followed by recrystallization from CH_2Cl_2/hexane yielded 81% of IAd·HBF_4 **175c** as a white crystalline powder.

Because IAd·HCl **174c**, ICy·HCl **174d** and I*t*Bu·HCl **174e** were all obtained as dark oils that could not be purified by flash chromatography nor crystallization (path B, Scheme **40**), the counterion of the desired imidazolium salts was changed from chloride to tetrafluoroborate in hope that, in analogy to IAd·HBF_4 **175c**, ICy·HBF_4 **175d** and I*t*Bu·HBF_4 **175e** would be easier to purify. Submitting amines

[65] Richter, H. ; Schwertfeger, H. ; Schreiner, P. ; Fröhlich, R.; Glorius, F. *Synlett* **2009**, *2*, 193-197.

170d-e to the reaction conditions described in path C (Scheme **40**) afforded crude ICy·HBF_4 **175d** and I*t*Bu·HBF_4 **175e**. The crude salts were purified by flash chromatography followed by recrystallization from hot H_2O, yielding the desired imidazolium salts as white crystals in 57% and 33% yields respectively.

Due to the ease of handling of the tetrafluoroborate salts, all the synthesized imidazol(in)ium chloride salts underwent counterion exchange to tetrafluoroborate (Scheme **41**). Imidazol(in)ium hydrochloride salts were reacted with $NaBF_4$ in MeOH. Counterion exchange occurred as NaCl precipitated out of solution, forming the desired imidazol(in)ium tetrafluoroborate salts.

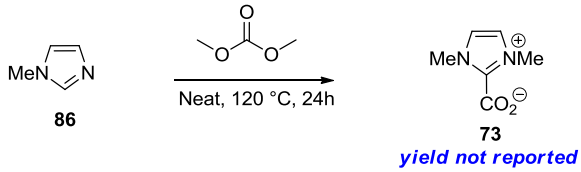


Scheme 41. Counterion exchange of imidazol(in)ium chloride salts to tetrafluoroborate salts.

In conclusion, mesityl, di*iso*propylphenyl, adamantyl and cyclohexyl substituted imidazolinium chloride salts were synthesized following the procedure developed by Arduengo and co-workers (Scheme **38**)[8] and underwent counterion exchange to generate their tetrafluoroborate analogs (Scheme **41**). Mesityl and di*iso*propylphenyl imidazolium chlorides were formed *via* a method developed by Hintermann and co-workers (path B, Scheme **39**) before undergoing counterion exchange (Scheme **41**).[63] Adamantyl, cyclohexyl and *t*butyl substituted imidazolium tetrafluoroborate salts were generated *via* Glorius' one-pot procedure (path C, Scheme **40**).[65] The salts were subsequently carboxylated to serve as *N*-heterocyclic carbene precursors for the generation of complexes of the type $Cu(NHC)_2X$ and Cu(NHC)X.

2.1 Synthesis of Imidazol(in)ium-2-Carboxylates as Masked Carbenes

As discussed in the introduction (Chapter 1, Section 1.3), *N*-heterocyclic carbene metal complexes may be generated *via* numerous methods, such as the deprotonation of an imidazolium salt with a base in the presence of a metal,[66] the use of a basic metal such as Ag_2O to generate transmetalating agents[67] and the use of masked carbenes heated in the presence of a metal to form the desired metal complex.[27] In the search for a new synthetic route for the formation of NHC-metal complexes, Rogers and co-workers developed the synthesis of 1,3-dimethylimidazolium-2-carboxylate (IMe·CO_2) **73** (Scheme **42**)[30b] which was later found to be a suitable carbene precursor by Crabtree and co-workers.[30c] Carboxylate **73** was formed from the reaction of methyl imidazole with dimethyl carbonate.



Scheme 42. Generation of the carboxylate **73** from methyl imidazole.

Further work by Louie[68] and Delaude[30a] showed the synthesis of such carboxylates from imidazolium salts. The method for the synthesis of imidazol(in)ium-2-carboxylates that will be presented in this chapter has been adapted from that developed by Delaude and co-workers in 2006.[30a] As such, an imidazol(in)ium tetrafluoroborate salt was deprotonated in the presence of a base in THF under an inert atmosphere. Deprotonation of the insoluble imidazol(in)ium salt at the 2-position generated the desired carbene which was soluble in THF (Figure **23**). Carbon dioxide gas was then bubbled through the solution and trapped the carbene to

[66] Kaur, H.; Zinn, F.; Stevens, E.; Nolan, S. *Organometallics* **2004**, *23*, 1157-1160.
[67] Huyn Park, K., Ku, I., Kim Jin, H.; Uk Son, S. *Chem. Mater*. **2008**, *20*, 1673-1675.
[68] Duong, H. A.; Tekavec, T. N.; Arif, A. M.; Louie, J. *Chem. Commun.* **2004**, 112-113.

form an air stable zwitterionic species that precipitated out of solution and was isolated by filtration.

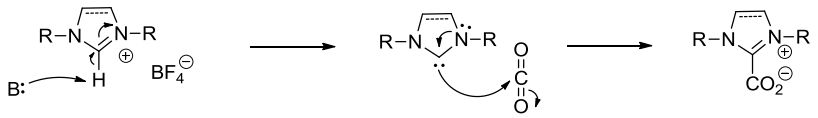
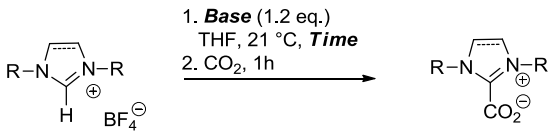
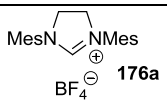
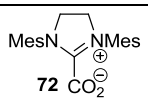
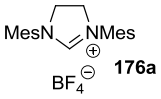
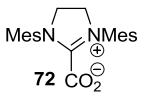
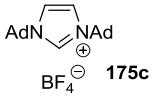
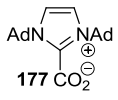
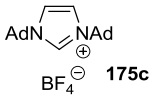
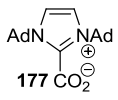
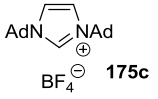
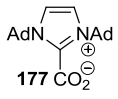
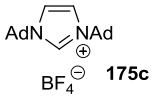
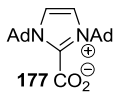
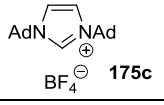
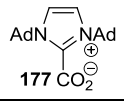


Figure 23. General mechanism for the formation of imidazol(in)ium-2-carboxylates.

The original procedure designed by Delaude made use of potassium hexamethyldisilylazide (KHMDS) as a base which was stirred in the presence of an imidazol(in)ium chloride precursor for 4h. Using the same procedure, the carboxylate product SIMes·CO_2 **72** was obtained in 71% yield (Table **1**) starting from the tetrafluoroborate precursor **176a**. When the base was stirred with the imidazolinium salt **176a** for a prolonged time of 15h, the yield of **72** was increased to 88%. A prolonged deprotonation time seems to increase the amount of carbene formed and thus subsequent reactions were done with a 15h run time.

Table 1. Optimization of the carboxylation of imidazol(in)ium precursors.



Entry	Precursor	Carboxylate Product	Base	Time (h)	Yield (%)
1	 **176a**	 **72**	KHMDS	4	71
2	 **176a**	 **72**	KHMDS	15	88
3	 **175c**	 **177**	KHMDS	15	87
4	 **175c**	 **177**	NaO*t*Bu	15	72
5	 **175c**	 **177**	KH	15	23
6	 **175c**	 **177**	*n*BuLi	15	0
7	 **175c**	 **177**	LiHMDS	15	0

Mes = 2,4,6-trimethylphenyl, Ad = adamantyl.

Although entries 1 and 2 (Table **1**) were performed with SIMes·HBF_4 **176a**, further attempts at optimization were done with IAd·HBF_4 **175c**. Indeed, SIMes·HBF_4 **176a** was formed *via* a four-step synthesis whereas IAd·HBF_4 **175c** could be generated *via* a one-pot synthesis in large quantities. When **175c** was submitted to the reaction conditions using KHMDS as a base, 87% yield of the desired IAd·CO_2 **177** was obtained. Other bases were tested but they proved less effective. Using NaO*t*Bu, the carboxylate **177** was obtained in 72% yield, a slightly lower yield when comparing to KHMDS. The low yield may be due to the lower pKa

of *t*BuOH/*t*BuO$^-$ (pKa = 18)[69] compared to NH(SiMe$_3$)$_2$/$^-$N(SiMe$_3$)$_2$ (pKa = 26).[70] One may also consider that the use of excess NaO*t*Bu can produce by-products *via* the addition of *t*butoxide to the imidazolium salt, which is in competition with the deprotonation of the imidazolium salt (Figure **24**).[28,71] Changing the base to KH also reduces the yield of **177** significantly (23%) possibly due to the poor solubility of KH in THF.

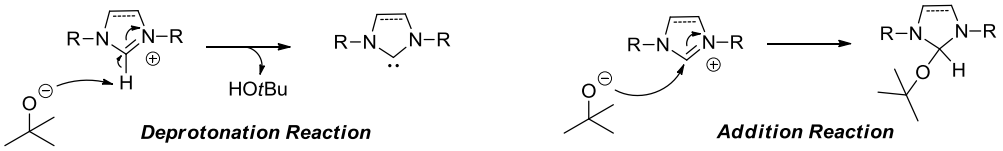


Figure 24. Possible competing reactions when using NaO*t*Bu as a base for the generation of carbenes.[28,71]

When using *n*BuLi as a base, solubilization of the solids suggests that deprotonation of the imidazolium salt **175c** occurred (Figure **25**). However, when CO_2 was bubbled through the resulting clear solution, the gas did not seem to trap the carbene to form the desired imidazolium carboxylate since no precipitation was observed. When water was added to the solution, the carbene reprotonated, thus generating an imidazolium salt that precipitated out of solution. It was thought that perhaps the lithium cation inhibited the carboxylation reaction.

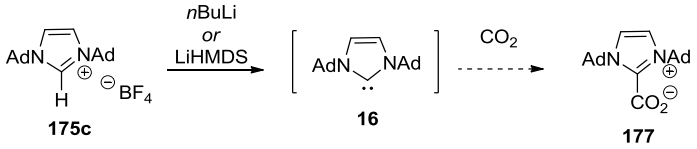


Figure 25. Attempted carboxylation of **175c** using *n*BuLi or LiHMDS as a base for carbene generation.

In 2006, Bertrand and co-workers reported that, when using *n*BuLi in the presence of the cyclopropenium salt **178**, the desired free carbene **179a** was not

[69] Serjeant, E. P.; Dempsey, B. *Ionization Constants of Organic Acids in Solution*, IUPAC Chemical Data Series No. 23, Pergamon Press, Oxford, UK, **1979**.
[70] Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50,* 3232-3234.
[71] Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, *3*, 430-432.

formed (Figure **26**, top).[72] Instead, the cyclopropenylidene·$LiBF_4$ adduct **179b** was isolated and its crystallographic structure showed that **179b** was a polymeric chain in the solid state. In view of these findings, it is possible that $LiBF_4$ formed an adduct with carbene **16**, thus inhibiting its carboxylation (Figure **26**, bottom). To investigate this hypothesis, LiHMDS was used as a base. Once again, solubilization of the solid suggested that efficient deprotonation of the imidazolium salt occurred, however carbon dioxide did not trap the carbene formed and imidazolium salt precipitated out of solution as H_2O was added. Considering that CO_2 gas is trapped efficiently when using KHMDS, it suggests that the lithium salts inhibit the formation of the imidazolium carboxylate.

