ABSTRACT

ANDERS, EVAN JAMES. Improved Synthesis and New Applications of N-Heterocyclic Carbenes for Catalysis. (Under the direction of Dr. Vincent Lindsay).

N-Heterocyclic Carbenes (NHC) have had a tremendous impact on the field of synthetic organic chemistry both as organocatalysts and metal ligands in C–C and C–X bond formation reactions. As organocatalysts, NHCs are well known to activate aldehydes and acyl electrophiles, leading to unique and accelerated reactivity. Their stability, strong σ-donating ability, and commercial availability also make then superior ligands for metals in cross-coupling and transition-metal catalysis. Herein, we demonstrate the utility of NHCs for the activation of strained ketones, an unreported chemical activation, via addition to cyclopropanone. This activated NHC-cyclopropanone adduct will seek to formally reverse the polarity (Umpolung) of such a strained ketone, leading to novel reactivity. Furthermore, we describe an expedient and improved synthesis of bis(azolium)dichloride salts for the formation of metal-bisNHC ligands. The high yields and wide scope of accessible products are a significant improvement to current literature standards that benefit the field of catalysis.

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Improved Synthesis and New Applications of N-Heterocyclic Carbenes for Catalysis

by
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LIST OF ABBREVIATIONS

BDE: bond dissociation energy

Bn: benzyl

Bu: butyl

^{13}C NMR: carbon nuclear magnetic resonance

$CDCl_3$: deuterated chloroform

$CHCl_3$: chloroform

CH_2Cl_2: dichloromethane; methylene chloride

DCE: 1,2-dichloroethane

DMF: N,N-dimethylformamide

DMSO: dimethyl sulfoxide

E: electrophile

EDG: electron-donating group

Et: ethyl

Et_2O: diethyl ether

Et_3N: triethylamine

EtOH: ethanol

equiv: equivalents

EWG: electron-withdrawing group

FT-IR: Fourier-transform infared

^1H NMR: proton nuclear magnetic resonance

h: hours

HCl: hydrochloric acid

HESI: heated electrospray ionization

HOMO: highest occupied molecular orbital

HRMS: high-resolution mass spectrometry

Me: methyl

Mes: mesityl

MeCN: acetonitrile

MeOH: methanol

mins: minutes

mmol: millimoles

NHC: N-heterocyclic carbene

N.R.: No reaction

Nu: nucleophile

Ph: phenyl

ppm: parts-per-million

rt: room temperature

S.M.: starting material

THF: tetrahydrofuran

TLC: thin-layer chromatography

CHAPTER 1

General Introduction

Abstract: N-Heterocyclic Carbenes have been a valuable resource in the fields of organocatalytic and organometallic chemistry. In this chapter, we will describe the discovery and characterization of N-Heterocyclic Carbenes, which have elucidated structural information that provided chemists the knowledge to use them as activating agents in catalysis and to improve upon well-known chemical transformations.

1.1 The History of N-Heterocyclic Carbenes and their Structure

Carbenes are defined as neutral compounds that contain a divalent carbon atom with a six-electron valence shell.[1] Due to their high reactivity and instability, it was not until the late 1980s and early 1990s that their isolation and characterization was carried out by the Bertrand and Arduengo groups. In 1988, Bertrand reported the isolation of a free carbene stabilized by neighboring silicon and phorophorous atoms,[2] while Arduengo then was the first to produce a crystalline, stable free carbene from 1,3-bis(1-adamantyl)imidazol-2-ylidene with the corresponding X-Ray crystallographic data.[3] Ardguengo's carbene, that which contain at least one nitrogen atom and one carbene carbon in a cyclic ring structure, is commonly referred to today as a N-Heterocyclic Carbene (NHC).

NHCs have seen a steady rise in popularity in the last decades due to their unique structure and electronic properties that allow them to be used in fields such as organocatalysis and organometallic catalysis. Traditional NHCs, those with an azolium core and a C(2) carbene carbon, exhibit both consistent and predictive reactivity due to the stability the carbene carbon owing to the adjacent nitrogens. The lone pairs of the neighboring heteroatoms allow for π-electron donation into the empty LUMO *p*-orbital of the carbene carbon, while the HOMO contains a sp^2-hybrizized lone pair, further stabilized by the σ-electron withdrawing character of these heteroatoms (Figure

1.1). The ring system backbone of the NHC additionally has aromatic character, further electronically stabilizing the high-energy carbene. Unlike classical electron-poor carbenes, NHCs are nucleophilic due to the carbene lone pair that its situated in the plane of the heterocycle. This nucleophilic characteristic is best demonstrated in the use of NHCs as reagents for activation of electrophilic organic functional groups for catalysis, such as aldehydes and acyl electrophiles.[4] Moreover, this strong σ-donating ability makes NHCs ideal as ligands for metals in a variety of organometallic and cross-coupling chemistry, akin to organophosphane ligands.

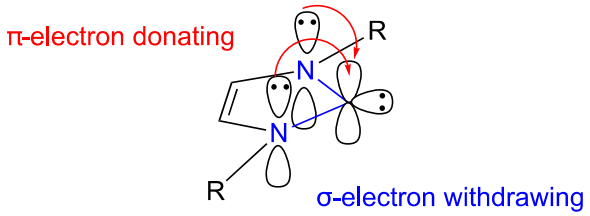
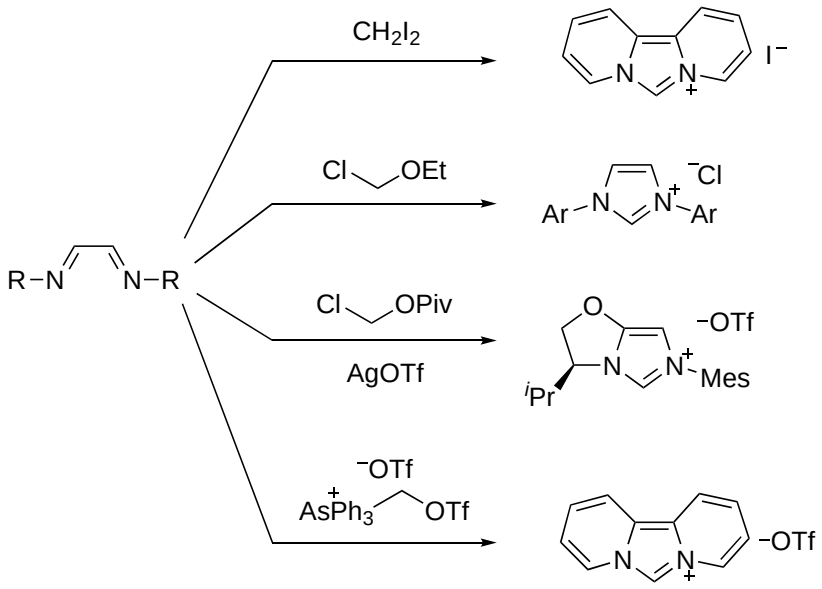


Figure 1.1: N-Heterocyclic Carbene Structure

1.2 Synthesis of N-Heterocyclic Carbenes

The ease of preparation of NHC cores is an additional reason for the rise in popularity of NHCs in catalysis. NHCs derived from an imidazole core constitute some of the most popular carbenes via straightforward heterocycle synthesis, such as formation of imidazoliums by cyclization of a diamine with one-carbon constituent, affording a diverse range of substituted NHCs (Scheme 1.1).[5] One-pot syntheses of imidazoles are well known and can be made starting with glyoxal, a primary amine, and formaldehyde.[7] *N*-substituted imidazole derivatives are easily synthesized via substitution reactions utilizing base-catalyzed deprotonation of the nitrogen proton or through use of the lone pair of the "imino" nitrogen as a nucleophile. Thiazoliums, the most popular early carbenes, can be prepared with treatment of thiazolin-2-thione with peroxides in

acidic conditions.[6] Thiazole-based NHCs can also be synthesized from the condensation of an α-chloro ketone with thioformamide.[7]

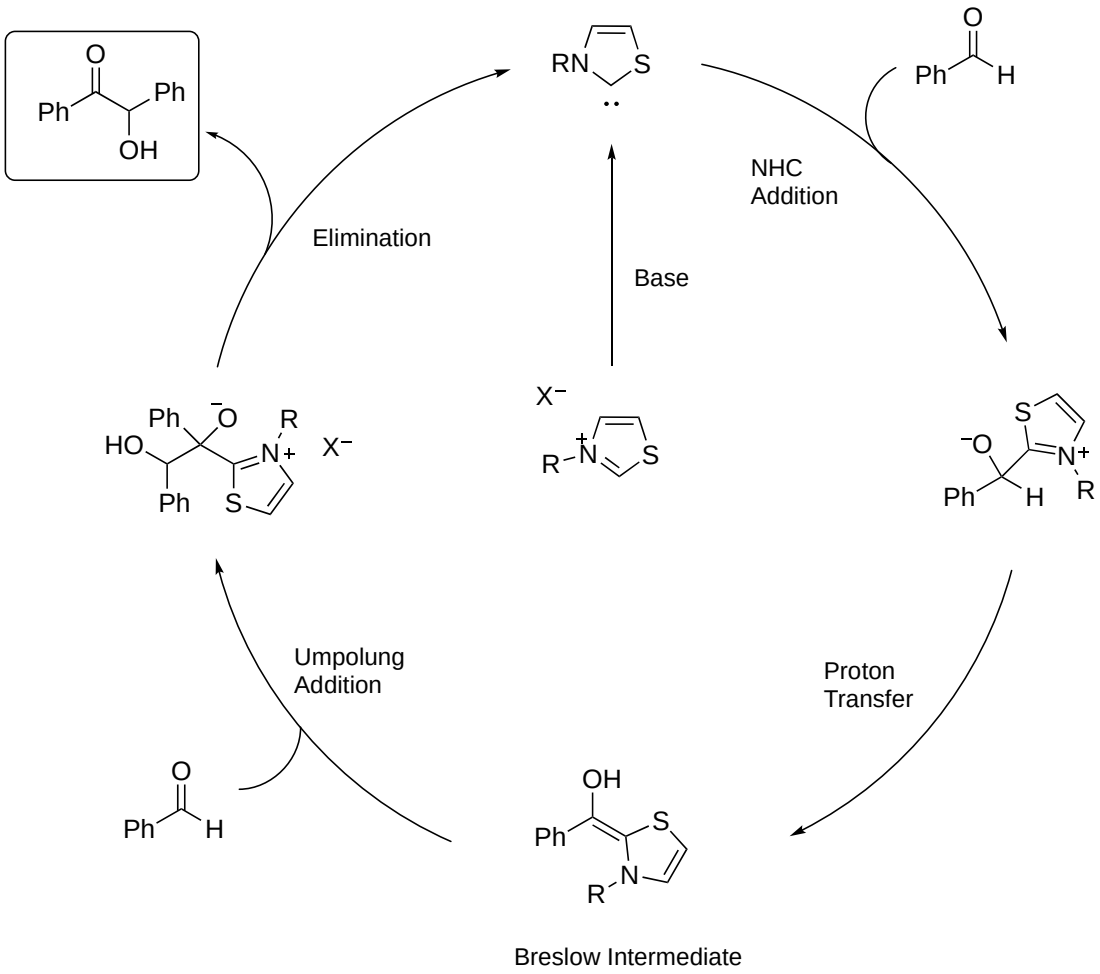


Scheme 1.1: Synthesis of NHCs by cyclization of diamine and one-carbon linchpin

1.3 N-Heterocyclic Carbenes as Organocatalysts

The field of NHC organocatalysis began in 1943 when Ukai discovered that aldehydes, catalyzed by thiazolium salts, could homodimerize via benzoin condensations.[8] Inspired by such benzoin condensations and their reaction catalysts, Breslow observed in 1958 that rapid C(2) proton-deuterium exchange of thiazolium salts could occur under mild conditions, noting that the C(2) carbon has anionic character under such equilibrium conditions. Breslow then proposed reaction mechanism of the thiazolium-catalyzed benzoin condensation, which relies on the generation of a NHC *in situ* (Scheme 1.2). Nucleophilic addition of the carbene to the aldehyde to form a tetrahedral intermediate, followed by subsequent proton transfer, leads to the now famous Breslow intermediate; an enamine-like NHC-aldehyde intermediate that is nucleophilic at carbon.[9] This shift of innate chemical reactivity, in this case the carbonyl carbon change from an

electrophilic to nucleophilic species, is called an umpolung process. Such an umpolung process of aldehydes catalyzed by NHCs, similar to an acyl anion, laid the groundwork for the field of NHC organocatalysis, which have undergone significant exploration and chemical transformations[10].