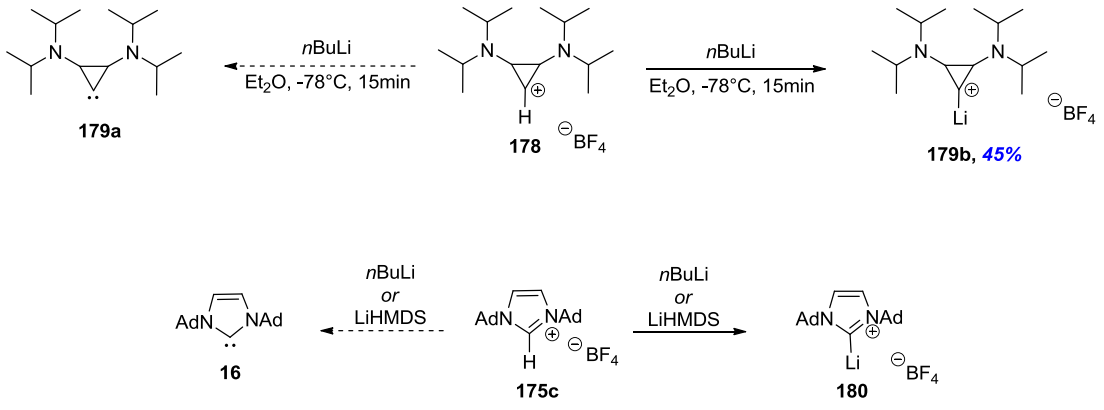
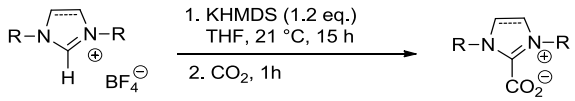


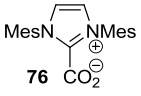
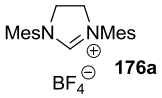
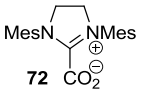
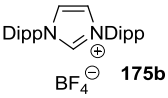
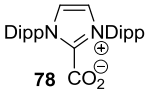
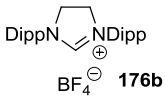
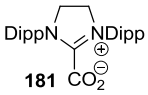
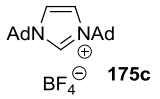
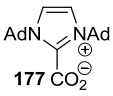
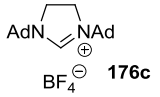
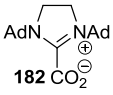
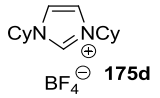
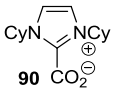
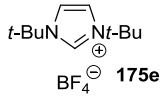
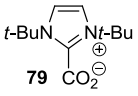
Figure 26. Cyclopropenylidene·$LiBF_4$ adduct **179b** obtained by Bertrand and co-workers (top) and hypothesized IAd·$LiBF_4$ **180** obtained in the attempted generation of IAd **16** (bottom).

After screening different reaction conditions, it was determined that using KHMDS as a base for 15h was the most suitable for carbene generation, followed by its trapping by CO_2 to form the desired imidazol(in)ium-2-carboxylate.

[72] Lavallo, V. Ishida, Y., Donnadieu, B., Bertrand, G. *Angew. Chem. Int. Ed. Engl*. **2006**, *45*, 6652-6655.

Table 2. Synthesis of imidazol(in)ium-2-carboxylates.



Entry	Precursor	Carboxylate Product	Yield (%)
1	 **175a**	 **76**	98
2	 **176a**	 **72**	88
3	 **175b**	 **78**	88
4	 **176b**	 **181**	61
5	 **175c**	 **177**	87
6	 **176c**	 **182**	89
7	 **175d**	 **90**	78
8	 **175e**	 **79**	78

Mes = 2,4,6-trimethylphenyl, DIPP = 2,6-di-*iso*-propylphenyl, Ad = adamantyl, Cy = cyclohexyl.

The mesityl substituted imidazolium salt **175a** was submitted to the reaction conditions and the carboxylate **76** was obtained in 98% yield (Table **2**). When its saturated analogue **176a** was deprotonated by KHMDS and reacted with CO_2, the product **72** was obtained in 88% yield. As a general trend, imidazolium-2-carboxylates are formed in higher yields than their imidazolinium analogs perhaps because they generate more stable carbenes.[7,73] As mentioned in the introduction (Chapter 1, Section 1.1), imidazolinylidenes are more prone to dimerization and by-product formation than their unsaturated analog (Figure **6**).

[73] (a) Magill, A. M.; Cavel, K. J.; Yates, B. F. *J. Am. Chem. Soc*. **2004**, *126*, 4366-4374. (b) Arduengo, A. J.; Krafcyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523-14534.

When reacting a more sterically hindered imidazol(in)ium salt such as IPR·HBF_4 **175b** or SIPR·HBF_4 **176b**, the DIPP substituted precursors generated the corresponding carboxylate in 88% and 61% yield respectively. In the case of alkyl substituted precursors, adamantyl substituted zwitterionic carboxylates were obtained in 87% in the case of the unsaturated **177**, and in 89% in the case of the saturated **182**. When less sterically substituted carboxylates such as ICy·CO_2 **90** and I*t*Bu·CO_2 **79** were formed, the yield decreased slightly to 78% for both cases.

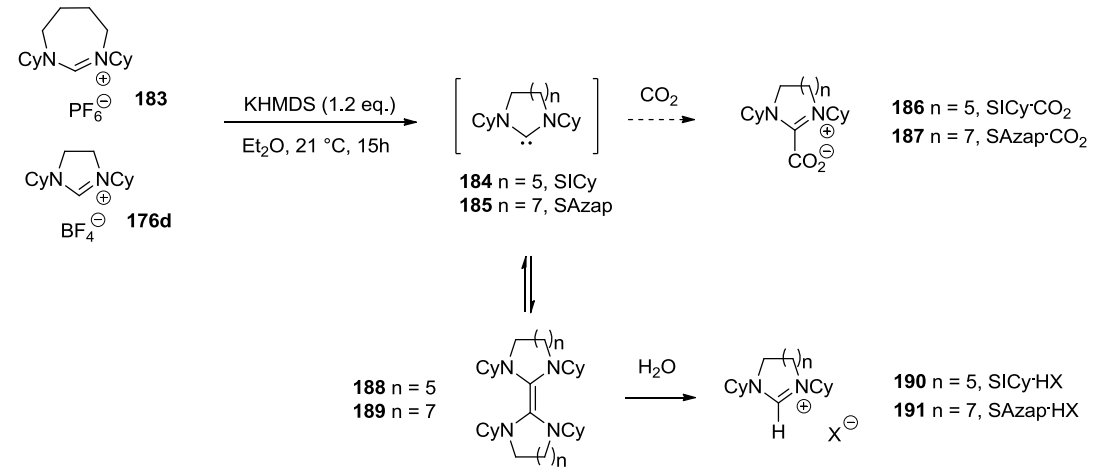


Figure 27. Attempt of carboxylation of SICy·HBF_4 **176d** and SAzap·HPF_6 **183**.

Fallis and co-workers synthesized the saturated 7-membered heterocyclic salt **183** and its carbene analog **185** (Figure **27**).[74] By studying diazapanylidene (SAzap) **185** and its properties as a ligand in Rh and Ir complexes, Fallis found that the expanded ring system provided a carbene with high basicity and increased σ-donor properties when compared to the analogous 5-membered ring NHCs. Given the interesting properties of carbene **185**, we envisaged the synthesis of the 7-membered heterocyclic carboxylate **187** as well as its analogous 5-membered heterocyclic carboxylate **186**.

When the saturated precursors **183** and **176d** were subjected to the carboxylation conditions, the formation of SICy·CO_2 **186** and SAzap·CO_2 **187** was

[74] Iglesias, M.; Beetstra, D. J.; Stasch, A.; Horton, P. N.; Hursthouse, M. B.; Coles, S. J.; Cavell, K.; Dervisi, A.; Fallis, I. A. *Organometallics* **2007**, *26*, 4800-4809.

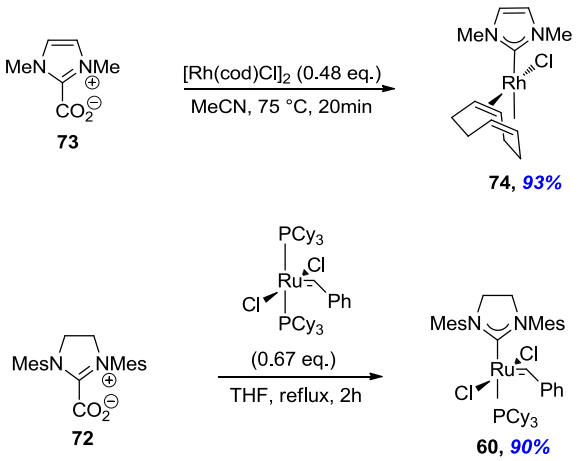
not observed (Figure **27**). However, solubilization of the salts suggests that deprotonation with KHMDS indeed occurred but the carbene generated was not trapped by CO_2. Azolium salts **190** and **191** were recovered upon addition of H_2O. The unsuccessful formation of the desired cyclic carboxylates **186** and **187** may be due to the fact that cyclic carbenes having a saturated backbone are more prone to dimer formation,[7,73] thus disfavoring the nucleophilic attack of the carbene on CO_2. An NMR study of the behavior of carbenes **184** and **185** in solution would be needed to further investigate this hypothesis.

In conclusion, the synthesis of an array of imidazol(in)ium-2-carboxylates was accomplished *via* the deprotonation of imidazol(in)ium salts and the reaction of their corresponding *N*-heterocyclic carbene with CO_2 gas. Mesityl, di*iso*propylphenyl and adamantyl substituted zwitterions were obtained in good to excellent yield for both their saturated and unsaturated analogs. Cyclohexyl substituted carboxylates bearing a saturated backbone could not be formed however *t*butyl and cyclohexyl substituted imidazolium-2-carboxylates were obtained in good yields. The application of these salts as *N*-heterocyclic carbene transfer agents for the synthesis of bis- and mono-NHC Cu(I) complexes was next evaluated.

Chapter 3. Synthesis of Mono- and Bis-*N*-Heterocyclic Carbene Copper(I) Complexes *via* the Decarboxylative Generation of Carbenes

3.1 Synthesis of Bis-*N*-Heterocyclic Carbene Copper(I) Complexes *via* the Decarboxylation of Masked Carbene of the Type Imidazol(in)ium-2-Carboxylate

Previous work by the research groups of Crabtree and Delaude has demonstrated that reacting an imidazol(in)ium-2-carboxylate in the presence of a metal source under the appropriate reaction conditions allows for the formation of a NHC metal complex (Scheme **43**). Pioneering work by Crabtree showed that reacting IMe·CO_2 **73** with $[Rh(cod)Cl]_2$ in acetonitrile at 75 °C for 20 min yielded the NHC complex **74** in 93% yield.[36c] About four years later, Delaude showed that reacting SIMes·CO_2 **72** with Grubbs' first generation catalyst in THF at reflux for 2h yielded 90% of Grubbs' second generation catalyst.[30a,37]



Scheme 43. Generation of NHC-metal complexes from imidazol(in)ium-2-carboxylates.

Imidazol(in)ium-2-carboxylates have the ability to serve as NHC transfer agents.[30a,36c,37] The synthesis of bis-NHC Cu(I) complexes *via* the decarboxylative

generation of carbenes was thus pursued (Figure **28**). With an array of imidazol(in)ium-2-carboxylates in hand, their application in the synthesis of bis-NHC Cu(I) complexes was evaluated. The carbene precursors were to be placed in a sealed tube in the presence of an appropriate copper source. Upon heating, decarboxylation occured in THF at 60 °C under inert atmosphere, forming the desired carbene *in situ*. The carbene coordinated to the metal source to generate the target complex.

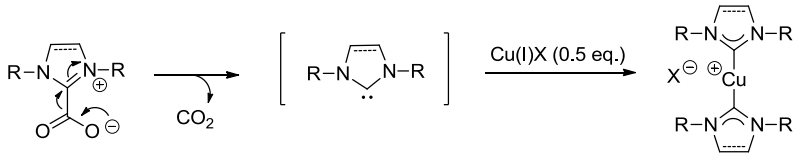


Figure 28. Planned decarboxylative generation of carbenes for the synthesis of $Cu(NHC)_2X$ complexes.

The initial attempt at forming a $Cu(NHC)_2X$ complex was undertaken with IMes·CO_2 **76** and $Cu(CH_3CN)BF_4$ as the copper source (Table **3**). Upon heating, the unsaturated $Cu(IMes)_2BF_4$ **192** was formed in an excellent 91% yield. No further optimization of the reaction conditions was deemed necessary. The method was found to be particularly efficient for mesityl-substituted NHC ligands. Complexes of the type $Cu(SIMes)_2X$ were formed with varying counterions, including iodide (**193**, 77%), bromide (**194**, 73%), chloride (**195**, 59%), triflate (**196**, 87%) and tetrafluoroborate (**40**, 83%). In the case of complexes **193**, **194** and **195**, the halide counterion may be outersphere or bound to the copper center (Figure **29**). No crystallographic data was obtained for these complexes at this time, although data for complexes of the form $Cu(SIMes)_2X$ (X = BF_4, PF_6, OTf) can be found in the literature.[20a,75]

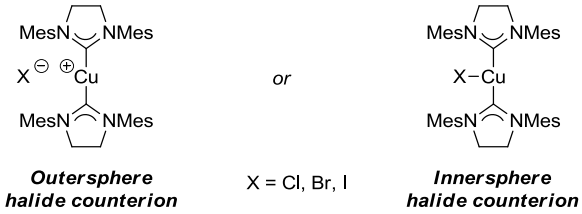
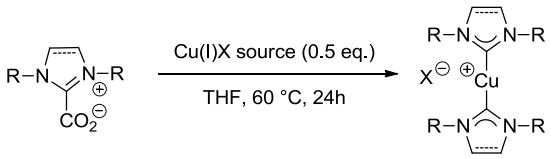
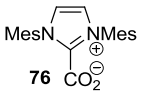
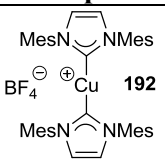
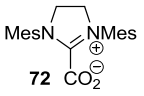
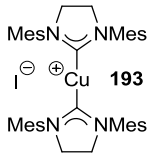
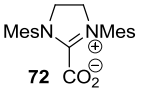
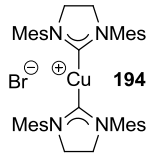
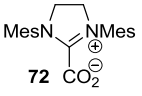
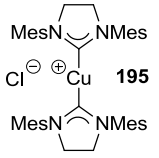
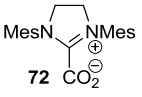
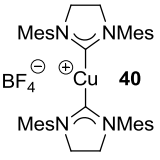
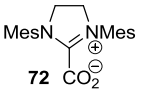
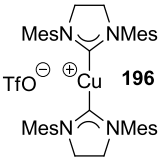
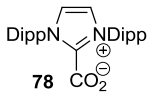
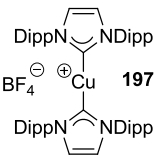


Figure 29. Possible coordinations of the halide counterion in complexes of the type $Cu(SIMes)_2X$.

[75] Arduengo, A.; Rasika Dias, H.; Calabrese, J. ; Davidson, F. *Organometallics*, **1993**, *12*, 3405-3409.

Table 3. Synthesis of bis-*N*-heterocyclic carbene copper complexes.

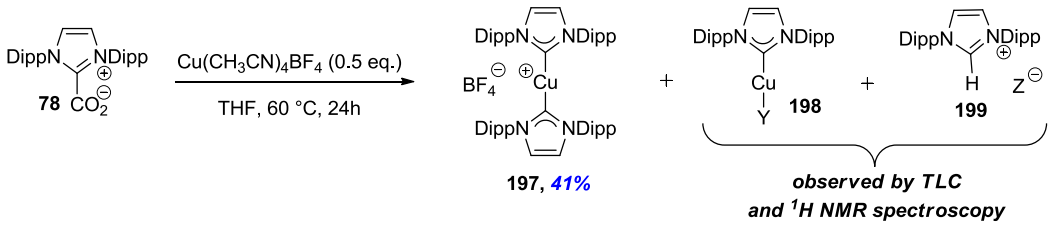


Entry	Carboxylate	Copper Source	Copper Complex	Yield (%)
1	 **76**	$Cu(CH_3CN)_4BF_4$	 **192**	91
2	 **72**	CuI	 **193**	77
3	 **72**	CuBr	 **194**	73
4	 **72**	CuCl	 **195**	59
5	 **72**	$Cu(CH_3CN)_4BF_4$	 **40**	83
6	 **72**	$Cu(CH_3CN)_4OTf$	 **196**	87
7	 **78**	$Cu(CH_3CN)_4BF_4$	 **197**	41

Mes = 2,4,6-trimethylphenyl, DIPP = 2,6-di-*iso*-propylphenyl.

Using the more sterically hindered DIPP-substituted carboxylate **78**, the corresponding copper complex **197** was synthesized in only 41% yield. The low yield is thought to be due to steric effects. Indeed, alongside the desired bis-NHC Cu(I) complex **197**, its mono-NHC Cu(I) analog was generated, as well as protonated

imidazolium **199** (Scheme **44**). It is assumed that the bulk conferred by the two *iso*propyl groups ortho to the aryl substituent of the NHC promotes the formation of the less hindered mono-NHC adduct **198**.



Scheme 44. Products obtained when reacting carboxylate **78** with $Cu(CH_3CN)_4BF_4$.

Although the method was efficient with aryl substituted NHC precursors, it was not successful with *N*-alkyl imidazol(in)ium carboxylates such as ICy·CO_2 **90**, IAd·CO_2 **177**, SIAd·CO_2 **182**, and I*t*Bu·CO_2 **79** in which cases a significant amount of protonated imidazol(in)ium salts was recovered after work-up of the reaction mixture (Figure **30**).

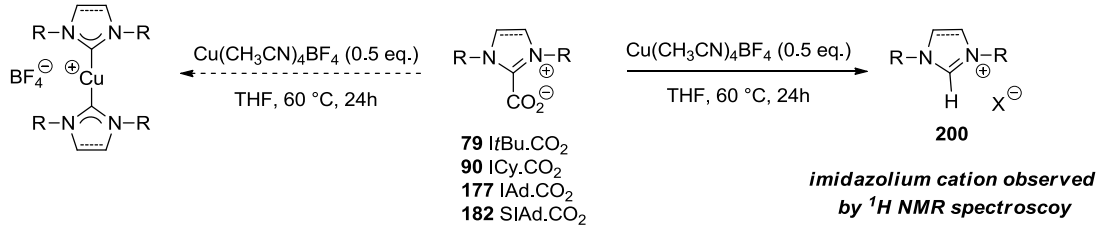
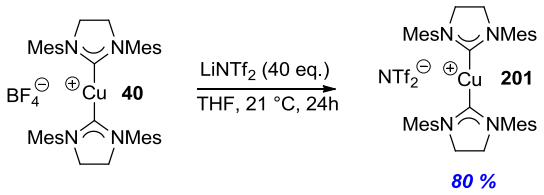


Figure 30. Attempted formation of $Cu(NHC)_2X$ from alkyl substituted carboxylates.

It is noteworthy that a counterion exchange from complex $Cu(SIMes)_2BF_4$ **40** is possible. When the latter is put in the presence of excess $LiNTf_2$ in THF, a counterion exchange occurs (Scheme **45**). The complex $Cu(SIMes)_2BF_4$ **40**, which is not soluble in THF, forms the complex $Cu(SIMes)_2NTf_2$ **201** which is soluble. A simple filtration allows for the removal of excess $LiNTf_2$ and unreacted starting material, and addition of pentane precipitated the target organometallic complex.



Scheme 45. Counterion exchange of $Cu(SIMes)_2BF_4$ **40** for a NTf_2^- anion.

One advantage of the current method is that the use of the carboxylate salts allows for the generation of copper complexes of the form $Cu(NHC)_2X$ under neutral conditions. In contrast, other methods for the formation of similar complexes use strong bases such as NaO*t*Bu or KO*t*Bu.[14,20,28,76] Previous reports in the literature show that using an excess of the alkoxide base can result in the coordination of *t*butoxide to the copper source, thus forming copper alkoxy species and other unwanted by-products (Figure **31**).[14,20] The decarboxylative generation of carbenes in the presence of a copper source allows for the generation of $Cu(NHC)_2X$ complexes under neutral conditions, avoiding the formation of such by-products.

A disadvantage of the "carboxylate method" is the failure to form alkyl substituted NHC complexes. However, using zwitterionic carboxylates as *N*-heterocyclic carbene transfer agents is particularly successful with mesityl substituted imidazol(in)ium-2-carboxylates, yielding bis-NHC Cu(I) complexes with diverse counterions in fair to excellent yields.

[76] Dubinina, G. G.; Ogikubo, J.; Vicic, D. A. *Organometallics* **2008**, *27*, 6233-6235.

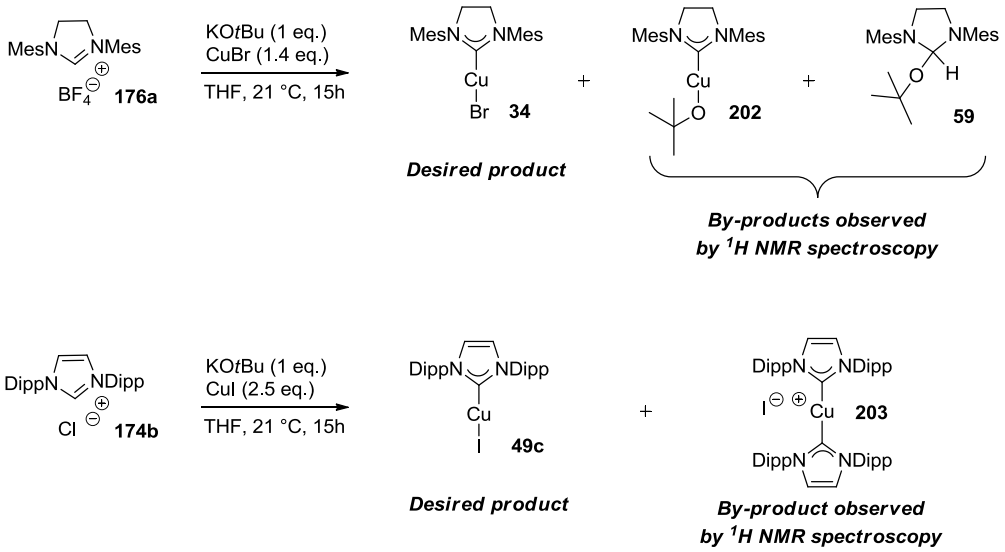


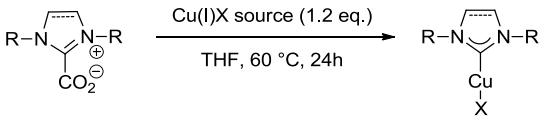
Figure 31. Examples of side reactions when using KO*t*Bu for the formation of NHC-Cu(I) complexes.[14,20]

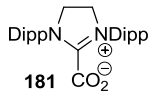
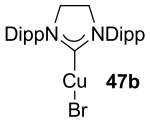
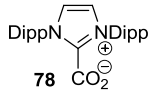
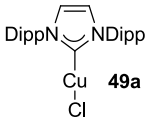
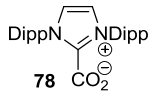
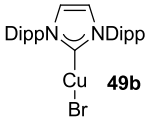
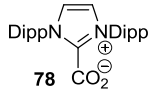
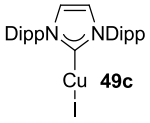
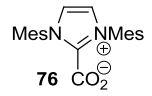
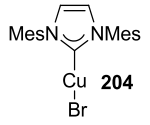
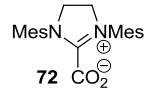
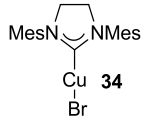
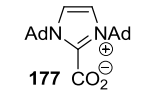
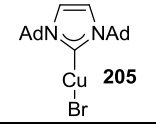
3.2 Synthesis of Mono-*N*-Heterocyclic Carbene Copper(I) Complexes *via* the Decarboxylation of Masked Carbene of the Type Imidazol(in)ium-2-Carboxylate

Mono-NHC Cu(I) complexes, have found extensive use in catalysis.[9] For example, they have been utilized as catalysts in the conjugate reduction of cyclic enones,[77] the generation of quaternary stereocenters from substitution reactions,[12] and Huisgen reactions with internal alkynes.[14] Due to their relevance in catalysis, a new synthetic route to access these complexes was sought. As shown in the previous section (Chapter 3, Section 3.1), the generation of carbenes *via* the decarboxylation of imidazol(in)ium-2-carboxylate precursors has been used for the synthesis of bis-NHC Cu(I) complexes. This method was adapted for the generation of mono-substituted NHC-Cu(I) complexes by using one equivalent of an imidazol(in)ium-2-carboxylate in THF in the presence of an excess of Cu(I) source (1.2 eq.) in a sealed tube under anhydrous conditions. At 60 °C, decarboxylation of the zwitterionic carboxylate generated the carbene *in situ*, which coordinated to the copper source. Excess metal was employed to favor the formation of the mono-NHC species. The generation of the mono-NHC complex over the bis-NHC complex was inferred by thin layer chromatography. Indeed, previous studies had shown that the bis-NHC Cu(I) complexes have a lower R_f value than their mono-coordinated analogs. Characterization by mass spectrometry may differentiate bis-NHC Cu(I) complexes, which show a major peak corresponding to the ionized structure $[Cu(NHC)_2]^+$, from mono-NHC Cu(I) complexes, which exhibit a major peak for the ionized structure $[Cu(NHC)XNa]^+$.