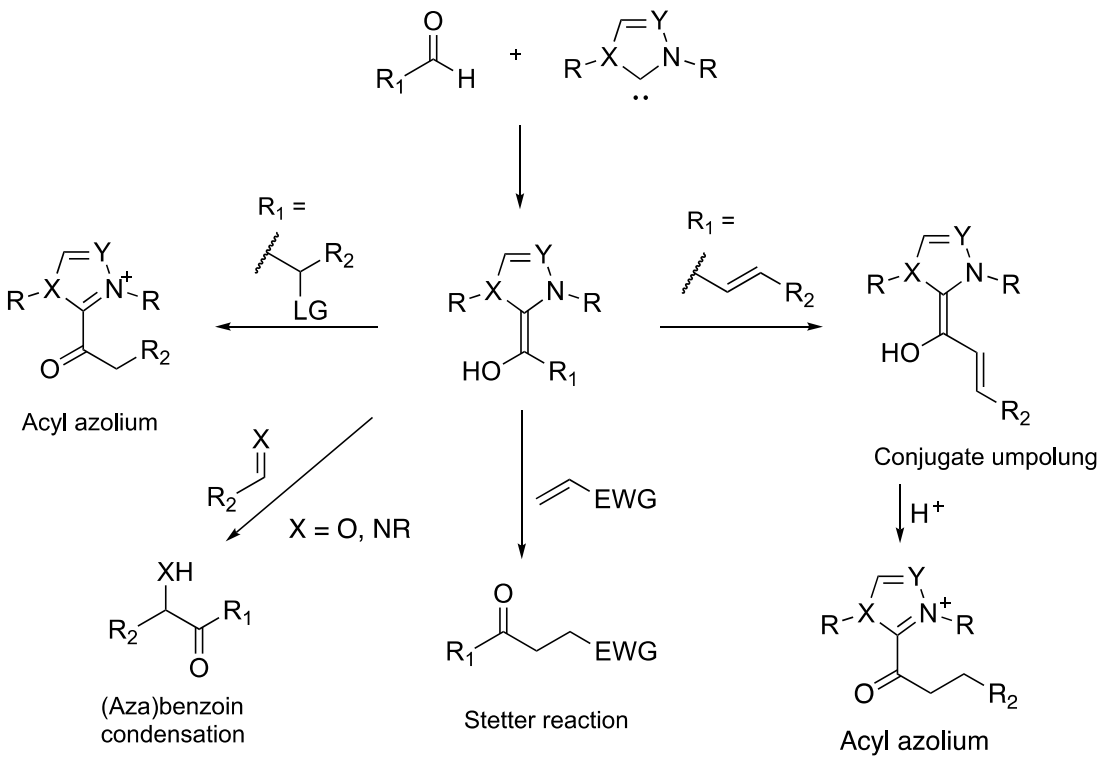


Scheme 1.2: NHC-catalyzed Benzoin Condensation via a Breslow Intermediate

Two of the most studied NHC catalyzed reactions include the (aza)benzoin condensation and the Stetter reaction, both utilizing the Breslow intermediate and reacting akin to acyl anions. The (aza)benzoin condensation involves the nucleophilic attack from the Breslow intermediate carbonyl carbon to another equivalent of imine or aldehyde and, after elimination of the NHC, leads to product formation (see Scheme 1.2). Similarly, the Stetter uses electron-deficient alkenes (Michael acceptors) as the electrophilic reaction partner to furnish conjugate-addition products

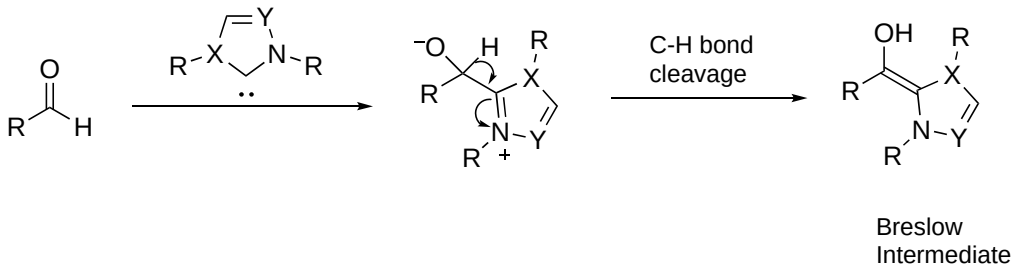
with β-functionalization. An extensive number of chiral NHCs have since been utilized that allow for numerous enantioselective benzoin condensation reactions.

Nucleophilic addition of an NHC to an α,β-unsaturated aldehyde instead allows for "conjugate umpolung" catalysis via an extended Breslow intermediates, which react similarly to homoenolates (Scheme 1.3). These intermediates are known to perform various annulation reactions, providing convenient access to a number of N, O, S, and C heterocycles. Controlled regioselectivity is a prominent feature of this mechanistic pathway; varying the substituents of the electrophilic reaction partner to the nucleophilic Breslow intermediate offers straightforward production of diverse carbo- and heterocycles. Alternatively, to avoid this conjugate reactivity, addition of a proton source to an α,β-unsaturated aldehyde leads to an electrophilic acylazolium intermediate, enabling nucleophilic catalysis. Similarly, addition of an NHC to an aldehyde with an α-leaving group or the use of an oxidant to the Breslow intermediate will also achieve acylazolium reactivity.



Scheme 1.3: NHC-Catalyzed Reaction Pathways

Although NHCs have been widely used in organocatalysis with aldehydes, the use of other functional groups such as ketones are less well known. This is largely due to the proton transfer step in the formation of the Breslow intermediate, which cannot happen with ketones. Indeed, NHC-aldehyde adducts require a C–H bond cleavage of the tetrahedral species to form the Breslow intermediate, while changing the electrophile to a ketone would demand an unfavored C–C bond cleavage of the tetrahedral intermediate to furnish the Breslow intermediate (Scheme 1.4).



Scheme 1.4: Breslow Intermediate formation via C–H bond cleavage

1.4 N-Heterocyclic Carbenes as Ligands in Organometallic Chemistry

While NHCs were initially thought to be highly-reactive intermediates incapable of isolation, the groups of Wanzlick and Öfele reported that NHCs can be isolated when bound to metals. In 1968, Wanzlick trapped a NHC dimer with mercury to form its mercury-carbene salt and confirmed its structure by spectroscopy.[11] That same year, Öfele isolated a chromium-bound 1,3-dimethylimidazole NHC while working with heterocyclic salts.[12] The chemistry of NHC-metal salts stability, while significant, was not greatly developed until the work of Bertrand and Arduengo some years later.

NHCs are attractive ligands in organometallic chemistry, especially in the field of palladium-catalyzed reactions, due to the nature of the strong bonds NHCs form with a wide variety of metals (Figure 1.2). This minimizes the amount of dissociated free carbene that exists in the reaction equilibrium, making NHC superior ligands compared to the previously popular phosphine ligands that form much weaker metal bonds. For example, the BDE for the IMes ligand is 41.1 kcal/mol, as where PPh_3 is only 26.7 kcal/mol. This robustness and stability is especially noticeable in reactions that require more harsh conditions such as high temperature in the presence of water, where preservation of the metal-ligand bond that will hold for the duration of a reaction is key.[13]

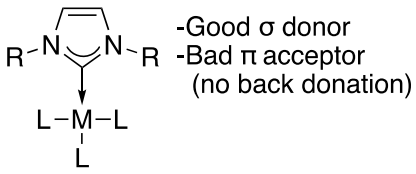
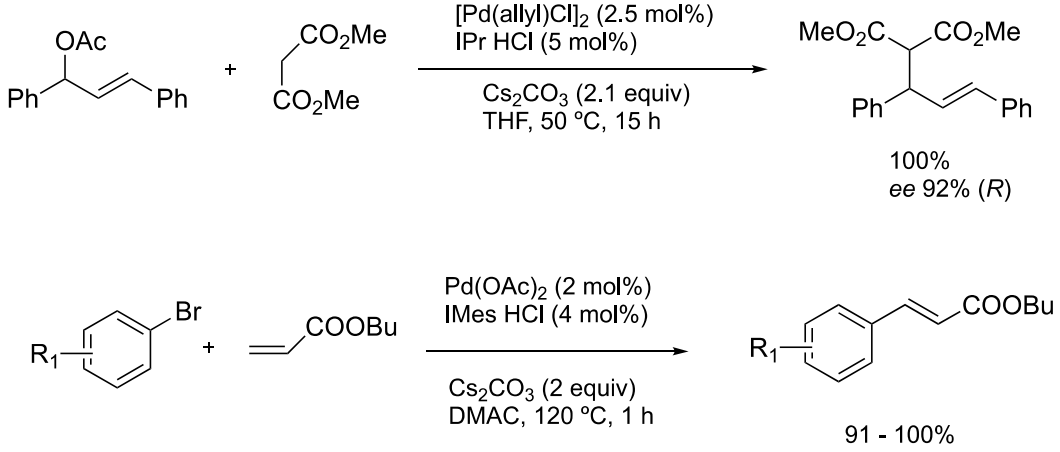


Figure 1.2: Metal-bound NHC

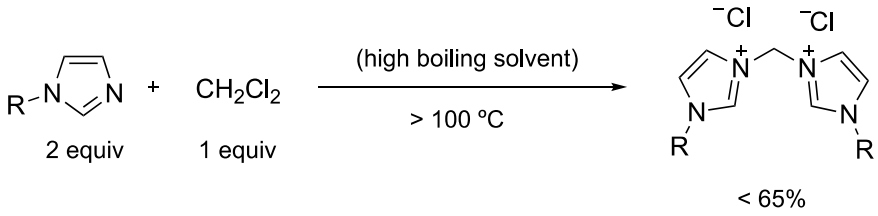
NHC-metal complexes have risen in popularity due to their versatility in C–C bond forming reactions. In addition to cross-couplings, NHCs have been found to be suitable ligands in other metal-catalyzed processes such as allylic substitutions (Scheme 1.5) and α-arylation of carbonyl

compounds.[14,15] A significant milestone, the first catalytic application of a NHC ligand in cross-coupling was reported in the palladium catalyzed Heck reaction in 1997.[16]



Scheme 1.5: Pd-NHC Heck and allylic substitution reactions

While there are numerous well-studied examples of monodentate NHCs, alkane-bridged chelating biscarbenes are becoming more popular ligands in catalysis due in part to their increased stabilizing ability as ligands. These NHC complexes are expected to be even more stable than previously-mentioned phosphanes and monodentate NHCs due to their restrictive and bulky steric hindrance that impedes and slows the reductive elimination decomposition pathway of the carbene.[17] While catalytically useful, the synthesis of such bis(azolium)dichloride salt precursors for metal catalysis are reported in noticeably low yields due to the use of high reaction temperatures and the use of low equivalents of dichloroalkanes (Scheme 1.6).[18] Analogous halide salts such as bis(azolium)dibromides and diiodides can be made in much higher yields, but their utility is impeded by the lower stability of the corresponding metal complexes.[19]



Scheme 1.6: Typical literature synthesis of bis(azolium)dichloride salts

1.5 Conclusions

NHCs have made a remarkable synthetic impact within the past 30 years alone. While their application toward the activation of aldehydes and acyl electrophiles in organocatalysis is well-established, much is left to explore for the activation of other electrophilic functional groups. Moreover, given their use as ligands in organometallic chemistry, especially cross-coupling reactions, a more efficient and high yielding manner of synthesizing metal bis(azolium)dichloride salts would be highly valuable. In this thesis, I will detail the work done to advance the scope of NHC-organocatalyzed reactions to activate cyclopropanones, an unknown reaction. I will also discuss the novel methodology established to synthesize a variety of metal bis(azolium)dichloride salts in excellent yields and demonstrate the efficacy of that methodology to perform a one-pot synthesis of a bis(NHC)palladiumchloride complex.

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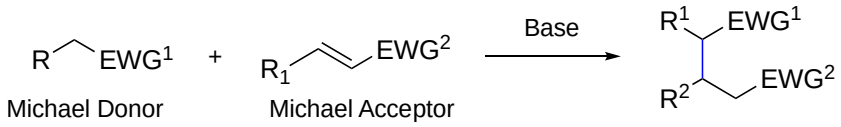
CHAPTER 2

Activation of Cyclopropanone by NHCs

Abstract: NHCs have been widely used in organocatalysis with aldehydes, but the use of other functional groups such as ketones are less well known. Herein, we detail the development of a novel umpolung reaction of cyclopropanone through the use of a N-Heterocyclic Carbene that, after the C–C bond breaking step of the cyclopropanone, results in the linkage of a nucleophile and electrophile through a three-carbon linchpin.

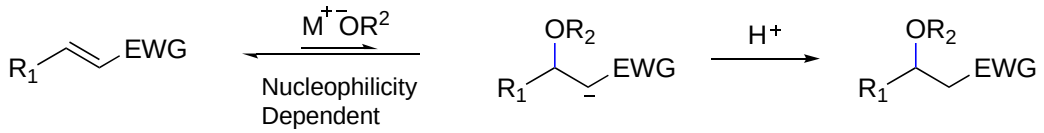
2.1 Long-standing Problems of Michael Addition Chemistry

The Michael addition is one of the most commonly used C–C bond forming methods and is ubiquitous in organic synthesis.[1] This 1,4-conjugate addition proceeds through the addition of a nucleophilic Michael donor (stabilized nucleophile) to an electron-deficient alkene acceptor (Scheme 2.1).