[77] Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett*. **2003**, *5*, 2417-2420.

Table 4. Synthesis of mono-*N*-heterocyclic carbene copper complexes.



Entry	Carboxylate	Copper Source	Copper Complex	Yield (%)
1	 **181**	CuBr	 **47b**	59
2	 **78**	CuCl	 **49a**	63
3	 **78**	CuBr	 **49b**	75
4	 **78**	CuI	 **49c**	57
5	 **76**	CuBr	 **204**	70
6	 **72**	CuBr	 **34**	N.A.
7	 **177**	CuBr	 **205**	45

Mes = 2,4,6-trimethylphenyl, DIPP = 2,6-di-*iso*-propylphenyl, Ad = adamantyl.
N.A. = Not applicable.

The decarboxylative synthesis of Cu(NHC)X complexes proved successful when using DIPP substituted precursors and the yields were consistent for diverse copper sources (Table **4**). When SIPR·CO_2 **181** was decarboxylated in the presence of CuBr, complex **47b** was formed in 59% yield. Its unsaturated analog **49b** was formed in a higher 75% yield when **78** was subjected to the identical reaction conditions. As previously explained, it is believed that unsaturated NHC precursors generate complexes in higher yield than saturated NHC precursors as they are less prone to by-

product formation due to the increased stability of their corresponding carbene (Figure **6**).[7] The DIPP substituted carboxylate **78** was also reacted with CuCl and CuI, generating **49a** and **49c** in 63% and 57% yield respectively. The mesityl substituted carboxylate **76** was employed for the formation of **204** and the desired complex was isolated in 70% yield. When the synthesis of **34** was attempted from the saturated SIMes·CO_2 **72**, a complex mixture of products was observed. Although the product was identified by mass spectrometry, purification was hampered by the numerous products.

Alkyl substituted carboxylate precursors **79**, **90** and **182** failed to afford the corresponding mono-NHC Cu(I) complexes. Decarboxylation was observed to generate the desired carbene; however, only the protonated imidazol(in)ium salts were recovered from the reaction mixture (Figure **32**). The sole exception was the unsaturated IAd·CO_2 **177** which formed the complex **205** in 45% yield (Table **4**, entry **7**).

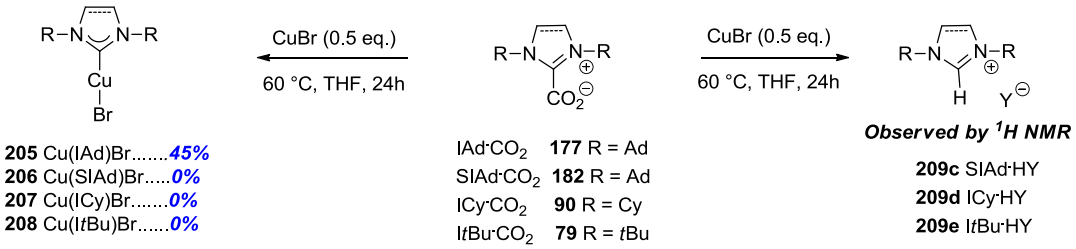


Figure 32. Attempted generation of complexes of the type Cu(NHC)X from alkyl substituted carboxylates **79**, **90**, **177** and **182**.

Chapter 4. Oxidative Coupling of 3-Methyl-2-Hydroxynaphthoate Catalyzed by *N*-Heterocyclic Carbene Copper(I) Complexes

2,2'-Binaphthol (BINOL) derivatives are useful ligands for asymmetric catalysis (Figure **33**).[41] Since their first use as ligands in the reduction of aromatic ketones and aldehydes in 1979,[78] they have been used in Michael-addition reactions,[79] olefin metathesis,[80] aldol reactions[81] and many other asymmetric transformations.

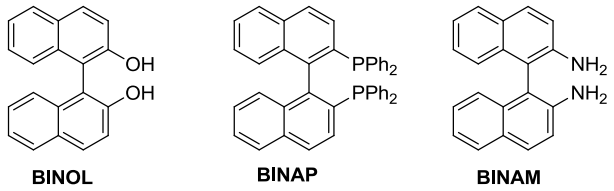


Figure 33. 2,2'-Binaphthol (BINOL) and commonly encountered BINOL derivatives.

Because of its privileged utility in organometallic catalysis, diverse ways have been explored to synthesize the BINOL motif. As discussed in length in the introduction (Chapter 1, Section 1.4), the most common synthetic route has been the oxidative coupling of 2-naphthols, achieved typically with Cu complexes[29,30,46,82,83] or oxovanadium complexes.[50,84] The generation of C_1-symmetric BINOLs remains a challenge which may be addressed by the heterocoupling of naphthol derivatives.[49d,53,55]

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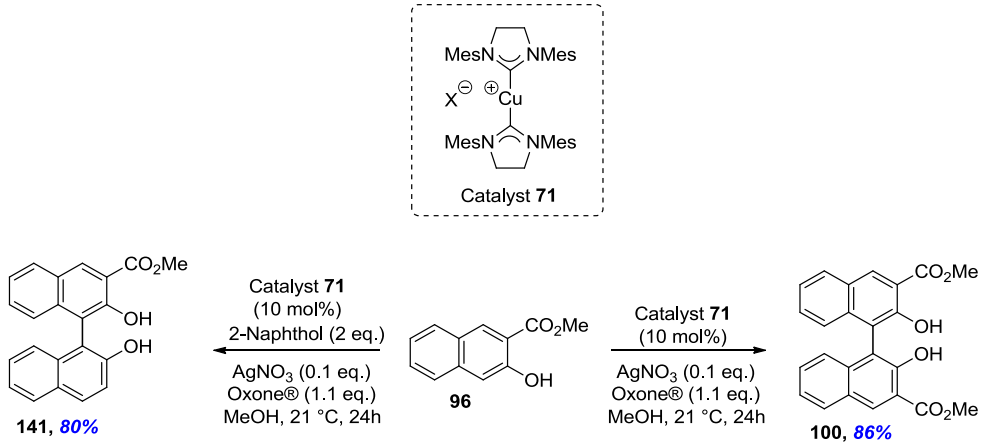
[78] Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129-3131.
[79] (a) Annamalai, V.; DiMauro, E. F.; Carroll, P. J.; Kozlowski, M. C. *J. Org. Chem*. **2003**, *68*, 1973–1981. (b) Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc*. **2004**, *126*, 7559–7570.
[80] (a) Zhu, S. S. ; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999,** *121,* 8251-8259. (b) Singh, R.; Czekelius, C.; Schrock, R. R.; Müller, P.; Hoveyda, A. H. *Organometallics* **2007,** *26,* 2528-2539.
[81] (a) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc*. **2003**, *125*, 2169-2178. (b) Schetter, B.; Ziemer, B.; Schnakenburg, G.; Mahrwald, R. *J. Org. Chem.* **2008**, *73*, 813-819. (c) Li, H.; Da, C.-S.; Xiao, Y.-H.; Li, X.; Su, Y.-N. *J. Org. Chem.* **2008**, *73*, 7398–7401.
[82] (a) Nasir, M. S.; Chen, B. I.; Karlin, K. D. *J. Am. Chem. Soc.* **1992***, 114,* 2482–2494. (b) Solomon, E. I.; Sundaram, U. M.; Machonkin, T. E.; *Chem. Rev*. **1996***, 96,* 2563–2606.
[83] Nakajima, M.; Kanayama, K.; Miyoshi, I.; Hashimoto, S. *Tetrahedron Lett.* **1995**, *36*, 9519-9520.
[84] Hwang, D.-R.; Chen, C.-P.; Uang, B.-J. *Chem. Commun.* **1999**,1207-1208.

In 2009, Collins *et al* developed a method for the heterocoupling of naphthol derivatives catalyzed by a cationic bis-NHC Cu(I) complex **71**.[32] In terms of homocoupling, **71** catalyzed the formation of BINOL derivative **100** in 86% yield (Scheme **46**). In addition, complex **71** catalyzed the selective heterocoupling of the electron poor ester **96** with various electron rich 2-naphthols in good yields. For example, naphthol ester **96** was selectively coupled with 2-naphthol to yield the C_1-symmetric BINOL **141** in 80% yield. The absence of homocoupling products in the reaction is in contrast to that observed for other amine-Cu complexes.



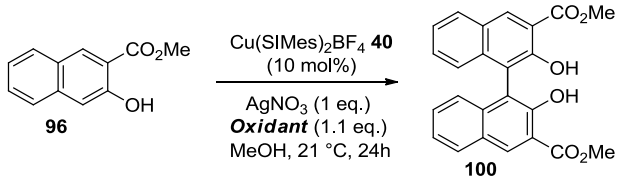
Scheme 46. Homo- and heterocoupling of naphthoate **96** catalyzed by the bis-NHC Cu complex **71**.

Complex **71** was ill-defined and had limited solubility which has hampered investigations to determine the nature of the X^- counterion. To further investigate the oxidative homo- and heterocoupling of naphthol derivatives, well-defined catalysts were targeted and various NHC-Cu catalysts were generated. The effects of the structure of the catalyst on the coupling reaction were studied by varying the number of NHC ligands coordinating to Cu, as well as the nature of the NHC ligand substituents and counterions. Optimization of the reaction was performed on the homocoupling of naphthoate **96**.

The optimization of the homocoupling began by exploring the reactivity of the complex $Cu(SIMes)_2BF_4$ **40**, a catalyst previously used in hydrosilylation by Nolan and co-workers, because the cationic structure was similar to catalyst **71** and possessed a defined BF_4^- counterion.[16b] Previous work by Dr Alain Grandbois showed that, when employing **40** as a catalyst, increasing the amount of $AgNO_3$ to 1 eq. resulted in improved yield of the desired BINOL ester **100**.[32]

The first objective was to identify the most suitable oxidant to oxidize the Cu(I) catalyst to a Cu(II) species. Cu(I) species are usually readily oxidized by air in the presence of H_2O to yield a Cu(II) species. The oxidation potential of the Cu^{2+}/Cu^+ couple (E° = -0.161V) compared to that of O_2/H_2O (E° = 1.229 V) illustrates the ease with which the process occurs.[85] For this reason, Cu(I) species are usually stored in a dessicator or a glovebox.

Table 5. Oxidant optimization for the oxidative coupling of **96**.