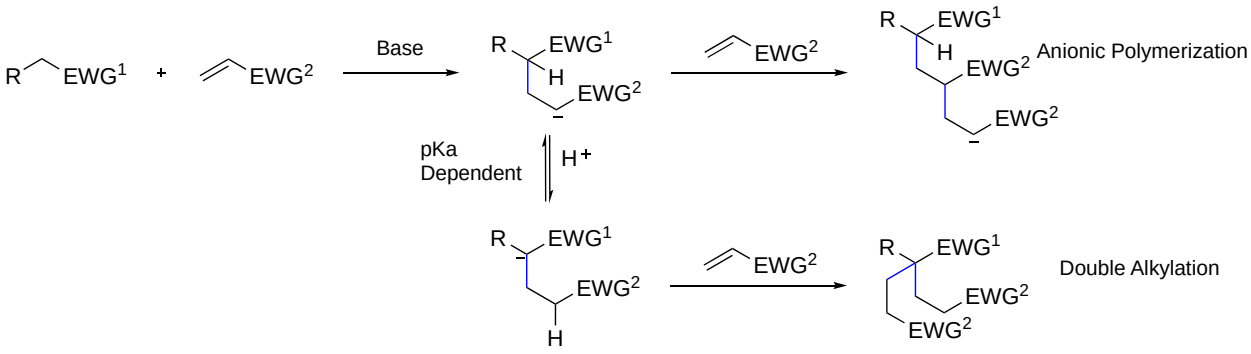
Scheme 2.1: General scheme of the Michael reaction

Directly after the addition, an anionic enolate intermediate is formed and protonated in the workup or by the conjugate acid formed during the initial deprotonation. This anionic intermediate, however, can cause a plethora of undesired products that can reduce yields of the Michael product dramatically or form the wrong product entirely, depending on the nature of the reactants. For example, with highly stabilized Michael donors such as alkoxides, this can lead to undesired retrogression to the starting materials, which has hampered the general use of this oxa-Michael reaction in organic synthesis (Scheme 2.2).[2]



Scheme 2.2: Reversibility issues of the oxa-Michael reaction

Moreover, when particularly reactive Michael acceptors are used such as acrylate derivatives,[3] anionic polymerization or double alkylation can occur following the initial addition, since the enolate intermediate formed is also a potential Michael donor (Scheme 2.3). In all cases, the problems associated with Michael additions stem from the inherent presence of a stabilized anionic intermediate. Considering the prominence of this reaction in organic synthesis, the development of an approach which obviates the intermediacy of enolates would thus be highly valuable.

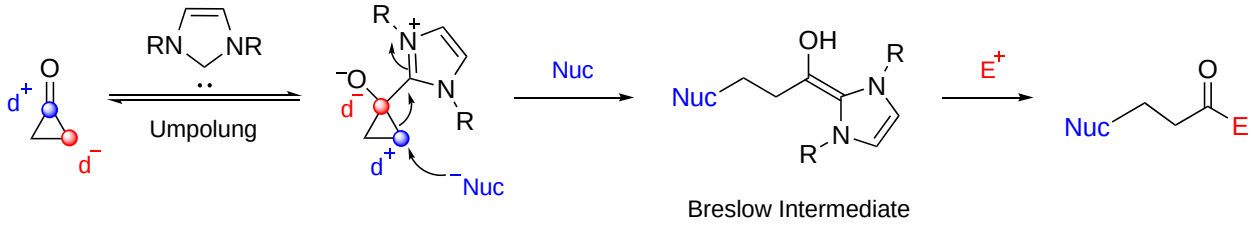


Scheme 2.3: Double alkylation or polymerization when using highly reactive substrates

2.2 Activation of cyclopropanone by NHC to avoid undesired anionic intermediates

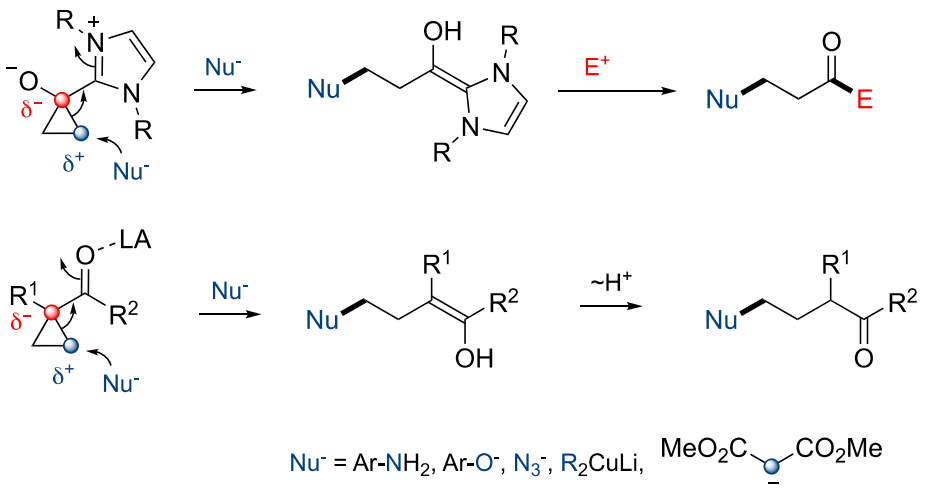
We propose an alternative method in order to provide an enhanced generality of the Michael reaction by avoiding the presence of anionic intermediates; this would result in the formation of the corresponding Michael adducts that have been traditionally difficult to form. The proposed reaction shown below (Scheme 2.4), one of an umpolung of a ketone through the use of a NHC catalyst, is enabled by strain release of cyclopropanones during the C–C bond breaking

step. The strain release of the cyclopropane after nucleophilic attack should make the process irreversible, which can typically be problematic in oxa-Michael additions. Directly after the nucleophilic addition, the resulting Breslow intermediate can react with various electrophiles, and the overall process consists formally in the linkage of a nucleophile and electrophile through a three-carbon linchpin. This will additionally allow for new libraries of reactions and scope expansion to be investigated.



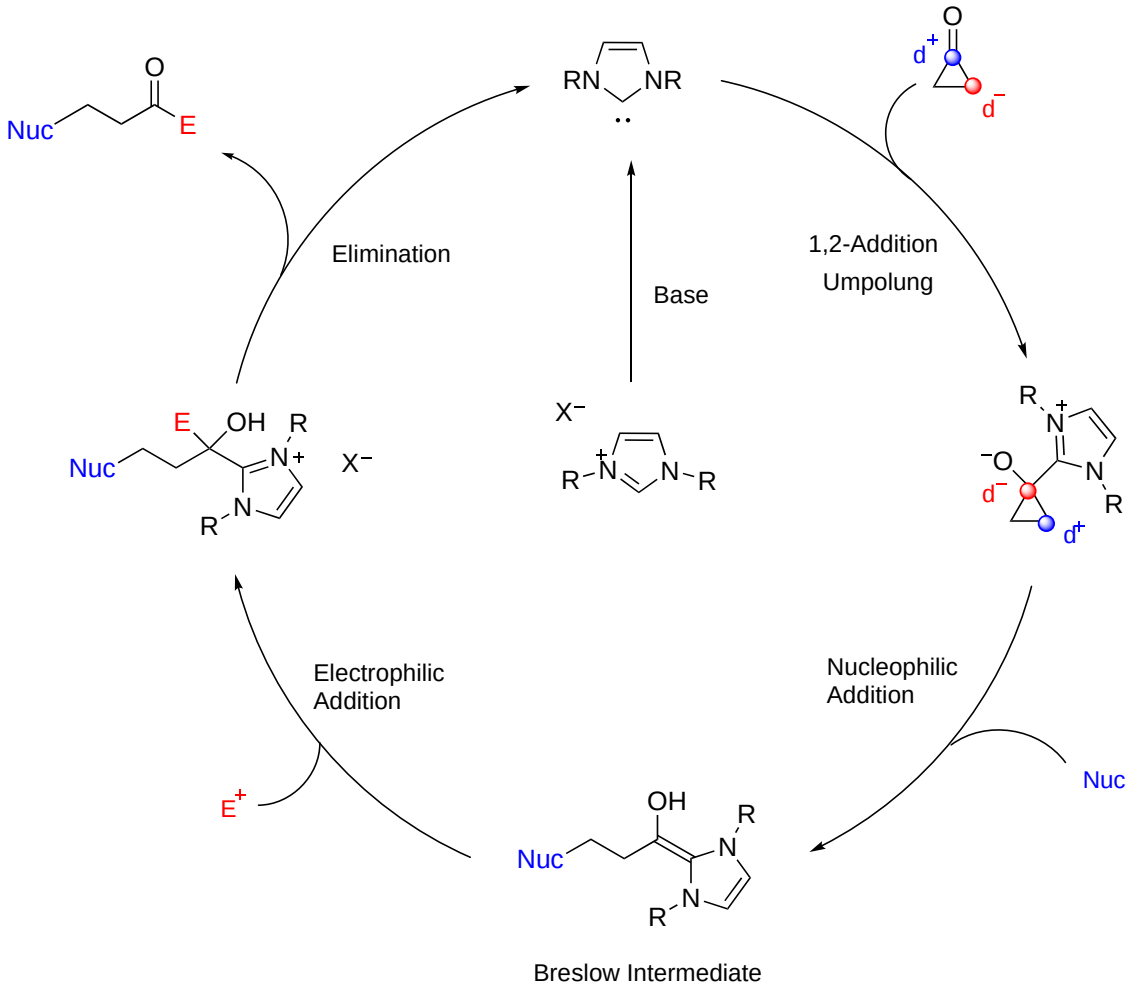
Scheme 2.4: Umpolung of cyclopropanone by NHC organocatalysis

The mechanism of the proposed umpolung reaction of a strained ketone via NHC catalysis is akin to current literature investigations[4], which demonstrate the viability of such ring-opening (Scheme 2.5). Indeed, recent findings have shown that electrophilic cyclopropanes (donor-acceptor cyclopropanes) can be reacted with nucleophiles in presence of a Lewis acid to afford the corresponding 1,5-adducts. Additionally, both the cyclopropanone and NHC precursors are commercially available or easy to synthesize; the former is made in situ from the acetal version in presence of a weak acid, while the latter is made from an imidazolium salt (*vide infra*).



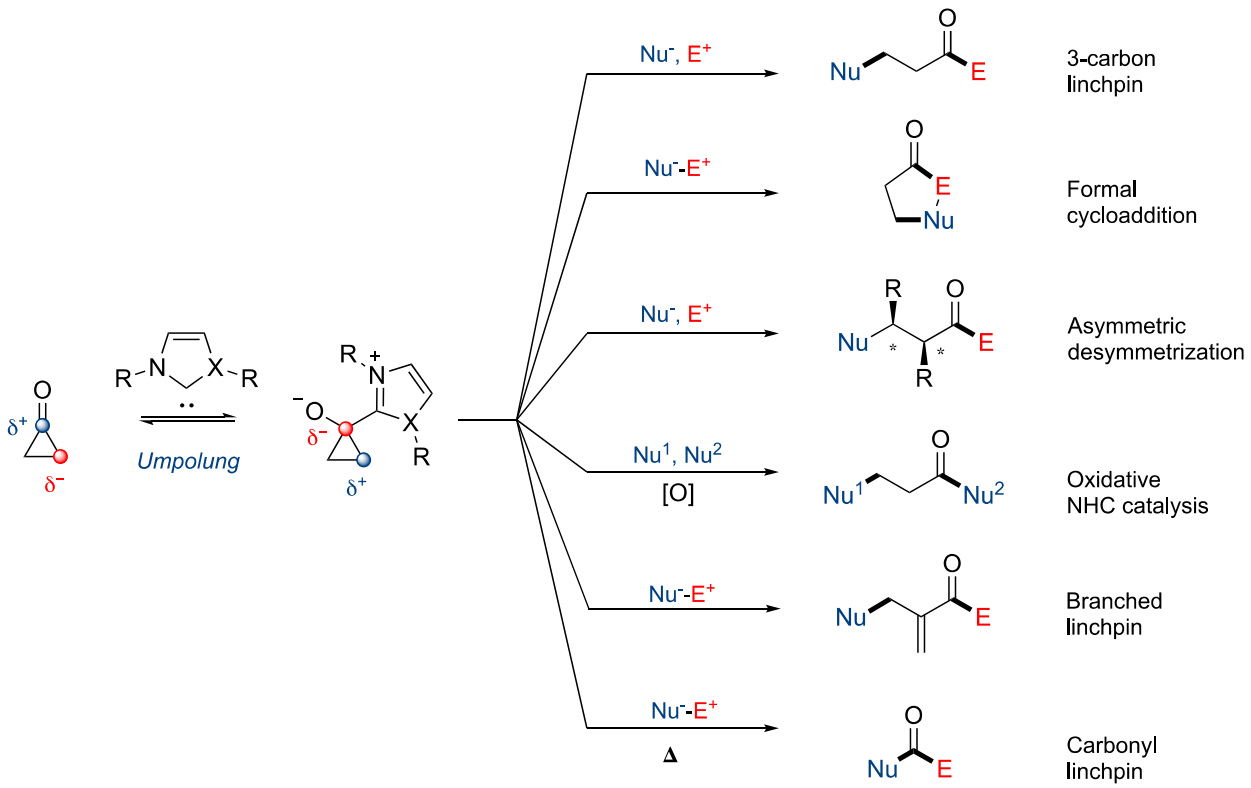
Scheme 2.5: Lewis-Acid mediated ring-opening of cyclopropane derivatives

Stoichiometric reaction conditions of the proposed reaction will first be investigated by isolation and evaluation of the cyclopropanone/NHC adduct intermediate. Catalytic conditions will then be evaluated (Scheme 2.6), and once optimized conditions have been established, a scope of various stabilized nucleophiles (alkoxides, malonates, amines) and electrophiles will be explored to generate products that have been difficult to form through the traditional Michael reaction.



Scheme 2.6: Possible catalytic cycle

Additional applications and libraries of this concept will be investigated to impact broad fields of synthesis, such as formal cycloadditions (when a nucleophile and electrophile are connected), metal-catalyzed versions, or using oxidative NHC catalysis to connect two nucleophiles via a three-carbon linchpin, as a complement to the initially proposed oxidant-free approach (Scheme 2.7). Since cyclopropanes and cyclobutanes are known to have similar strain energies, the proposed research will also be extended to four-carbon linchpin reagents starting from cyclobutanones, leading to homo-Michael adducts.

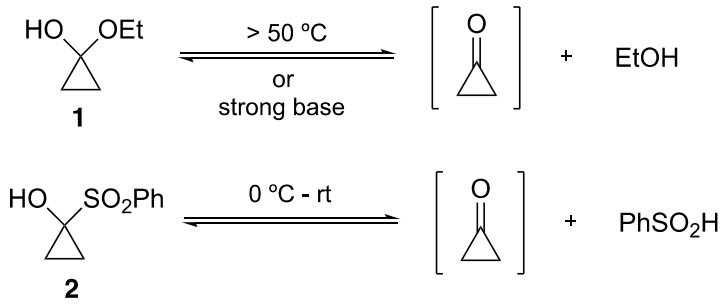


Scheme 2.7: Possible synthetic manipulations of novel NHC-cyclopropanone intermediate

2.3 Formation of NHC-cyclopropanone adducts

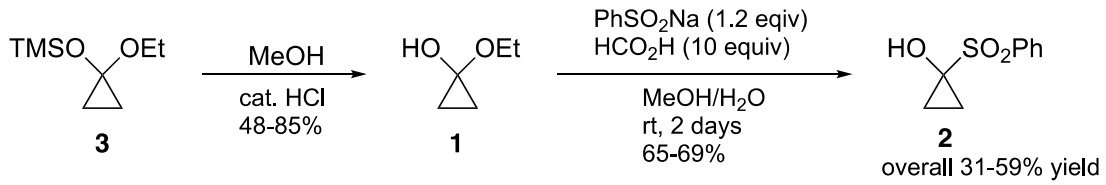
In order to investigate the reactivity of the proposed NHC-cyclopropanone adduct towards novel reaction conditions, it is imperative to first study the effects of nucleophilic addition of NHCs towards the cyclopropanone equivalent. The first goal of this methodology, therefore, is to have a reliable source of cyclopropanone equivalent. Cyclopropanones are inherently unstable and only a few established methods offer a reliable synthesis of cyclopropanone precursors, though these are poorly reactive and require high temperature or harsh basic conditions to produce the cyclopropanone *in situ*. For example, some hemiketals such as **1** can be transformed under such conditions to form the volatile cyclopropanone *in situ*, which may not be suitable reaction conditions for subsequent reaction transformations using the newly formed cyclopropanone. A more suitable cyclopropanone equivalent would be the sulfinic acid adduct **2**, which exists as a

stable white solid and can generate the cyclopropanone *in situ* at 0 ºC in mildly basic conditions (Scheme 2.8).



Scheme 2.8: Reactivity of cyclopropanone precursor

In 2008, the Chen group published a procedure for the formation of the sulfinic salt cyclopropanone adduct **2** from a commercially available precursor, but in poor and variable yield due to the difficult isolation of the hemiketal intermediate **1** and the recrystallization of the product needed (Scheme 2.9).[5]

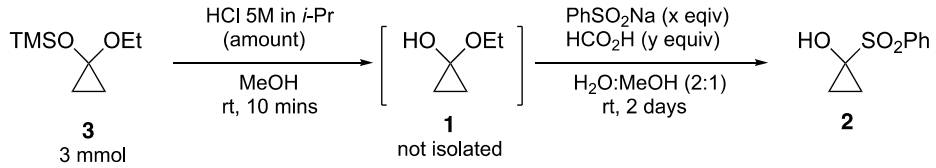


Scheme 2.9: Formation of sulfinic acid cyclopropanone adduct **2**

While this is a viable literature procedure, our lab hypothesized that the same procedure could be made in a one-pot method by avoiding isolating the hemiketal intermediate and manipulating the reaction conditions to form a clean product without the need for a recrystallization purification (work of Yujin Jang). Indeed using HCl to deprotect the starting material and using an excess of sulfinate salt to quench the remaining HCl for the subsequent steps led to improve yields. In order to drive the reaction to completion and avoid some decomposition observed in the reaction, the amount of HCl was decreased and, after aqueous workup, the sulfinate cyclopropanone adduct was afforded in 92% yield without the need for any further purification

(Table 2.1, entry 4). This is additionally a superior method because it is reproducible on gram-scale and the white solid product can be stored safely at low temperature for several months.

Table 2.1: Optimization of the one-pot formation of cyclopropanone precursor **2**



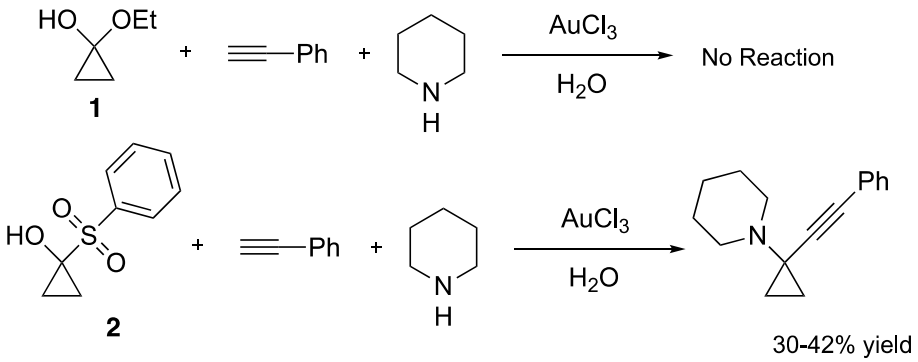
3
3 mmol

1
not isolated

2

Entry	HCl amount	$PhSO_2Na$ x equiv	HCO_2H y equiv	Concentration (second step)	Yield (%)	Note
1	4 drops	1.2	0	0.33 M	<9	Contains impurities
2	4 drops	1.2	10	0.67 M	74	Some 1 remaining
3	4 drops	4.0	10	0.67 M	87	Some 1 remaining
4	1 drop	2.0	10	0.67 M	92	Pure product 2

Interestingly, while this cyclopropanone precursor is more stable than **1** in its solid form, it is also more reactive in solution, allowing the use of milder conditions for its use as a cyclopropanone equivalent. This was demonstrated by the Chen group in the reaction with phenylacetylene and piperidine in water using $AuCl_3$ as catalyst (Scheme 2.10). Indeed, the sulfinic acid adduct affords the substituted cyclopropylamine product in moderate yield, while the hemiketal precursor did not undergo any reaction.



Scheme 2.10: Reactivity comparison of known cyclopropanone precursors

With a robust method for the production of cyclopropanone precursor **2** established, the next step of the project was to synthesize a library of NHCs in order to evaluate their nucleophilic addition toward cyclopropanone. This should provide information as to which azolium cores, substitution patterns, and electronic effects produce the desired reactivity. The heterocyclic core was differentiated to afford various imidazolium (Figure 2.1), triazolium, thiazolium and oxazolium salts, along with their corresponding fused NHC counterparts which focused on probing the electronic and steric properties of the NHC in the reaction.

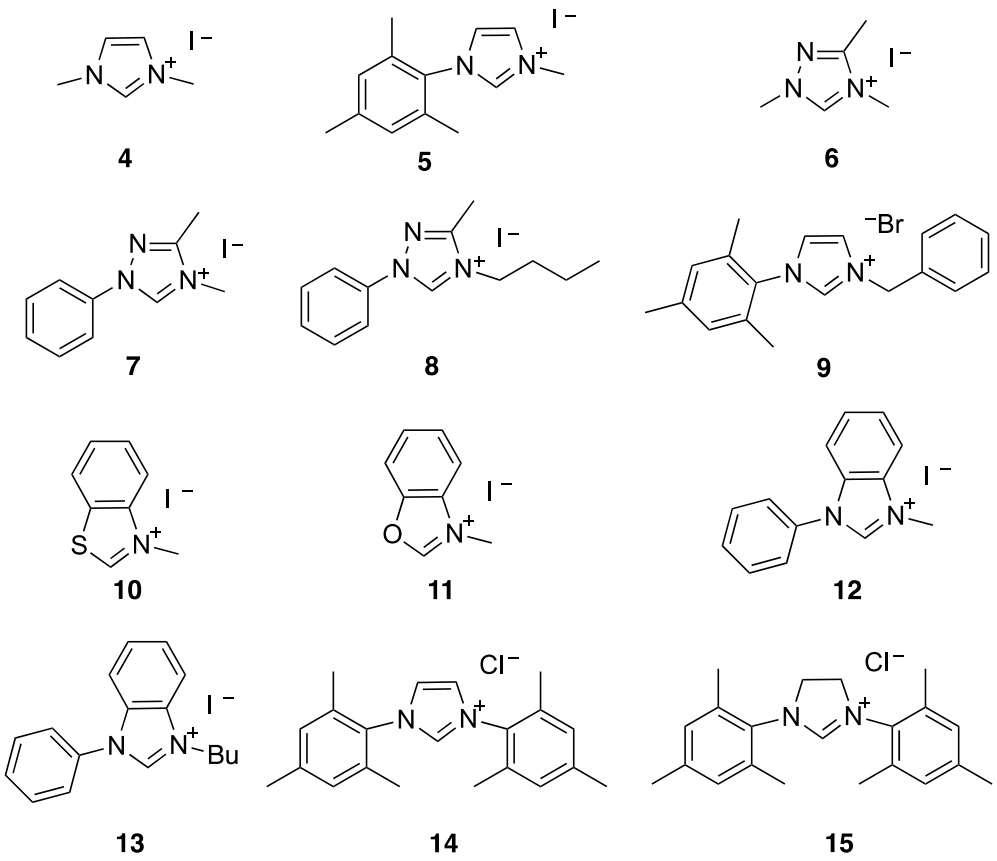


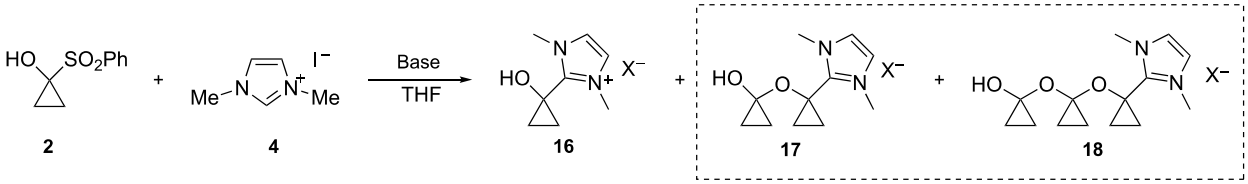
Figure 2.1: Library of Azolium Salts synthesized

The reaction investigations began with the selection of a NHC precursor, corresponding base, and solvent in which to test the addition towards the synthesized cyclopropanone equivalent **2**. We selected 1,3-dimethylimidazole as a suitable model NHC and NaH as our base, as it is known in the literature to be a proven reagent for the formation of NHC and its conjugate acid byproduct (H_2) would not react later in the reaction. THF was selected as the solvent of choice after a screen revealed that is can solubilize the chosen reagents and that more polar solvents (e.g. DMF) promoted NaH reduction of cyclopropanone precursor **2** to cyclopropanol.

Initial evaluations revealed that some of these early conditions selected successfully formed the desired NHC-cyclopropanone adduct **16**, but significant amounts of oligomeric side products were also formed, mainly the dimer and trimer products **17** and **18** (Table 2.2). This

reactivity is most likely due the nucleophilic character of the alkoxide formed following the addition of NHC. The dimer and trimer side products formed in this reaction are especially problematic since their polarity is almost identical to that of the desired product **16** and the imidazolium starting material **4**, making purification impossible by chromatography.

Table 2.2: Evaluation of 1,3-dimethylimidazole NHC, NaH towards NHC-cyclopropanone adduct formation



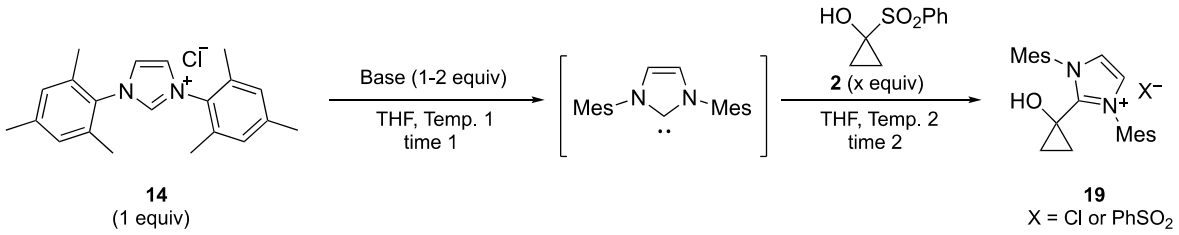
2 **4** **16** **17** **18**

Entry	Cyclopropanone (**2**)	NHC (**4**)	Base	Solvent	Temperature	Time	Result
1	1 equiv	1 equiv	-	THF	rt	6 h	**2** , **17**
2	1 equiv	1 equiv	NaH (2 equiv)	THF	0 °C	1 h	**4**, **16**, **17**, **18**
5	1 equiv	3 equiv	NaH (2 equiv)	THF	0 °C	1 h	**4**, **16**

Minimization of the oligomerization became the immediate focus of the investigation. In an effort to decrease the nucleophilic character of the alcohol, the NHC precursor was changed to a more sterically-hindered IMes·HCl (**14**) substrate that, after addition to the cyclopropanone, would form a hindered tertiary alcohol less susceptible to attack another equivalent of cyclopropanone starting material. Additionally, the reaction was separated into to sequential steps in order to minimize the observed undesired reactivity: complete deprotonation of the NHC in an initial step, then followed by addition of the cyclopropanone precursor at lower temperatures. This change to a sterically-hindered NHC and temperature optimization proved to be a significant step

toward favoring the desired reactivity, as the amount of oligomers formed was noticeably reduced (Table 2.3).