Entry	Oxidant	Yield (%)
1	60 PSi O_2	8
2	H_2O_2	12
3	Oxone®	33
4	$Na_2S_2O_8$	13

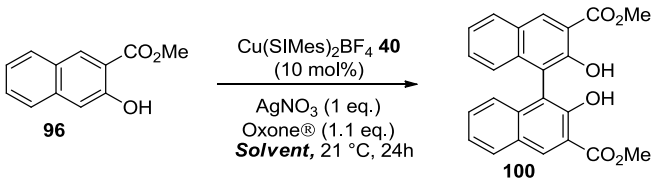
Investigations began using a high pressure of oxygen (60 PSi) which yielded 8% of the desired coupling product **100** (Table **5**). The low yield may reflect the difficult oxidation of **40**, due to the NHC bearing Cu(I) receiving strong sigma donation from the carbene to the metal center. Such stabilization of the low oxidation state renders the complex stable to water and air.[20a] To surmount such increased stability, stronger external oxidants were investigated for the generation of the Cu(II)

[85] Harris, D. C. *Quantitative Chemical Analysis*, 6th Ed.; Freeman: New York, **2003**; Appendix H, p25

species. Changing the oxidant to the more reactive H_2O_2 (30 mol% aqueous solution) did not give a significant improvement (12% yield). Employing potassium peroxymonosulfate (Oxone®) improved the yield to 33%. Considering the increase obtained with Oxone®, another oxidant of the "peroxysulfate" type was used; however, sodium peroxodisulfate ($Na_2S_2O_8$) only gave 13% of the desired **100**. Oxone® was thus chosen as oxidant for the coupling of naphthoate **96**.

Once the oxidant was optimized, it was necessary to determine which solvent was the most suitable for the coupling reaction. A screening of different solvents showed that alcohol containing solvents promoted a more efficient coupling reaction (Table **6**). Methanol, *iso*propanol and 1,1,1-trifluoroethanol all gave yields of about 30%, whereas solvents such as CH_2Cl_2, THF, DMF or CH_3CN resulted in less than 10% yield of product. MeOH was subsequently used, because it gave the best yield of BINOL **100**. Success obtained with alcoholic solvents may be due to the increased solubility of Oxone® in the more polar medium. Employing dioxane as a solvent (Entry **8**) resulted in a yield similar to that of methanol (33% yield); however, the lower boiling point of methanol made it easier to handle as subsequent treatment of the reaction involves evaporation of the solvent.

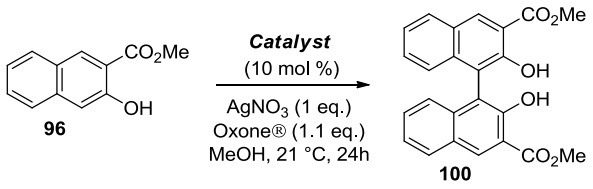
Table 6. Solvent optimization for the oxidative coupling of **96**.



Entry	Solvent	Yield (%)
1	MeOH	33
2	*n*BuOH	11
3	*i*PrOH	29
4	*n*PrOH	4
5	TFE	32
6	CH_2Cl_2	7
7	THF	9
8	Dioxane	33
9	DMF	5
10	CH_3CN	6

Catalyst screening with complexes of the type $Cu(NHC)_2X$ was then performed to investigate the effect of NHC structure (Table **7**). Relative to complex **71**, complexes **40**, **193** and **194** exhibited significantly inferior activity (≥33%). When changing the counterion of the catalyst to NTf_2^-, **201** showed no conversion of the starting material. These entries show that changing the counterion of the catalyst has a strong impact on its activity. A possible explanation could be that the counterion affects the electrophilicity of the copper center, and hence its affinity to the substrate. When the unsaturated $Cu(IMes)_2BF_4$ **192** is used, 13% of **100** is obtained and when DIPP substituted **197** was employed as a catalyst, no coupling product was observed. The bulk conferred by the four DIPP ligands might have blocked the approach of the substrate, inhibiting product formation. $Cu(SIMes)_2BF_4$ **40** thus seems to be the most suitable well-defined bis-NHC catalyst for the oxidative coupling of 3-methyl-2-hydroxynaphthoate **96**.

Table 7. Catalyst optimization for the oxidative coupling of **96**.



Entry	Catalyst	Yield (%)
1	$Cu(SIMes)_2X$ **71**	86[a,b]
2	$Cu(SIMes)_2BF_4$ **40**	33
3	$Cu(SIMes)_2I$ **193**	21
4	$Cu(SIMes)_2Br$ **194**	24
5	$Cu(SIMes)_2NTf_2$ **201**	0
6	$Cu(IMes)_2BF_4$ **192**	13
7	$Cu(IPR)_2BF_4$ **197**	0

[a] Reaction done with 10% $AgNO_3$ [b]Yield obtained by Dr Alain Grandbois

In 2008, Vicic and co-workers synthesized the trifluoromethyl NHC-Cu complex **210**.[76] By performing a ^{19}F NMR analysis, they demonstrated that the mono-NHC Cu complex **210** existed in equilibrium with the bis-NHC Cu complex **211**, bearing a cuprate counterion (Figure **34**). Considering that the catalyst **71** was synthesized from a chloroform-NHC adduct (Scheme **18**), we wondered if the counterion of the cationic bis-NHC Cu(I) complex **71** was not in fact a bis(trichloromethyl) cuprate anion. If this was the case, the bis-NHC complex could be in equilibrium with the trichloromethyl mono-NHC Cu complex **213**. Supposing an existing equilibrium between bis-NHC **212** and mono-NHC **213**, it was hypothesized that a mono-NHC copper species could be the active catalyst in the oxidative coupling of 3-methyl-2-hydroxynaphthoate **96**.

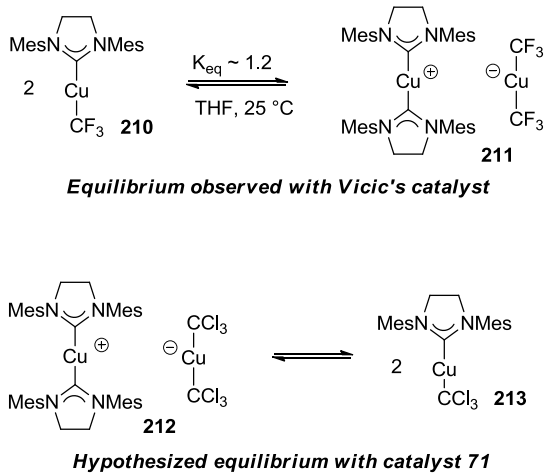


Figure 34. Equilibrium between a haloformyl mono-NHC Cu(I) complex and a bis-NHC Cu(I) complex bearing a bis(haloformyl)cuprate counterion.

To verify such a hypothesis, the role of additives in the coupling reaction was investigated. Previous work by Dr. Alain Grandbois had demonstrated that the presence of an additive could significantly increase the yield of the reaction. Different additives were surveyed (LiCl, $AgNO_3$, $AgSbF_6$ and K_2CO_3) and $AgNO_3$ proved to be the most efficient using catalyst **71**. Considering the improved yield obtained with $AgNO_3$, it was theorized that transmetalation of one NHC ligand from the $Cu(NHC)_2X$ complex to the silver metal may generate a mono-NHC Cu(I) complex, which may be the active species in the catalytic cycle (Figure **35**).

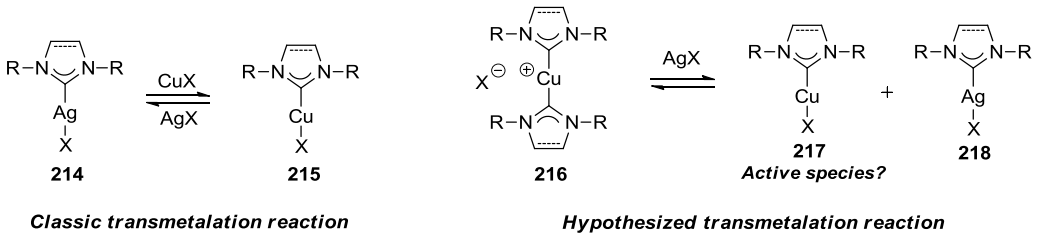
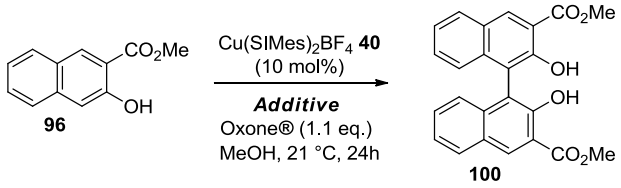


Figure 35. Hypothesis concerning the role of $AgNO_3$ in the oxidative coupling of **96**.

To investigate this hypothesis, the additive of the reaction was changed from $AgNO_3$ to $NaNO_3$ (Table **8**). Using $NaNO_3$ showed reactivity (23% yield) although with a lower yield than with silver nitrate (33% yield) demonstrating that the silver cation may have a role albeit unclear; however, no evidence was obtained to support

a mono-NHC Cu(I) complex during the reaction. To investigate whether an additional Cu source would promote the formation of such a mono-NHC Cu(I) species, different copper sources were used as additives for the coupling reaction, in the presence of $AgNO_3$. When using 5 mol% of CuCl (Entry **4**) and $Cu(CH_3CN)_4BF_4$ (Entry **5**) as additives, **100** was formed in respectively 35% and 38% yields, which does not represent a significant difference from entry **2** (33% yield) in the absence of copper additive. Using Cu_2O as additive (Entry **6**) seemed to inhibit the reaction, yielding 14% of **100**.

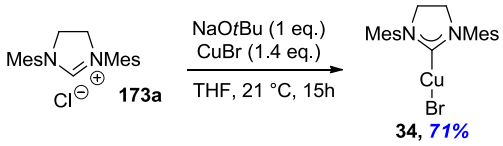
Table 8. Additive optimization for the oxidative coupling of **96**.



Entry	Additive	Yield (%)
1	None	0
2	$AgNO_3$ (1eq.)	33
3	$NaNO_3$ (1eq.)	23
4	CuCl (0.05 eq.) $AgNO_3$ (1eq.)	35
5	$Cu(CH_3CN)_4BF_4$ (0.05 eq.) $AgNO_3$ (1eq.)	38
6	Cu_2O (0.05 eq.) $AgNO_3$ (1eq.)	14

After attempting to promote the formation of a mono-NHC Cu(I) species *in situ*, we investigated the activity of such a complex in a more direct manner, and employed Cu(SIMes)Br **34**, which has an analogous structure to $Cu(SIMes)_2BF_4$ **40**, in the oxidative coupling of **96**. Although mono-NHC catalyst **34** could not be generated by decarboxylation of precursor **72**, the base method developed by Nolan and co-workers was successfully employed (Scheme **47**).[14] 1,3-Bis(2,4,6-trimethylphenyl)imidazolinium tetrafluoroborate **173a** was deprotonated with

NaO*t*Bu to generate a carbene, which coordinated to CuBr and formed the desired complex **34** in 71% yield.

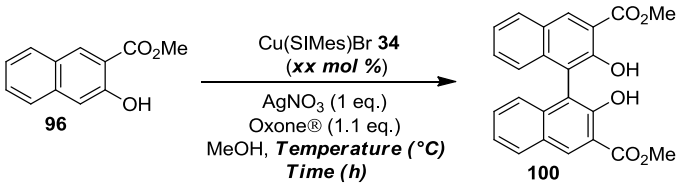


Scheme 47. Synthesis of Cu(SIMes)Br **34** *via* the base method.

When naphthoate **96** was reacted with 10 mol% of Cu(SIMes)Br **34**, $AgNO_3$ (1 eq.) and Oxone® (1.1 eq.) in MeOH at room temperature, the coupled product **100** was formed in 13% yield (Table **9**), which is 20% less than the yield observed when the bis-NHC **40** was used (Table **7**, Entry **2**). The lower yield suggests that a mesityl substituted mono-NHC Cu(I) species may not be more active than its mesityl substituted bis-NHC Cu(I) analog.