Table 2.3: Optimization of NHC-cyclopropanone formation



14
(1 equiv)

19
X = Cl or $PhSO_2$

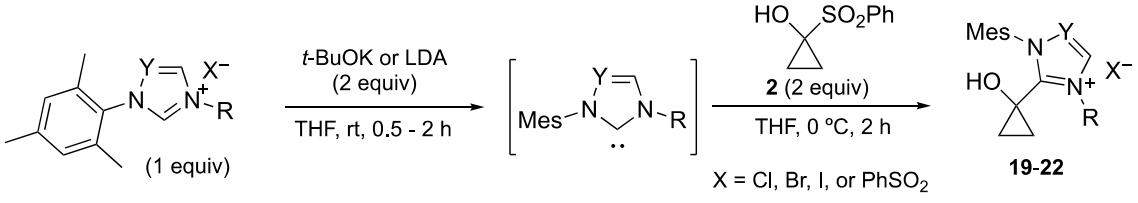
Entry	Base (equiv)	Temp.1/ time1	2 equiv	Temp2/ time2	H_2O quech	8 remains/ dimer	Yield (%)	Note
1	NaH(1.3)	0°C/1h	1.1	0°C/1h	No	Yes/No	N.D	>30% **14**
2	NaH(1.3)	rt/2h	1.1	rt/2h	No	Yes/Yes	N.D	22% dimer
3	NaH(1.3)	rt/2h	1.1	0°C/2h	No	Yes/No	N.D	20% **14**
4	NaH(2)	rt/2h	1.1	0°C/2h	No	No/No	N.D	Complex
5	NaH(2)	rt/2h	2.0	0°C/2h	No	No/Yes	51[c]	Pure **19**
6[b]	NaH(2)	rt/2h	2.0	0°C/2h	No	No/Yes	47[c]	7% dimer
7[b]	NaH(2)	rt/2h	2.0	0°C/2h	Yes	No/Yes	70[c]	3% dimer
8	NaH(1.9)	rt/2h	1.9	0°C/2h	Yes	No/Yes	80[c]	4% dimer
9[b]	NaH(1.9)	rt/2h	1.9	0°C/2h	Yes	No/Yes	80[c]	6% dimer
10	DIPEA(2)	rt/2h	2.0	0°C/2h	Yes	Yes/No	<5[d]	No reaction
11	Et_3N(2)	rt/2h	2.0	0°C/2h	Yes	Yes/No	<5[d]	No reaction
12	DBU(2)	rt/2h	2.0	0°C/2h	Yes	Yes/No	45[d]	-
13	*n*-BuLi(2)	rt/2h	3.0	0°C/2h	Yes	No/Yes	82[d]	27% dimer
14	*t*-BuOK(2)	rt/2h	2.0	0°C/2h	Yes	No/No	76[d]	Pure **19**
15	LDA(2)	rt/2.5h	2.0	0°C/2h	Yes	No/No	78[c]	Pure **19**

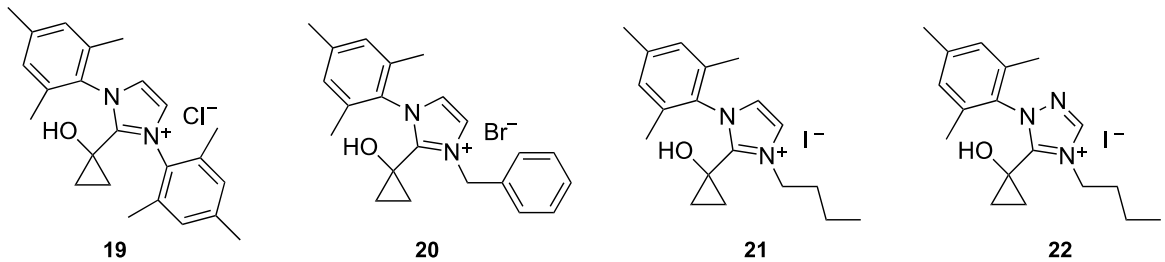
[a]Reaction prefrom at 20 mg scale of 8. [b] 100 mg of **14** used. [c] Isolated yield.
[d] NMR yield using 1,3,5-trimethoxybenzene as internal standard

Further evaluation revealed that the equivalents of base, **14**, and **2** were crucial to driving to reaction to the desired reactivity. We observed that an excess of cyclopropanone precursor is needed to consume the NHC (entries 4, 5), and that the equivalent of base needs to closely mirror that of the cyclopropanone precursor, suggesting that base can accelerate cyclopropanone formation from the sulfinic acid precursor. A water quench of any leftover base at the end of the reaction was crucial to impede dimer formation (entry 7). While NaH did afford pure product, these optimized conditions on small-scale were not reproducible on larger scale, so an evaluation

of various bases was performed. Strong, hindered bases gave improved yields with *t*-BuOK proving to give the most consistent and pure product formation (entry 14).

This established method for the formation of the IMes-cyclopropanone adduct **19** led us to test other NHCs for their viability in the same reaction conditions. It quickly became apparent that bulky steric hindrance of the NHC core was essential to formation of the NHC-cyclopropanone adduct **19**, as all of the pure isolated adducts contain at least one mesityl group. To date, only the four variants shown below yield product formation without any oligomers, inseparable side-products, or starting imidazolium salt (Scheme 2.11). Moreover, experiments to form an adduct with more electron-withdrawing characteristics were significantly more difficult, as noticed with compound **22** which afforded a lower yield in the transformation.





19
84%

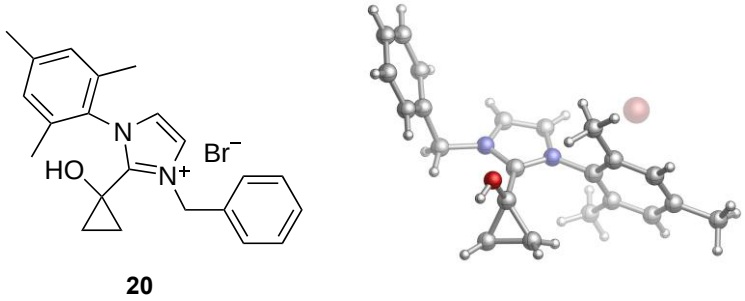
20
78%

21
70%

22
46%

Scheme 2.11: Variation of NHCs towards the formation of cyclopropanone adduct

Gratifyingly, compound **20** could be crystallized and its structure was confirmed via X-Ray analysis.



20

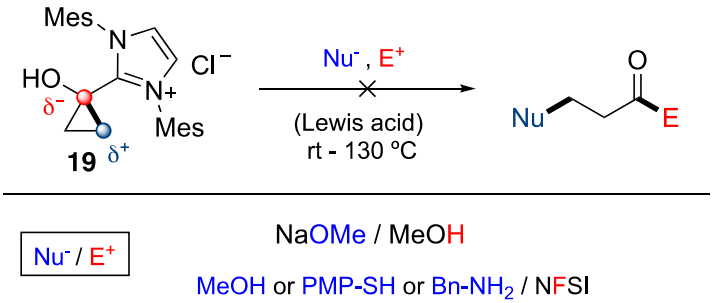
Figure 2.2: X-Ray Crystal Structure of NHC-cyclopropanone adduct **20**

2.4 Nucleophilic ring-opening attempts of NHC-cyclopropanone adduct

After the successful method development of addition of a few NHC adducts towards cyclopropanone, we began efforts to manipulate this novel intermediate for different synthetic reactions. Inspiration for the reactivity of this NHC-cyclopropanone was found in literature reagents of reactivity with similar electrophilic cyclopropanes and their nucleophilic ring-opening reactions. Established donor-acceptor cyclopropanes and Lewis-activated cyclopropanes are known to be electrophilic at the C(2) position due to the polarization of the donor-acceptor character of the adjacent functional groups and the strong electron-withdrawing nature of the Lewis Acid coordination. It was reasonable to hypothesize, therefore, that activated NHC-cyclopropanone adducts **19**-**22** would exhibit similar reactivity towards nucleophiles to ring-open and produce a functionalized product (see Scheme 2.5).

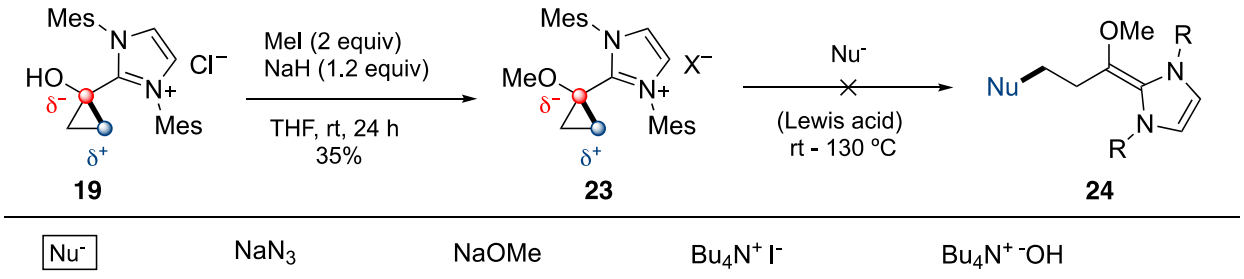
Proper selection of the nucleophile and electrophile is required in order to avoid the reagents reacting with each other instead of the adduct. Therefore, we began investigations with literature-reported one-pot conditions of ring-openings with reagent compatibility. Analysis of these tests consistently showed that the NHC-cyclopropanone adduct does not react under a variety

of reagents and increasingly harsh conditions, with each reaction resulting in the recovery of the starting materials (Scheme 2.12).



Scheme 2.12: One-pot ring-opening attempts of adduct

In light of these results, we speculated that reactivity could be occurring at the hydroxyl group instead of the desired C(2) cyclopropane carbon. The selected reaction conditions, especially the nucleophile, could be deprotonating the alcohol which could interfere with the desired ring-opening by deactivating the electrophilic nature of the cyclopropane region of the substrate. The next logical step was to protect the alcohol in a way that would prevent such hypothesized reactivity; this then allowed us to test this side reaction hypothesis. The IMes·NHC-cyclopropanone adduct **19** was methylated and isolated before subjecting this new variant to even stronger conditions (**23**). This methylated adduct additionally allowed us to study only the first ring-opening step of the reaction by making isolation of the Breslow-type intermediate possible.[6] Reducing the amount of variable reactivity that could interfere with the proposed reaction pathway also permits the use of extremely strong nucleophiles. However, this methylated adduct proved as stable as the previous adduct, with no observed product formation (Scheme 2.13).



Scheme 2.13: Ring-opening attempts of methylated adduct

We hypothesize that there could be several additional factors that play into the stability of this adduct toward ring opening, the first of which could be the steric hinderance of the bulky substituents on the NHC that hinder approach of nucleophiles to the cyclopropane unit. Moreover, the hydroxyl electron-donating capability could be neutralizing, in part, the electron-withdrawing power of the azolium core, which leads to a less polarized C–C bond. Additionally, formation of the Breslow intermediate requires breaking aromaticity of the imidazolium core, which is a less unfavored process. These factors led us to begin efforts to synthesize NHC-cyclopropanone adducts that possess a more electron-withdrawing character (**25**), more polarizing of the C–C bond with an adjacent donor group (**26**), and one that does not contain aromaticity in the azolium core (**15**) (Figure 2.3).