To optimize the conditions of the oxidative coupling reaction, the concentration was changed from 0.04M to 0.1M, assuming an increase in concentration would favor a bimolecular reaction (Table **9**). The yield went from 13% at 0.04M (Table **9**, Entry **1**) to 21% at 0.1M (Table **9**, Entry **2**). Reducing the catalyst loading to 5 mol% or 1 mol% caused a drop in yield to 17% and 4% respectively. Entries **2**, **3** and **4** were repeated with a longer reaction time of 48h (entries **5**, **6** and **7**) and the yields reflected no significant difference in the product formation with extended reaction time. Increased yield were observed upon varying the reaction temperature. For example, heating to 70 °C for 24h at 0.1M gave BINOL derivative **100** in 58% yield. Due to the low scale of the reaction (0.1316 mmol of substrate in 1.3 mL of MeOH), entry **8** was performed in a sealed tube to avoid evaporation of the solvent.

Table 9. Optimization of the oxidative coupling of **96** with Cu(SIMes)Br **34**.

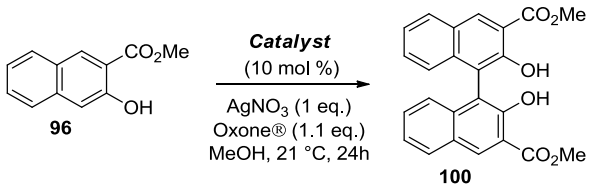


Entry	Concentration (M)	Catalyst Loading (mol%)	Time (h)	Temperature (°C)	Yield (%)
1	0.04	10	24	21	13
2	0.1	10	24	21	21
3	0.1	5	24	21	17
4	0.1	1	24	21	4
5	0.1	10	48	21	30
6	0.1	5	48	21	14
7	0.1	1	48	21	3
8	0.1	10	24	70[a]	58

[a]The reaction was ran in a sealed tube

Once the reaction conditions were optimized (employing 10 mol% of catalyst, 1 eq. of $AgNO_3$ and 1.1 eq. of Oxone® in MeOH at 70°C for 24h), complexes of the type Cu(NHC)X were screened (Table **10**), initially at room temperature for comparison with the bis-NHC catalyst profile (Table **7**). Employing the sterically hindered complex Cu(IPR)Br **49b** in the oxidative coupling of naphthoate **96** gave BINOL **100** in 39% yield. Changing the anionic ligand to chloride and iodide decreased the yield to 25% and 12% respectively, suggesting the importance of counterion for catalyst activity. The saturated Cu(SIPR)Br **47b** performed poorly in the formation of **100**, giving 4% yield. Similarly, adamantyl substituted catalysts **205** and **206** gave less than 10% yield of product, likely due to the steric hindrance of the metal center by the bulky adamantyl substituents.

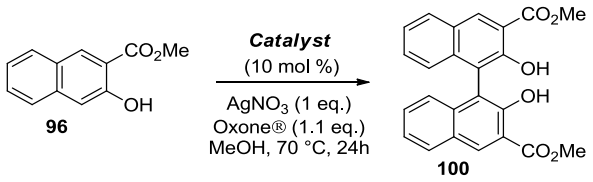
Table 10. Catalyst optimization for the oxidative coupling of **96**.



Entry	Catalyst	Yield (%)
1	Cu(IPR)Br **49b**	39
2	Cu(IPR)Cl **49a**	25
3	Cu(IPR)I **49c**	12
4	Cu(SIPR)Br **47b**	4
5	Cu(SIMes)Br **34**	13
6	Cu(SIAd)Br **206**	<10
7	Cu(IAd)Br **205**	8

Employing the optimized conditions, *i.e.* 10 mol% of catalyst, 1 eq. of $AgNO_3$ and 1.1 eq. of Oxone® in MeOH at 70°C for 24h, the best yielding catalyst, Cu(IPR)Br **49b** was compared to $Cu(SIMes)_2BF_4$ **40** and CuBr (Table **11**). The effect of bearing two, one or no NHC ligand was thus studied on the efficiency of the catalysis of the oxidative coupling of **96**. Entry **1** shows that CuBr, bearing no NHC ligand, yields 39% of the desired **100** under the optimized conditions. The bis-NHC complex **40** exhibited a greater activity than CuBr, providing 57% yield and demonstrating the utility of the NHC ligand. When mono-NHC complex Cu(IPR)Br **49b** was subjected to the optimized reaction conditions, the product **100** was obtained in 78% yield. The increase of activity of Cu(IPR)Br **49b** (39% yield at RT) relative to $Cu(IPR)_2BF_4$ **197** (no conversion at RT) may be due to the decrease in steric bulk around the metal center. In the case of mesityl substituted complexes, the inverse trend was observed: mono-NHC Cu(SIMes)Br **34** was less active than bis-NHC analog $Cu(SIMes)_2BF_4$ **40**.

Table 11. Catalyst optimization for the oxidative coupling of **96**.



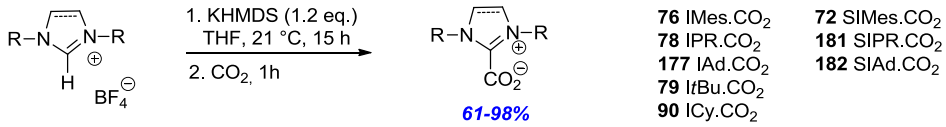
Entry	Concentration (M)	Catalyst	Yield (%)[a]
1	0.1	CuBr	39
2	0.1	$Cu(SIMes)_2BF_4$ **40**	57
3	0.1	Cu(IPR)Br **49b**	78

[a]The reaction was ran in a sealed tube

In conclusion, the oxidative homocoupling of naphthoate **96** was investigated with a variety of well-defined NHC-Cu catalysts. The counterion and the *N*-substituents of the NHC ligand strongly affected catalyst activity in the coupling reaction. For example, catalysts such as $Cu(IPR)_2BF_4$ **197**, Cu(SIAd)Br **206** or Cu(IAd)Br **205** bearing sterically demanding substituents seemed to hinder the catalytic process and gave lower yields in the coupling of **96**. The mono-NHC Cu species was hypothesized to be more active than the bis-NHC Cu counterparts; however, $Cu(SIMes)_2Br$ **40** catalyzed the formation of **100** (24% yield at 21 °C) better than the analogous Cu(SIMes)Br **34** (13% yield) under the same reaction conditions. Finally, Cu(IPR)Br **49b** was found to be the most suitable catalyst for the oxidative coupling of **96** under optimized conditions (10 mol% of catalyst, 1 eq. of $AgNO_3$ and 1.1 eq. of Oxone® in MeOH at 70°C for 24h), yielding **100** in 78% yield.

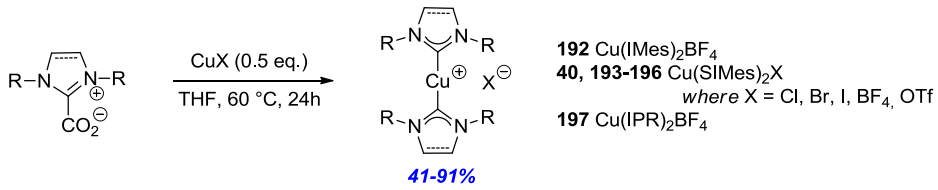
Chapter 5. Conclusion and Future Work

A variety of imidazol(in)ium-2-carboxylates has been prepared by the deprotonation of an imidazol(in)ium tetrafluoroborate salt and subsequent trapping with CO_2 gas. The masked carbenes were synthesized with *N*-alkyl and *N*-aryl substituents with a saturated or unsaturated heterocyclic backbone in yields ranging from 61 to 98% (Scheme **48**).



Scheme 48. Formation of zwitterionic masked carbenes.

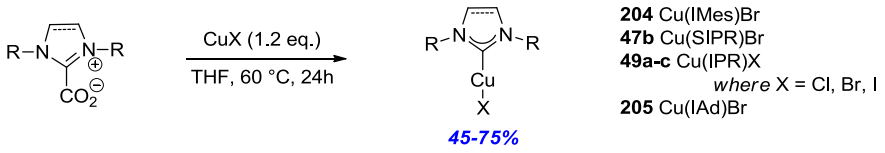
Imidazol(in)ium-2-carboxylates were reacted with 0.5 equivalent of a copper source under thermolytic conditions to afford, the bis-NHC Cu complexes **40** and **192-197** in 41-91% yield (Scheme **49**). Although unsuccessful with alkyl substituted zwitterionic precursors, the method could be employed for the formation of DIPP and Mes substituted complexes bearing various counterions.



Scheme 49. Synthesis of bis-NHC Cu complexes *via* the decarboxylative generation of carbenes.

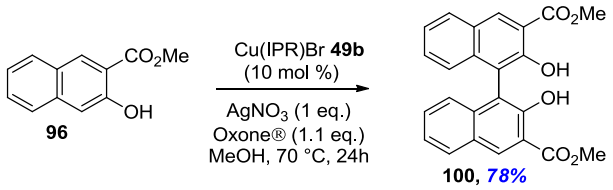
The decarboxylative generation of carbenes could also be employed to form mono-NHC Cu complexes bearing aryl substituted NHC ligands as well as the alkyl substituted IAd ligand. Reacting imidazol(in)ium-2-carboxylates with 1.2 equivalents

of Cu source afforded mono-NHC Cu complexes with various halide counterions in 45% to 75% yields (Scheme **50**).



Scheme 50. Synthesis of mono-NHC Cu complexes *via* the decarboxylative generation of carbenes.

The various NHC-Cu complexes were evaluated in the oxidative homocoupling of naphthoate **96**. It was found that changing the counterion of the catalyst greatly affected reactivity in the coupling reaction. When NHC-Cu complexes bearing sterically demanding NHC ligands were employed as catalysts, the yield of the BINOL derivative **100** was significantly diminished. Upon optimization of the reaction conditions, it was found that the oxidative homocoupling of **96** was most efficient with the mono-NHC Cu catalyst Cu(IPR)Br **49b** at 70 °C (Scheme **51**). Under these reaction conditions, binaphthoate **100** was formed in 78% yield. This result is similar to that obtained with the ill-defined bis-NHC Cu catalyst **71** (86% yield of **100**) and the diazadecalin-Cu complex **105**·CuI (85% yield of **100**).



Scheme 51. Oxidative homocoupling of naphthoate **96** with mono-NHC Cu catalyst **49b**.

Future work may focus on the application of the NHC-Cu complex **49b** in the heterocoupling of various naphthol derivatives. Given the tunability of NHCs,

developing a chiral NHC-Cu catalyst for the asymmetric oxidative heterocoupling of naphthols may also be a target (Figure **36**).

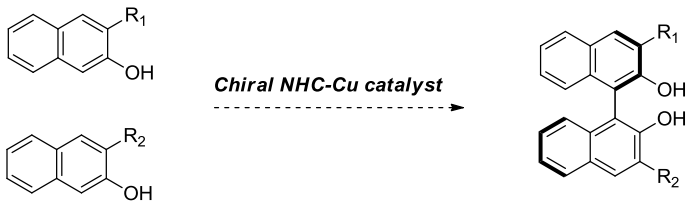


Figure 36. Envisaged heterocoupling of naphthol derivatives catalyzed by a chiral NHC-Cu catalyst.

Chapter 6. Experimental Section

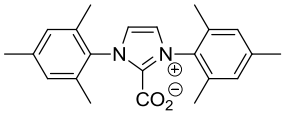
General:

All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 ^{o}C or had been flame dried and cooled under a stream of argon or nitrogen.[86] All chemical products were obtained from Sigma-Aldrich Chemical Company or Strem Chemicals and were reagent quality. These products were used without further purification. Technical solvents were obtained from VWR International Co. Anhydrous solvents (Et_2O and THF) were dried and deoxygenated using a GlassContour system (Irvine, CA). Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by W. C. Still[62] and using silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on aluminum-backed silica gel 60 coated with a fluorescence indicator (Silicycle Chemical division, 0.25 mm, F_{254}.). Visualization of TLC plate was performed by UV (254 nm) or $KMnO_4$ stain. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported compounds were homogeneous by thin layer chromatography (TLC) and by ^{1}H NMR spectroscopy. NMR spectra were taken in deuterated $CDCl_3$ or *d6*-acetone using Bruker AV-400, AV-500 and AV-700 instruments unless otherwise noted. Signals due to the solvent served as the internal standard. The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet), br (broad); the list of coupling constants (*J*) corresponds to the order of the multiplicity assignment. High resolution mass spectroscopy (HRMS) was done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université

[86] Shriver, D. F.; Drezdon M. A. in *The Manipulation of Air-Sensitive Compounds*; Wiley-VCH: New York, 1986.

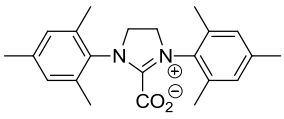
de Montréal from an Agilent LC-MSD TOF system using ESI mode of ionization. Infrared spectra were recorded on a Bruker Alpha-P FT-IR spectrometer. The melting point of compound **100** was recorded on a Laboratory Devices USA Mel-Temp II apparatus.

General Procedure for the Synthesis of Imidazol(in)ium-2-Carboxylates



76

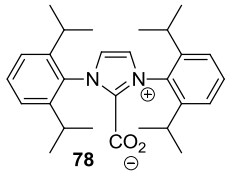
1,3-Bis(2,4,6-trimethylphenyl)imidazolium-2-carboxylate (76): A flame-dried 50 mL conical vial was charged with imidazolium salt **175a** (784 mg, 2 mmol) and KHMDS (480 mg, 2.4 mmol). The flask was purged with nitrogen before the addition of anhydrous THF (20 mL). The mixture was stirred at ambient temperature overnight (approximately 15 h) and then stirring was stopped and the heterogeneous mixture was allowed to settle (1-2 h). The clear supernatant was then cannulated to a new dry flask and carbon dioxide was bubbled through this solution for 1 h. The product precipitated from solution and the mixture was then filtered. The collected solid was washed with ether (Et_2O) and dried under vacuum. The product was obtained as a white solid (683 mg, 98%) whose ^{1}H NMR and IR spectra were consistent with published data.[30a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 2H), 6.99 (s, 4H), 2.32 (s, 6H), 2.21 (s, 12H). IR (neat) 3159, 2914, 2854, 1674 (CO_2), 1489, 1296, 1077 cm^{-1}.



72

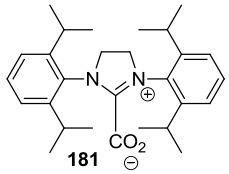
1,3-Bis(2,4,6-trimethylphenyl)imidazolinium-2-carboxylate (72): The title compound **72** was prepared according to the representative procedure described above (p97) from imidazolinium tetrafluoroborate salt **176a** (788 mg, 2 mmol). The product was obtained as a white solid (616 mg, 88%) whose ^{1}H NMR and IR spectra

were consistent with published data.[60a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 2H), 4.20 (s, 4H), 2.47 (s, 12H), 2.27 (s, 6H). IR (neat) 2973, 2915, 2858, 1675 (CO_2), 1608, 1547, 1481, 1293, 1264 cm^{-1}.



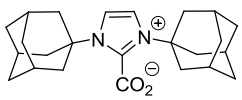
78

1,3-Bis(2,6-di-*iso*-propylphenyl)imidazolium-2-carboxylate (78): The title compound **78** was prepared according to the representative procedure described above (p97) from imidazolium tetrafluoroborate salt **175b** (953 mg, 2 mmol). The product was obtained as a white solid (761 mg, 88%) whose ^{1}H NMR and IR spectra were consistent with published data.[60a] ^{1}H NMR (400 MHz, $CDCl_3$) 7.47 (t, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 4H), 7.08 (s, 2H), 2.61 (sept, *J* = 6.7 Hz, 4H), 1.34 (d, *J* = 6.8 Hz, 12H), 1.21 (d, *J* = 6.8 Hz, 12H). IR (neat) 3151, 3073, 2960, 2869, 1671 (CO_2), 1489, 1321, 1305 cm^{-1}.



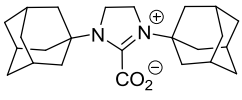
181

1,3-Bis(2,6-di-*iso*-propylphenyl)imidazolinium-2-carboxylate (181): The title compound **181** was prepared according to the representative procedure described above (p97) from imidazolinium tetrafluoroborate salt **176a** (956 mg, 2 mmol). The product was obtained as a white solid (530 mg, 61%) whose ^{1}H NMR and IR spectra were consistent with published data.[30a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, *J* = 7.9 Hz, 2H), 7.21 (d, *J* = 7.7 Hz, 4H), 4.20 (s, 4H), 3.19 (sept, *J* = 6.7 Hz, 4H), 1.44 (d, *J* = 6.8 Hz, 12H), 1.33 (d, *J* = 6.9 Hz, 12H). IR (neat) 3074, 2961, 2930, 2867, 1675 (CO_2), 1546, 1464, 1276 cm^{-1}.



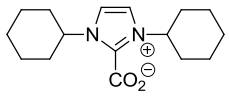
177

1,3-Diadamantylimidazolium-2-carboxylate (177): The title compound **177** was prepared according to the representative procedure described above (p97) from imidazolium tetrafluoroborate salt **175c** (848 mg, 2 mmol). The product was isolated as a white solid (660 mg, 87%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.39 (s, 2H), 2.30-2.33 (br m, 6H), 2.27-2.30 (br m, 12H), 1.79-1.84 (br m, 6H), 1.74-1.79 (br m, 6H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 133.5, 124.8, 117.7, 61.1, 42.8, 35.3, 29.5. HRMS (ESI) m/z calculated for $[C_{24}H_{33}N_2O_2]^+$, 381.2536, found 381.2539. IR (neat) 3161, 2908, 2853, 1620 (CO_2), 1542, 1454, 1374, 1156 cm^{-1}.



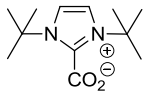
182

1,3-Diadamantylimidazolinium-2-carboxylate (182): The title compound **182** was prepared according to the representative procedure described above (p97) from imidazolinium tetrafluoroborate salt **176c** (852 mg, 2 mmol). The solid isolated was dissolved in dichloromethane and filtered. A small amount of pentane was added to the filtrate and the imidazolinium salt that precipitated was filtered. More pentane was then added to the filtrate to yield a white solid that was isolated by filtration and dried under vacuum (683 mg, 89%). Compound **182** is very difficult to separate from the corresponding imidazolinium and traces of the starting material can be seen in both the ^{1}H and ^{13}C NMR spectra. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (s, 4H), 2.20-2.23 (br m, 6H), 2.00-2.07 (br m, 12H), 1.70-1.78 (br m, 12H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 161.5, 151.8, 57.4, 43.5, 40.7, 35.6, 29.2. IR (neat) 3328, 2034, 1661 (CO_2), 1427, 1292 cm^{-1}.



90

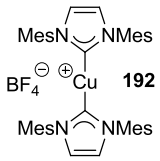
1,3-Dicyclohexylimidazolium-2-carboxylate (90): The title compound **90** was prepared according to the representative procedure described above (p97) from imidazolium tetrafluoroborate salt **175d** (640 mg, 2 mmol). The product was obtained as a white solid (431 mg, 78%) whose ^{1}H NMR and IR spectra were consistent with published data.[30a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 2H), 5.15-5.04 (br m, 2H), 2.18-2.25 (br m, 4H), 1.84-1.93 (br m, 4H), 1.71-1.80 (m, 4H), 1.46-1.55 (br m, 6H), 1.12-1.30 (br m, 2H). IR (neat) 3150, 3090, 2935, 2868, 1659 (CO_2), 1406, 1316 cm^{-1}.



79

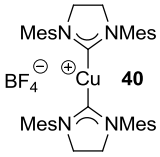
1,3-Di-*tert*-butylmidazolium-2-carboxylate (79): The title compound **79** was prepared according to the representative procedure described above (p97) from imidazolium tetrafluoroborate salt **175e** (536 mg, 2 mmol). The product was obtained as a white solid (350 mg, 78%) whose ^{1}H NMR and IR spectra was consistent with published data.[64] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 2H), 1.75 (s, 18H). IR (neat) 3128, 3061, 2975, 2831, 1669 (CO_2), 1547, 1438, 1376, 1274 cm^{-1}.

General Procedure for the Synthesis of Bis-*N*-Heterocyclic Carbene Copper(I) Complexes



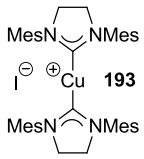
192

Bis[1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene]copper(I) tetrafluoroborate (192): A flame-dried 15 mL sealed tube was charged with NHC carboxylate **76** (174 mg, 0.5 mmol) and $Cu(MeCN)_4BF_4$ (79 mg, 0.25 mmol). The tube was purged with nitrogen before addition of dry THF (12 mL). The reaction vessel was sealed with a screw cap and placed in an oil bath at 60 °C. After stirring for 24h, the mixture was brought back to ambient temperature. The solid formed was isolated by filtration and washed with THF until a white solid was obtained. The solid was subsequently washed with ether and dried under vacuum (173 mg, 91%). The ^{1}H NMR spectrum of **192** was consistent with published data.[20a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 4H), 6.90 (s, 8H), 2.43 (s, 12H), 1.68 (s, 24H). HRMS (ESI) m/z calculated for $[C_{42}H_{48}CuN_4]^+$, 671.3170, found 675.3142.

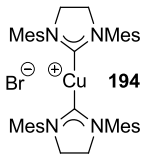


40

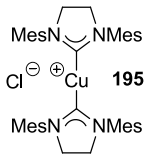
Bis[1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene]copper(I) tetrafluoroborate (40): The title compound **40** was prepared according to the representative procedure described above (p101) from imidazolinium carboxylate **72** (175 mg, 0.5 mmol) and $Cu(MeCN)_4BF_4$ (79 mg, 0.25 mmol). The solid formed was isolated by filtration and washed with THF until a white solid was obtained. The solid was subsequently washed with ether and dried under vacuum (159 mg, 83%). The ^{1}H NMR spectrum of **40** was consistent with published data.[20a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 8H), 3.85 (s, 8H), 2.38 (s, 12H), 1.83 (s, 24H). HRMS (ESI) m/z calculated for $[C_{42}H_{52}CuN_4]^+$, 675.3483, found 675.3454.



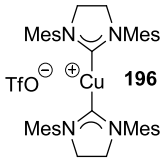
Bis[1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene]copper(I) iodide (193): The title compound **193** was prepared according to the representative procedure described above (p101) from imidazolinium carboxylate **72** (175 mg, 0.5 mmol) and CuI (48 mg, 0.25 mmol). The solid formed was isolated by filtration and washed with THF until a white solid was obtained. The solid was subsequently washed with ether and dried under vacuum (155 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 8H), 3.89 (s, 8H), 2.37 (s, 12H), 1.83 (s, 24H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 139.4, 136.3, 135.2, 130.4, 52.2, 22.0, 18.6. HRMS (ESI) m/z calculated for $[C_{42}H_{52}CuN_4]^+$, 675.3483, found 675.3480.



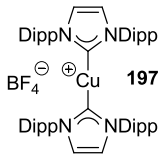
Bis[1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene]copper(I) bromide (194): The title compound **194** was prepared according to the representative procedure described above (p101) from imidazolinium carboxylate **72** (175 mg, 0.5 mmol) and CuBr (36 mg, 0.25 mmol). The solid formed was isolated by filtration and washed with THF until a white solid was obtained. The solid was subsequently washed with ether and dried under vacuum (138 mg, 73 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 8H), 3.85 (s, 8H), 2.37 (s, 12H), 1.82 (s, 24H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 138.1, 135.1, 134.1, 129.0, 50.7, 20.7, 16.9. HRMS (ESI) m/z calculated for $[C_{42}H_{52}CuN_4]^+$, 675.3483, found 675.3488.