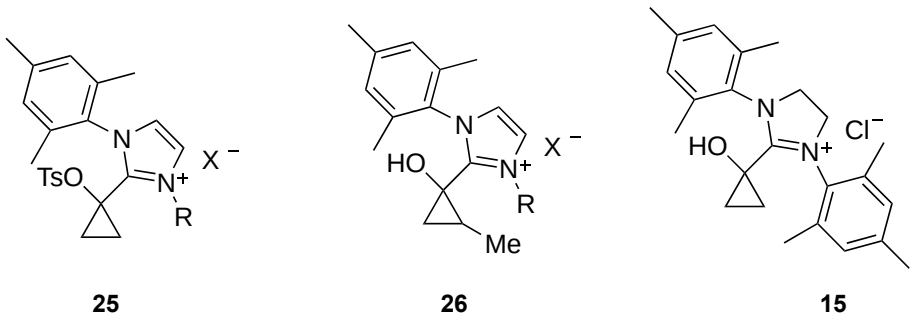
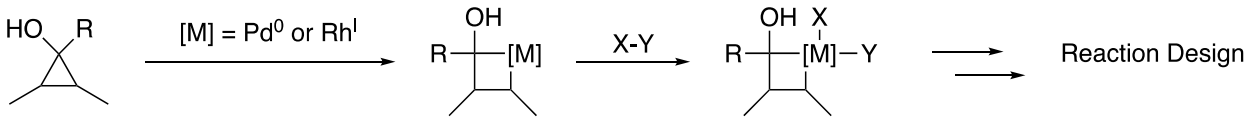


Figure 2.3: Various strategic adducts envisioned to increase ring-opening propensity

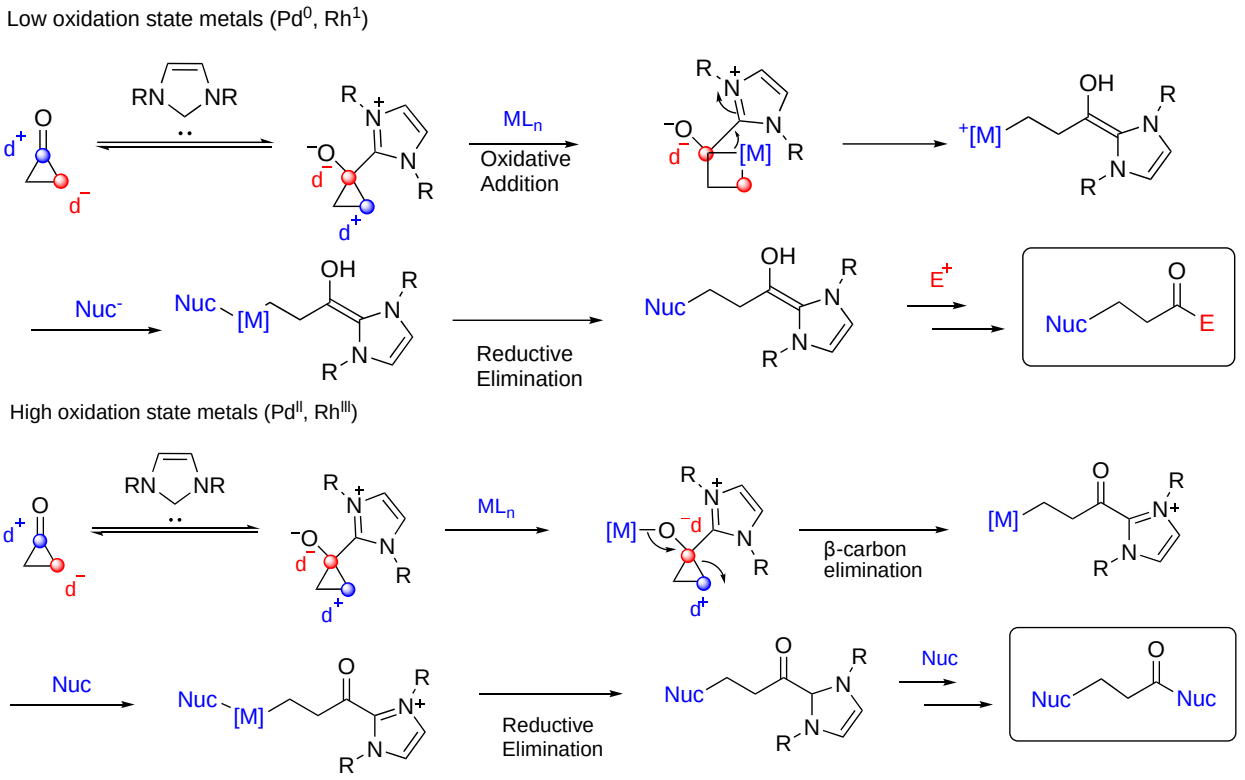
2.5 Transition-metal catalyzed ring-opening attempts of NHC-cyclopropanone adduct

Having formed an adduct analogous to many reported cyclopropanol derivatives, we took further inspiration from reports that use transition-metals to catalyze reactions of comparable strained rings. Low oxidation state metals such as Pd^0 and Rh^I are known to do oxidative addition into strained rings, forming a metallacycle that can drive ring-opening assisted by the high strain release energy of such systems.[7] Furthermore, electrophilic cyclopropanes can react with high oxidation metals (Pd^{II}, Rh^{III}), resulting in a β-carbon elimination pathway that can also promote ring-opening and further react with nucleophiles (Scheme 2.14).



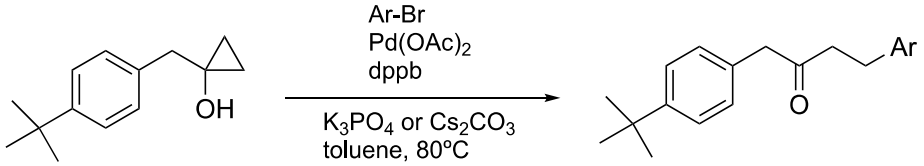
Scheme 2.14: C–C Activation of Cyclopropanols by Transition Metals

In a similar mode of reactivity, we propose that the NHC-cyclopropanone model would be a capable reaction partner to both high- and low-state transition metals and their distinct reaction pathways (Scheme 2.15).



Scheme 2.15: Proposed transition-metal catalyzed ring-opening pathways

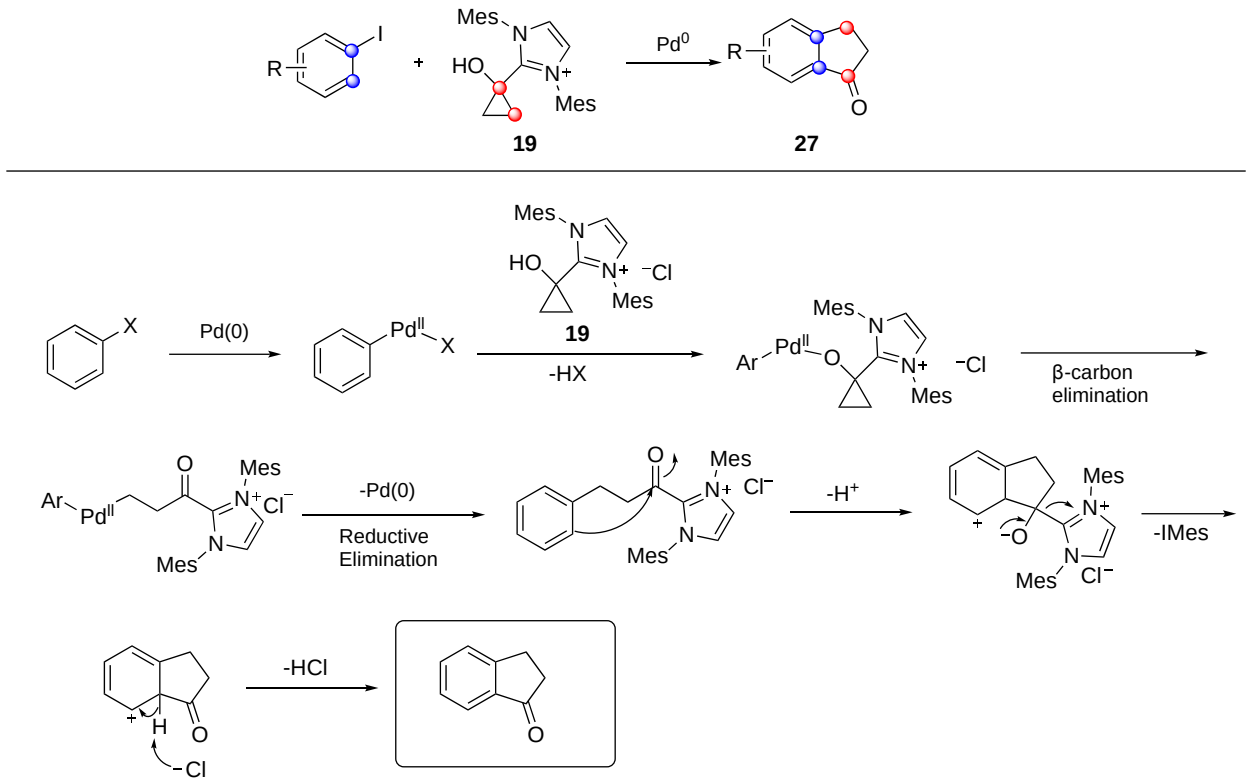
A report that especially caught our attention is work from the Orellana group, utilizing cyclopropanols as cross-coupling partners with aryl bromides for the formation of β-aryl ketones.[8] This tertiary cyclopropanol is similar in both steric hinderance and electronics to the NHC-cyclopropanone adduct, which serves as a comparable model system for transition-metal manipulation (Scheme 2.16).



Scheme 2.16: Palladium-catalyzed cross-coupling of cyclopropanols reported by Orellana

As our first attempts to apply a similar type of chemistry, we sought to exploit the cyclopropanol character of the NHC-cyclopropanone adduct to proceed through a β-carbon

elimination pathway that would then promote an intramolecular cyclization, eventually resulting in an indanone product, resulting overall a formal [3+2] cycloaddition of an aryl halide with cyclopropanone (Scheme 2.17).

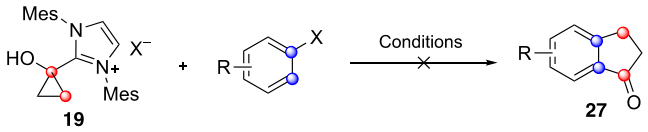


Scheme 2.17: Proposed mechanism to form indanones via NHC-cyclopropanone TM-catalyzed ring-opening.

Initial studies indicated that reactivity of the NHC-cyclopropanone adduct under transition-metal conditions occurred at high temperatures (>80ºC) without the assistance of other ligands or reagents. Combining this information with known cyclopropanol transformations, we explored a variety of palladium-catalyzed reaction conditions as shown in Table 2.4 below. Most notably, we failed to see any product formation under these selected conditions, regardless of the palladium source, coupling partner, or other reaction condition changes, each producing a similar complex mixture of undesired products with various amounts of recovered starting material. As observed

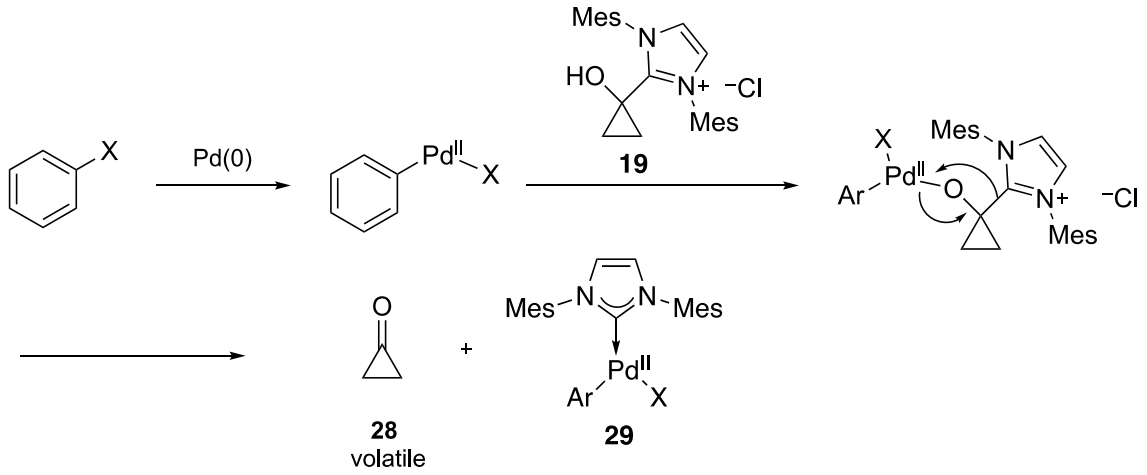
in entries 1 and 2, addition of palladium metals to **19** in the presence of heat was found to liberate protonated IMes as the major product observed.

Table 2.4: Palladium-catalyzed indanone formation attempts



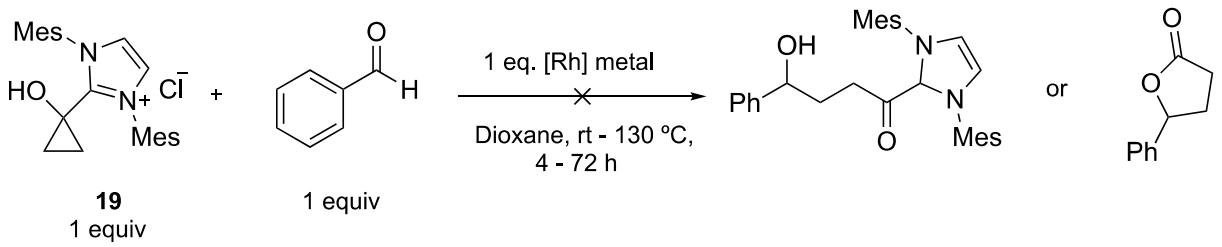
Entry	Ar-X (equiv)	Metal (equiv)	Ligand (equiv)	Base (equiv)	Temp	Time	Solvent	Yield (%)	Note
1	-	$Pd_2(dpa)_3$ (1.0)	-	-	40-100°C	16 h	THF:Tol	N.D	NHC formed
2	-	$Pd(OAc)_2$ (1.0)	-	-	40-100°C	16 h	THF:Tol	N.D	NHC formed
3	Iodobenzene (1.0)	$Pd(OAc)_2$ (0.01)	dppb (0.02)	Cs_2CO_3 (1.0)	80°C	3 h	Tol	N.D	-
4	Bromobenzene (1.0)	$Pd(OAc)_2$ (0.10)	dppb (0.20)	Cs_2CO_3 (2.0)	80°C	4 h	THF:Tol	N.D	-
5	3-methoxy-iodobenzene (1.0)	$Pd_2(dba)_3$ (0.10)	dppb (0.20)	Cs_2CO_3 (2.0)	80°C	6 h	THF:Tol	N.D	-
6	3-methoxy-bromobenzene (1.0)	$Pd_2(dba)_3$ (0.10)	dppb (0.20)	Cs_2CO_3 (2.0)	80°C	6 h	THF:Tol	N.D	-
7	3-methoxy-phenylboronic acid (1.0)	$Pd_2(dba)_3$ (0.10)	dppb (0.20)	Cs_2CO_3 (2.0)	80°C	6 h	THF:Tol	N.D	-
8	3-methoxy-bromobenzene (1.0)	$Pd(PPh_3)_4$ (0.10)	dppb (0.20)	Cs_2CO_3 (2.0)	80°C	18 h	THF:Tol	N.D	SM recovered

We hypothesize that, instead of the desired β-carbon elimination pathway with cleavage of the cyclopropanol C–C bond, elimination could be occurring at the bond between the cyclopropanol and the C(2) of the NHC. This would result in liberation of the free and volatile cyclopropanone **28**, along with the NHC-palladium coordinated byproduct **29** (Scheme 2.18). This reactivity could explain the results of these experiments between our adduct and various palladium sources.