Bis[1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene]copper(I) chloride (195): The title compound **195** was prepared according to the representative procedure described above (p101) from imidazolium carboxylate **72** (175 mg, 0.5 mmol) and CuCl (25 mg, 0.25 mmol). The solid formed was isolated by filtration and washed with THF until a white solid was obtained. The solid was subsequently washed with ether and dried under vacuum (105 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 8H), 3.86 (s, 8H), 2.37 (s, 12H), 1.82 (s, 24H). ^{13}C NMR (100 MHz, *d6*-acetone) δ 201.8, 139.2, 136.6, 135.7, 130.2, 51.6, 21.1, 17.5. HRMS (ESI) m/z calculated for $[C_{42}H_{52}CuN_4]^+$, 675.3483, found 675.3483.

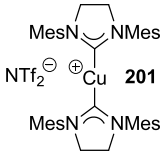


Bis[1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene]copper(I) triflate (196): The title compound **196** was prepared according to the representative procedure described above (p101) from imidazolinium carboxylate **72** (175 mg, 0.5 mmol) and $Cu(MeCN)_4OTf$ (94 mg, 0.25 mmol). The solid formed was isolated by filtration and washed with THF until a white solid was obtained. The solid was subsequently washed with ether and dried under vacuum (180 mg, 87%). The ^{1}H and ^{19}F NMR spectra of **196** were consistent with published data.[75] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 8H), 3.84 (s, 8H), 2.37 (s, 12H), 1.82 (s, 24H). ^{19}F NMR (300 MHz, $CDCl_3$) δ -78.15 (s, 3F). HRMS (ESI) m/z calculated for $[C_{42}H_{52}CuN_4]^+$, 675.3483, found 675.3483.



Bis[1,3-bis(2,6-di-*iso*-propylphenyl)imidazol-2-ylidene]copper(I) tetrafluoroborate (197): The title compound **197** was prepared according to the representative procedure described above (p101) from imidazolinium carboxylate **78** (216 mg, 0.5 mmol) and $Cu(MeCN)_4BF_4$ (79 mg, 0.25 mmol). The reaction mixture was filtered and the filtrate was purified by flash column chromatography on silica gel (CH_2Cl_2 : MeOH, 9:1) to afford **197** as a white solid (95 mg, 41%) whose ^1H NMR was consistent with published data.[87] ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (t, *J* = 7.9 Hz, 4H), 7.31 (d, *J* = 7.6 Hz, 8H), 7.13 (s, 4H), 2.57 (sept, *J* = 6.9 Hz, 8H), 1.31 (d, *J* = 6.8 Hz, 24H), 1.23 (d, *J*= 7.0 Hz, 24H); HRMS (ESI) m/z calculated for $[C_{54}H_{72}CuN_4]^+$, 839.5048, found 839.5022.

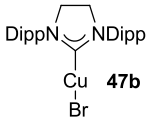
Synthesis of $Cu(SIMes)_2NTf_2$



Bis[1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene]copper(I) bis(trifluoromethane)sulfonimide (201): A round bottom flask was charged with $Cu(SIMes)_2BF_4$ **40** (176 mg, 0.23 mmol), $LiNTf_2$ (2.65 g, 9.22 mmol) and THF (6 mL). After stirring for 24 h at room temperature, the reaction mixture was filtered and pentane was added to the filtrate. The white crystals were isolated by filtration and dried under vacuum (178 mg, 80%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 8H), 3.81 (s, 8H), 2.38 (s, 12H), 1.82 (s, 24H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 138.3, 135.1, 133.9, 129.1, 50.6, 20.7, 16.9. ^{19}F NMR (300 MHz, $CDCl_3$) δ -78.84 (s, 6F). HRMS (ESI) m/z calculated for $[C_{42}H_{52}CuN_4]^+$, 675.3483, found 675.3484.

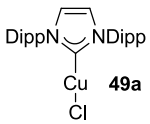
[87] Diez-Gonzalez, S.; Scott, N.; Nolan, S. *Organometallics* **2006**, *25*, 2355-2358.

General Procedure for the Synthesis of Mono-*N*-Heterocyclic Carbene Copper(I) Complexes



47b

[1,3-bis(2,6-di-*iso*-propylphenyl)imidazolin-2-ylidene]copper(I) bromide (47b): A flame-dried 15 mL sealed tube was charged with imidazolinium carboxylate **181** (217 mg, 0.5 mmol) and CuBr (86 mg, 0.6 mmol). The sealed tube was purged with nitrogen before addition of anhydrous THF (6 mL). The reaction vessel was sealed with a screw cap and placed in an oil bath at 60 °C. After stirring for 24h, the mixture was cooled to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (CH_2Cl_2 : MeOH, 99:1) to afford **47b** as a white solid (158 mg, 59%) whose ^{1}H NMR spectrum was consistent with published data.[66] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, J = 7.8 Hz, 2H), 7.25 (d, J = 8.0 Hz, 4H), 4.03 (s, 4H), 3.08 (sept, J = 6.9 Hz, 4H), 1.36 (d, J = 6.8 Hz, 12H), 1.35 (d, J = 7.0 Hz, 12H). HRMS (ESI) m/z calculated for $[C_{27}H_{38}BrCuN_2Na]^+$, 555.1407, found 555.1406.

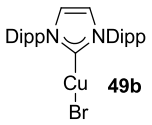


49a

[1,3-bis(2,6-di-*iso*-propylphenyl)imidazol-2-ylidene]copper(I) chloride (49a): The title compound **49a** was prepared according to the representative procedure described above (p105) from imidazolium carboxylate **78** (216 mg, 0.5 mmol) and CuCl (59 mg, 0.6 mmol). The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (CH_2Cl_2 : MeOH, 99:1) to afford **49a** as a white solid (154 mg, 63%) whose ^{1}H NMR spectrum was consistent with published data.[88] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, J = 7.8 Hz, 2H), 7.30 (d, J = 7.9 Hz, 4H), 7.13 (s, 2H), 2.57 (sept, J = 6.9 Hz, 4H), 1.30 (d, J = 6.8 Hz, 12H), 1.23 (d, J = 6.9 Hz,

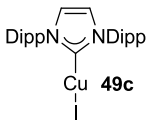
[88] Diez-Gonzalez, S.; Stevens, E. D.; Nolan, S. P. *Chem. Commun*. **2008**, *39*, 4747-4749.

12H). HRMS (ESI) m/z calculated for $[C_{27}H_{36}ClCuN_2Na]^+$, 509.1755, found 509.1772.



49b

[1,3-bis(2,6-di-*iso*-propylphenyl)imidazol-2-ylidene]copper(I) bromide (49b): The title compound **49b** was prepared according to the representative procedure described above (p105) from imidazolium carboxylate **78** (216 mg, 0.5 mmol) and CuBr (86 mg, 0.6 mmol). The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (CH_2Cl_2 : MeOH, 99:1) to afford **49b** as a white solid (200 mg, 75%) whose ^{1}H NMR spectrum was consistent with published data.[89] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 7.7 Hz, 4H), 7.14 (s, 2H), 2.57 (sept, *J* = 6.9 Hz, 4H), 1.31 (d, *J* = 6.8 Hz, 12H), 1.23 (d, *J* = 6.9 Hz, 12H). HRMS (ESI) m/z calculated for $[C_{27}H_{36}BrCuN_2Na]^+$, 553.1250, found 553.1262.



49c

[1,3-bis(2,6-di-*iso*-propylphenyl)imidazol-2-ylidene]copper(I) iodide (49c): The title compound **49c** was prepared according to the representative procedure described above (p105) from imidazolium carboxylate **78** (216 mg, 0.5 mmol) and CuI (114 mg, 0.6 mmol). The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (CH_2Cl_2 : MeOH, 99:1) to afford **49c** as a white solid (165 mg, 57%) whose ^{1}H NMR spectrum was consistent with published data.[20b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 7.7 Hz, 4H), 7.14 (s, 2H), 2.57 (sept, *J* = 6.9 Hz, 4H), 1.31 (d, *J* = 6.8 Hz, 12H), 1.23 (d, *J* = 6.8 Hz, 12H). HRMS (ESI) m/z calculated for $[C_{27}H_{36}CuIN_2Na]^+$, 601.1111, found 601.1105.

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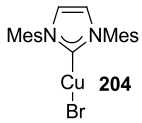
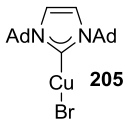
[89] Goj, L.; Blue, E.; Delp, S.; Gunnoe, T.; Cundari, T.; Pierpont, A.; Peterson, J.; Boyle, P. *Inorg. Chem*. **2006**, *45*, 9032-9045.



204

[1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene]copper(I) bromide (204): The title compound **204** was prepared according to the representative procedure described above (p105) from imidazolium carboxylate **76** (174 mg, 0.5 mmol) and CuBr (86 mg, 0.6 mmol). The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (CH_2Cl_2 : MeOH, 99:1) to afford **204** as a white solid (157 mg, 70%). The high resolution MS data for **204** was not obtained as **204** seemed to decompose upon ionization. The ^{1}H NMR spectrum of **204** was consistent with published data.[90] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 2H), 7.01 (s, 4H), 2.35 (s, 6H), 2.11 (s, 12H).

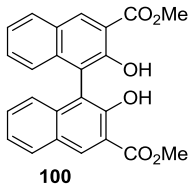


205

[1,3-Diadamantylimidazol-2-ylidene]copper(I) bromide (205): The title compound **205** was prepared according to the representative procedure described above (p105) from imidazolium carboxylate **177** (190 mg, 0.5 mmol) and CuBr (86 mg, 0.6 mmol). The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (CH_2Cl_2 : MeOH, 99:1) to afford **205** as a white solid (108 mg, 45%) whose ^{1}H NMR spectrum was consistent with published data.[20b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 2H), 2.44-2.37 (br m, 12H), 2.31-2.24 (br m, 6H), 1.84-1.71 (br m, 12H). HRMS (ESI) m/z calculated for $[C_{23}H_{32}BrCuN_2Na]^+$, 501.0937, found 501.0942.

[90] Broggi, J.; Diez-Gonzalez, S.; Petersen, J.; Berteina-Raboin, S.; Nolan; Agrofoglio, L. *Synthesis* **2008**, *1*, 141-148.

Oxidative Coupling of 3-Methyl-2-Hydroxynaphthoate Catalyzed by *N*-Heterocylic Carbene Copper(I) Complexes



100

Dimethyl-2,2′-dihydroxy-1,1′-binaphthalene-3,3′-dicarboxylate (100): A sealed tube was charged with catalyst Cu(IPR)Br **49b** (7 mg, 0.01316 mmol), 3-methyl-2-hydroxynaphthoate **96** (27 mg, 0.1316 mmol), Oxone® (89 mg, 0.1447 mmol) and silver nitrate (22 mg, 0.1316 mmol), followed by methanol (1.3 mL). The reaction vessel was sealed, covered with tin foil and the mixture was allowed to stir at 70 °C. After stirring for 24h, the mixture was cooled to ambient temperature. Silica gel was added to the mixture and the volatiles were evaporated under reduced pressure. The crude solid was purified by flash column chromatography on silica gel (Hexane: Ethyl Acetate, 4:1) to afford BINOL ester **100** as a white solid (21 mg, 78%). The ^{1}H NMR spectrum and mass spectrometric data for **100** were consistent with published data.[91] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 2H), 8.69 (s, 2H), 7.91-7.94 (m, 2H), 7.33-7.36 (m, 4H), 7.14-7.17 (m, 2H), 4.06 (s, 6H). HRMS (ESI) m/z calculated for $[C_{24}H_{19}O_6]^+$, 403.1176, found 403.1173. Mp: 274-276°C, lit. mp: 276-278°C.[91]

[91]Feringa, B.; Wynberg, H. *Bioorg. Chem.* **1978** , *7*, 397-406.