Scheme 2.18: Possible undesired reactivity between palladium and NHC-cyclopropanol adduct

With this new information in hand, we opted to investigate if a change in the metal source would produce desired reactivity. Rhodium(I) complexes have been known in the literature to insert into strained C–C bond, especially into cyclobutane ring systems, and perform inter- and intramolecular cycloadditions and rearrangements.[9] Rhodium insertion in our cyclopropanol equivalent could occur, and we hypothesized the resulting intermediate could be trapped with an electrophile such as benzaldehyde. This product could exist as the homo-enolate product or the cyclized lactone, depending on whether the NHC is eliminated at the end of the reaction (Scheme 2.19). However, even with a range of rhodium (I) and (III) sources, this desired product was never observed. We can conclude from these tests that rhodium either cannot insert into our C–C cyclopropanol bond or insertion does not lead to any ring-opening or rearrangement activity.

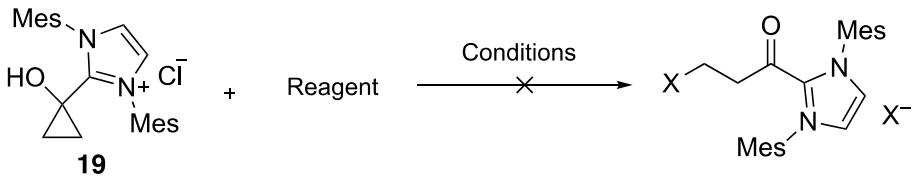


Scheme 2.19: Rhodium-catalyzed ring-opening attempts

2.6 Miscellaneous ring-opening attempts of NHC-cyclopropanone adduct and future work

Proving to be unpredictably stable, we subjected our NHC-cyclopropanone adduct to various catalytic conditions in hopes of observing similar reactivity of cyclopropanols known in the literature.[10] These conditions ranged from reacting the adduct with electrophiles and UV light, which would probe any possible reactivity of the hydroxy group in ring-opening of the cyclopropane, to microwave irradiation and photocatalytic chemistry to further investigate C–C bond cleavage. Reactivity, however, was not observed in most reactions and starting material **19** was recovered, with only a few reactions affording starting material decomposition (Table 2.5).

Table 2.5: Miscellaneous ring-opening attempts



Entry	Reagent	Temp	Solvent	Time	Additive	Result
1	Selectfluor, hv	50ºC	MeCN	16 h	Xanthone	N.D.
2	Selectfluor	rt	DCM/H_2O	24 h	$AgNO_3$	N.R.
3	AgF_2	-15ºC	DCE	24 h	-	N.R.
4	242 nm hv	rt	MeCN	48 h	Xanthone	N.R.
5	Selectfluor	rt	DCM/H_2O	24 h	$Fe^{III}(acac)_3$	N.R.
6	Microwave	150ºC	DMSO	20 mins	-	N.D.

There is a plethora of ongoing work still to be investigated in our group regarding this project of ring-opening reactions of a NHC-strained ring intermediate. In addition to the use of more reactive NHC-cyclopropanone adducts mentioned in Figure 2.4, more work is needed to try to override the possible undesired liberation of free cyclopropanone in transition-metal-catalyzed reactions. Different metals and their corresponding ligands could have a significant steric influence

in the direction of desired reactivity. Moreover, NHC addition to form a cyclobutanone adduct (analogous to the cyclopropanone adduct) could have unique reactivity that would still utilize the aforementioned chemistry. This would be beneficial in the sense that there are several known cyclobutanone C–C bond cleavage reactions specifically regarding transition metals.[11]

2.7 Conclusions

We successfully have developed a method for the formation of a stable, yet more reactive cyclopropanone starting material and examined its reactivity toward a variety of N-Heterocyclic carbenes. By synthesizing and evaluating a library of different NHCs, we have established a reliable methodology for the formation of an NHC-cyclopropanone adduct via nucleophilic attack of the IMes carbene towards the cyclopropanone sulfinic acid precursor. Initial examination of nucleophilic and transition-metal catalyzed ring-opening has revealed the unexpected stability of the synthesized NHC-cyclopropanone adduct. Future work could attempt to overcome this by altering the NHC-cyclopropanone adduct to promote nucleophilic ring-opening (Figure 2.3) and by continuing to evaluate unexamined transition-metal catalyzed ring-opening reaction conditions.

2.8 Experimental Section

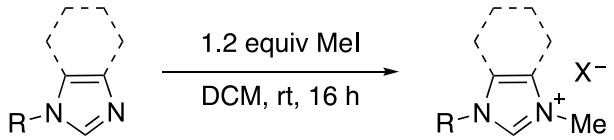
General: Unless stated otherwise, all non-aqueous reactions were performed in oven-dried glassware sealed with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stir bars. Liquid reagents and solvents were transferred by syringe using standard Schlenk techniques. Tetrahydrofuran (THF), toluene (PhMe), acetonitrile (MeCN), Dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), chloroform ($CHCl_3$), and methanol (MeOH) were dried by passage over a column of activated alumina (solvent filtration system). DMF was

obtained in a Sure Seal bottle from Aldrich. All other solvents and reagents were used as received unless otherwise noted. Thin layer chromatography was performed using Silicycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde, potassium permanganate, or iodine stain. Sorbent silica gel (particle size 40-63 μm) was used for flash chromatography of the indicated solvent system according to standard techniques. Nuclear magnetic resonance (NMR) spectra (^{1}H, ^{13}C) were recorded on Bruker spectrometers operating at 700 MHz for ^{1}H and ^{13}C experiments, or using Variant spectrometers at 300 MHz for ^{1}H. Chemical shifts (δ) for ^{1}H NMR spectra are recorded in parts per million with the solvent resonance as the internal standard (chloroform, δ 2.54 ppm or dimethylsulfoxide, δ 2.54 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), coupling constant in Hz, and integration. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million using the central peak of deuterochloroform (δ 77.16 ppm) as the internal standard. All spectra were obtained with complete proton decoupling. Only select ^{1}H and ^{13}C spectra are reported. Infrared (IR) spectra were collected on a Thermo Scientific Nicolet iS5 instrument using attenuated total reflectance (ATR) mode and signals are reported in reciprocal centimeters (cm^{-1}). Only selected IR frequencies are reported. Low and high-resolution mass spectral data were obtained from the North Carolina State University Mass Spectral Facility, on a *Thermo Fisher Scientific Exactive Plus MS*, a benchtop full-scan Orbitrap™ mass spectrometer – using Heated Electrospray Ionization (HESI).

Reagents: NMI, MeI, Benzothiazole, Benzoxazole, Acetamide Hydrochloride, Ethanol, NaOMe, Formic Hydrazide, CuI, Cs_2CO_3, Iodobenzene, Benzyl Bromide, Butyl Iodide, (1-ethoxycyclopropoxy)trimethylsilane, $PhSO_2Na$, Formic Acid, 5-6N HCl, IMes·HCl, NaH (60%

dispersion in mineral oil) were purchased from commercial sources and used without further purification.

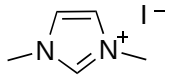
GENERAL PROCEDURE A: Synthesis of methylated imidazole salts



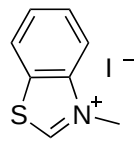
A flame-dried 5 mL microwave vial was equipped with a magnetic stirbar was charged with the imidazole reagent (1.0 mmol, 1.0 equiv), then capped with a microwave cap and flushed with N_2. Added DCM (3 mL), then methyl iodide (1.20 mmol, 1.20 equiv), and the resulting mixture was stirred at rt for 16 h. The reaction mixture was then concentrated under vacuum to afford the pure bis(azolium) product unless otherwise noted.

Specific procedures and characterization data methylated NHCs

1,3-dimethyl-1*H*-imidazol-3-ium iodide (4). 1-methylimidazole (0.403 mL, 5.0 mmol, 1.0 equiv) was added to a 5mL microwave vial flushed with N_2, followed by DCM (0.1 mL). MeI was added under N_2 over the course of 30 min, and then the mixture was stirred at room temperature for 1 h. The reaction mixture was then concentrated under vacuum to afford the pure product (811 mg, 72%) without further purification. All analyses were consistent with previously reported data.[12]

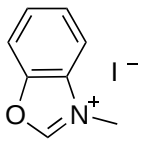


3-methylbenzo[*d*]thiazol-3-ium iodide (11). General procedure A for the synthesis of methylimidazole salts was followed, starting with benzothiazole (0.545 mL, 5.0 mmol, 1.0 equiv), MeI (0.373 mL, 6 mmol, 1.2 equiv) and DCM (1mL) for 48 h instead of 24 h, affording the product (663 mg, 88% yield) after purification by flash

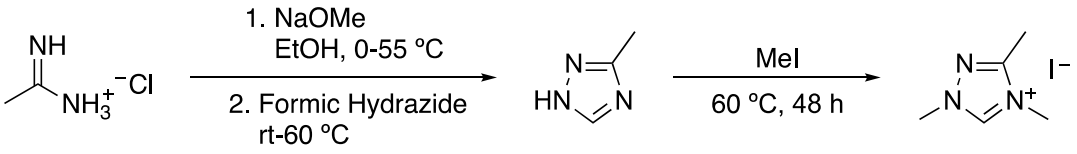


chromatography, eluting with 5-20% MeOH in DCM (elution gradient). All analyses were consistent with previously reported data.[13]

3-methylbenzo[*d*]oxazol-3-ium iodide (5). General procedure A for the synthesis of methylimidazole salts was followed, starting with benzoxazole (0.595 mL, 5.0 mmol, 1.0 equiv), MeI (0.684 mL, 11 mmol, 2.2 equiv), and DCM (1mL) for 48 h at 45 °C, affording the product (159.6 mg, 24% yield) after purification by flash chromatography, eluting with 5-20% MeOH in DCM (elution gradient). All analyses were consistent with previously reported data.[14]

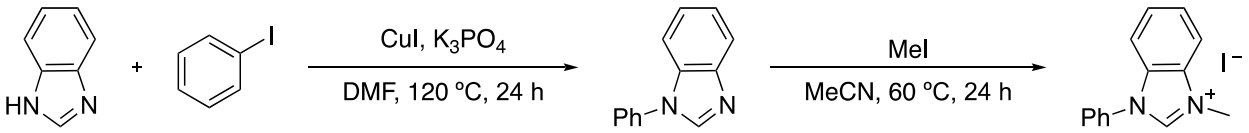


1-mesityl-3-methyl-1*H*-imidazol-3-ium iodide (10). General procedure A for the synthesis of the methylimidazole salt was followed, starting with the production of 1-mesityl-1*H*-imidazole (1.15 g, 62% yield) prepared according to literature procedure.[18] To this product (0.93 mg, 0.5 mmol, 1.0 equiv) was added MeI (0.050 mL, 0.80 mmol, 1.6 equiv) and stirred at room temperature for 16 h, affording the product (163 mg, 99% yield) after purification by flash chromatography, eluting with 1-20% MeOH in DCM (elution gradient). All analyses were consistent with previously reported data.[17]



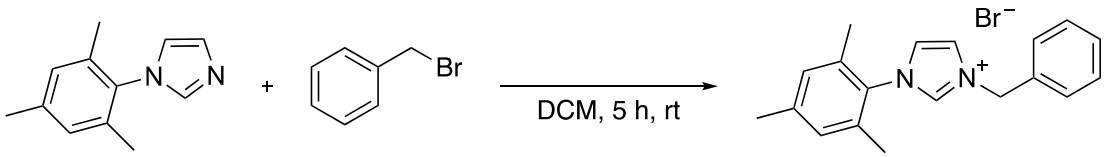
1,3,4-trimethyl-1*H*-1,2,4-triazol-4-ium iodide (6). Synthesis of the triazole salt **6** was synthesized in multiple steps, where acetamide hydrochloride (2.39 g, 25 mmol, 1.0 equiv) and ethanol (35 mL) were added to a dried and N_2 purged 100 mL RBF at 0 °C. NaOMe (1.35 g, 25

mmol, 1 equiv) was then added to the stirred reaction mixture under N_2 at 0 °C, followed by formic hydrazide (1.50 g, 25 mmol, 1 equiv), which was stirred at 55 °C for 16 h. Crude product was cooled to room temperature, filtered over celite and washed with butyl acetate (3 x 10 mL), and concentrated under vacuum to afford 3-methyl-1*H*-1,2,4-triazole (2.07 g, 99% yield). To this product (720 mg, 7 mmol, 1 equiv) was added MeI (1.74 mL, 28 mmol, 4 equiv) in MeCN (2 mL) in a dried, N_2-purged 5 mL microwave vial, and stirred at 60 °C for 48 h, affording the product (296.4 mg, 28% yield) after purification by flash chromatography, eluting with 10-30% MeOH in DCM (elution gradient). All analyses were consistent with previously reported data.[15]

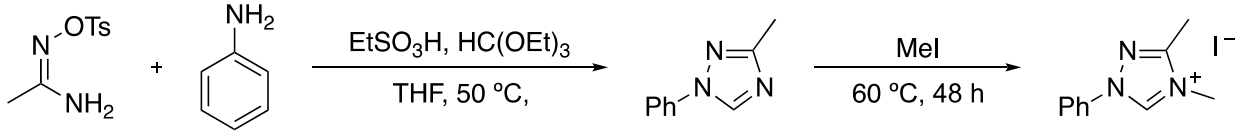


3-methyl-1-phenyl-1*H*-benzo[*d*]imidazol-3-ium iodide (12). Synthesis of the benzimidazole salt **12** was synthesized in multiple steps, where benzimidazole (118 mg, 0.1 mmol, 1.0 equiv), CuI (9.52 mg, 0.05 mmol, 0.05 equiv), Cs_2CO_3 (651.6 mg, 2.0 mmol, 2.0 equiv), then iodobenzene (0.134 mL, 1.2 mmol, 1.2 equiv) were added to a dried and N_2 purged 5 mL microwave vial in DMF (2 mL). Mixture was stirred at 110 °C for 24 h and then allowed to cool to room temperature. The resulting mixture was then quenched with water, extracted with Et_2O (3 x 20 mL). The combined organic fractions were washed with brine (4 x 20 mL), dried over $MgSO_4$, and concentrated under vacuum to give the crude salt, which was purified by flash chromatography of 2-15% MeOH in DCM (elution gradient), affording the *N*-phenylbenzimidazole product (99.0 mg, 51% yield). To this product (66 mg, 0.34 mmol, 1 equiv) was added MeI (.043 mL, 0.68 mmol, 2 equiv) and MeCN (1 mL) in a dried, N_2-purged 2 mL microwave vial and stirred at 60 °C for 24 h. The resulting mixture was concentrated under vacuum, purified by flash chromatography,

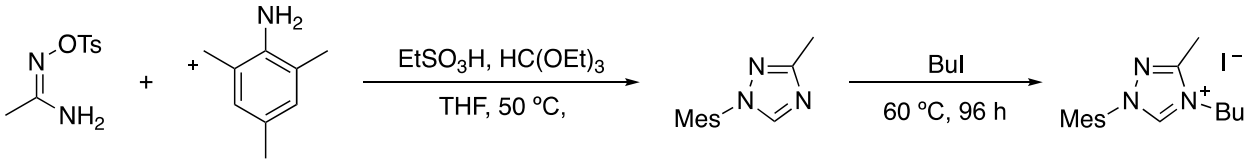
eluting with 2-15% MeOH in DCM (elution gradient), affording the pure product (198.3 mg, 92% yield). All analyses were consistent with previously reported data.[17]



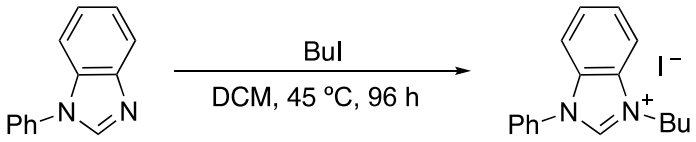
3-Benzyl-1-mesityl-1*H*-imidazol-3-ium bromide (9). Synthesis of the 1-mesityl-1*H*-imidazole (1.15 g, 62% yield) was prepared according to literature procedure.[18] 1-mesityl-1*H*-imidazole (200 mg, 1.07 mmol, 1.0 equiv), was added to a dried and N_2 purged 2 mL microwave vial in DCM (1 mL). Benzyl bromide (0.237 mL, 2.14 mmol, 2 equiv) was added at room temperature over five min, then the mixture was stirred at room temperature for 5 h. The resulting mixture was concentrated under vacuum, purified by flash chromatography, eluting with 2-20% MeOH in DCM (elution gradient), affording the pure product (365.1 mg, 95% yield). All analyses were consistent with previously reported data.[18]



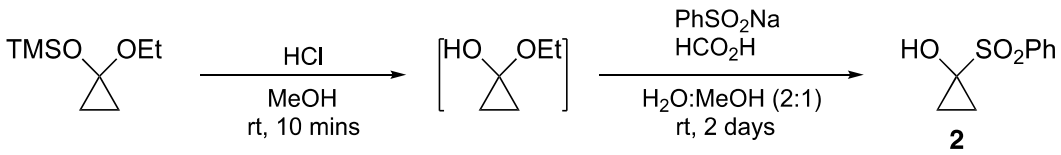
3,4-dimethyl-1-phenyl-1*H*-1,2,4-triazol-4-ium iodide (7). 3-methyl-1*H*-1,2,4-triazole (242.5 mg, 35% yield) was synthesized according to literature procedure.[19] To this product (66 mg, 0.34 mmol, 1 equiv) was added MeI (.043 mL, 0.68 mmol, 2 equiv) and MeCN (1 mL) in a dried, N_2-purged 2 mL microwave vial and stirred at 60 °C for 24 h. The resulting mixture was concentrated under vacuum affording the pure product (66.0 mg, 98% yield). All analyses were consistent with previously reported data.[19]



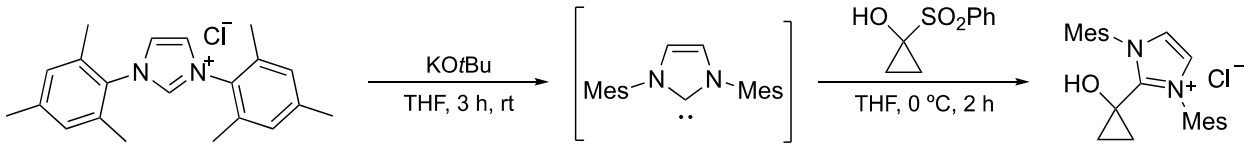
4-butyl-3-methyl-1-phenyl-1*H*-1,2,4-triazol-4-ium iodide (8). 3-methyl-1*H*-1,2,4-triazole (242.5 mg, 35% yield) was synthesized according to literature procedure[19]. To this product (242.5 mg, 1.20 mmol, 1 equiv) was added butyl iodide (.342 mL, 3.01 mmol, 2.5 equiv) and MeCN (2 mL) in a dried, N_2-purged 5 mL microwave vial and stirred at 60 °C for 96 h. The resulting mixture was concentrated under vacuum, purified by flash chromatography, eluting with 2-15% MeOH in DCM (elution gradient), affording the pure product (120.4 mg, 39% yield). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 11.30 (s, 1H), 7.05 (s, 2H), 4.73 (t, *J* = 7.5 Hz, 2H), 2.95 (s, 3H), 2.70 (s, 3H), 2.11 (s, 6H), 2.06 – 1.86 (m, 2H), 1.52-1.42 (m, 2H), 1.01 (t, *J* = 7.3 Hz, 3H).



3-butyl-1-phenyl-1*H*-benzo[*d*]imidazol-3-ium (13). *N*-phenyl-benzimidazole was synthesized according to previous procedure reports for **12**. To this product (133.9 mg, 0.69 mmol, 1.0 equiv) was added butyl iodide (0.235 mL, 2.07 mmol, 3 equiv) and DCM (1.5 mL) in a dried, N_2-purged 5 mL microwave vial and stirred at 45 °C for 96 h. The resulting mixture was concentrated under vacuum, purified by flash chromatography, eluting with 2-20% MeOH in DCM (elution gradient), affording the pure product (195.9 mg, 75% yield). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 11.06 (s, 1H), 7.96 – 7.85 (m, 2H), 7.85 – 7.76 (m, 2H), 7.76 – 7.60 (m, 5H), 4.90 (t, *J* = 7.5 Hz, 2H), 2.21 – 1.99 (m, 2H), 1.57-1.43 (m, 2H), 1.02 (t, *J* = 7.3, 1.0 Hz, 3H).

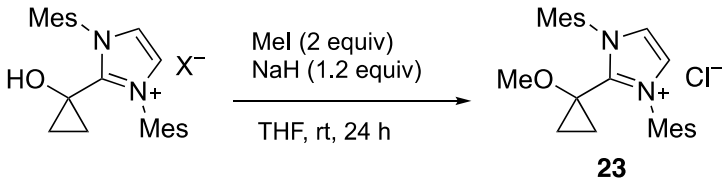


1-(phenylsulfonyl)cyclopropan-1-ol (2). To a flame-dried 20 mL microwave vial was purged with N_2, then added MeOH (3 mL), (1-ethoxycyclopropoxy)trimethylsilane (1.15 mL, 5.74 mmol, 1 equiv), and then 5-6N HCl (2 drops) under N_2. Mixture was stirred at room temperature for 10 mins, then added $PhSO_2Na$ (1.88 g, 11.48 mmol, 2 equiv), formic acid (2.16 mL, 57.4 mmol, 10 equiv) and H_2O (6 mL) and stirred at room temperature for 48 h. The resulting mixture was then extracted with DCM (3 x 20 mL) and the combined organic fractions were dried over $MgSO_4$, filtered over a plug of cotton, and concentrated under vacuum, affording a white solid pure product without further purification (1.05 g, 92% yield). All analyses were consistent with previously reported data.[5]



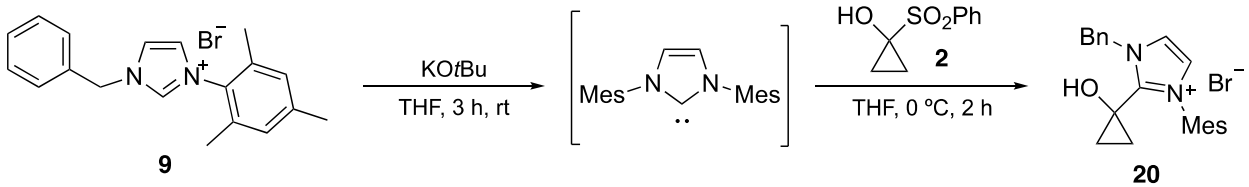
2-(1-hydroxycyclopropyl)-1,3-dimesityl-1*H*-imidazol-3-ium chloride (19). To a flame-dried 100 mL RBF was added IMes·HCl (500 mg, 1.47 mmol, 1.0 equiv) and KO*t*Bu (329 mg, 2.93 mmol, 2.0 equiv) under a N_2 environment and capped. THF (25 mL) was added under N_2 and mixture was stirred at room temperature for 3 h. Reaction was then cooled to 0 °C for 20 min, and a solution of 1-(phenylsulfonyl)cyclopropan-1-ol (581.6 mg, 2.93 mmol, 2.0 equiv) in THF (5 mL) was added under N_2 at 0 °C and stirred for 2 h. The resulting mixture was then quenched at 0 °C with 10 drops H_2O and extracted with DCM (3 x 20 mL). The combined organic fractions were washed with brine (3 x 20 mL), dried over $MgSO_4$, filtered over a plug of cotton, and concentrated under vacuum, affording a pure product after purification by flash chromatography, eluting with

2-20% MeOH in DCM (elution gradient) (490.3 mg, 84% yield). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.27 (m, 2H), 7.10 – 7.04 (m, 4H), 5.30 (s, 1H), 2.38 (s, 6H), 2.20 – 2.16 (s, 12H), 1.40 – 1.29 (m, 2H), 0.56 – 0.48 (m, 2H).



23

1,3-dimesityl-2-(1-methoxycyclopropyl)-1*H*-imidazol-3-ium chloride (23). To a flame-dried 2 mL microwave vial was added 2-(1-hydroxycyclopropyl)-1,3-dimesityl-1*H*-imidazol-3-ium chloride (20.0 mg, 0.048 mmol, 1 equiv), MeI (0.00579 mL, 0.096 mmol, 2.0 equiv), and THF (1mL) and flushed with N_2. NaH (60% dispersion in mineral oil, 2.39 mg, 0.058 mmol, 1.2 equiv) was then added and mixture was stirred at room temperature for 24 h. The resulting mixture was then quenched with 4 drops H_2O and concentrated under vacuum, affording pure product after purification by flash chromatography, eluting with 2-20% MeOH in DCM (elution gradient) (6.8 mg, 35% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.28 – 7.22 (m, 2H), 7.09 (m, 4H), 3.05 (d, *J* = 1.9 Hz, 3H), 2.39 (s, 6H), 2.13 (s, 12H), 1.08 – 0.99 (m, 2H), 0.78 – 0.70 (m, 2H).



9 **20**

3-benzyl-1-mesityl-1*H*-imidazol-3-ium bromide (20). To a flame-dried 5 mL microwave vial was charged **9** (18.02 mg, 0.0504 mmol, 1.0 equiv), KO*t*Bu (11.03 mg, 0.101 mmol, 2.0 equiv), capped and flushed with N_2, and added 0.80 mL THF. Stir mixture at room temperature for 3 h. Cool reaction mixture to 0 °C for 5 mins and add solution of **2** (20 mg, 0.101 mmol, 2 equiv) in

THF (0.20 mL) under N_2 and stir at 0 °C for 2 h. Resulting mixture was then concentrated under vacuum, affording a pure product after purification by flash chromatography, eluting with 2-20% MeOH in DCM (elution gradient) (14.3 mg, 78% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 2.1 Hz, 1H), 7.45 – 7.35 (m, 5H), 7.05 (d, *J* = 2.1 Hz, 1H), 6.10 (s, 2H), 5.28 (s, 1H), 2.35 (s, 3H), 2.05 (s, 6H), 1.37 – 1.28 (m, 2H), 0.70 – 0.53 (m, 2H).

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CHAPTER 3

Simple and Expedient Synthesis of bis(azolium)dichloride Salts from dichloromethane and imidazoles

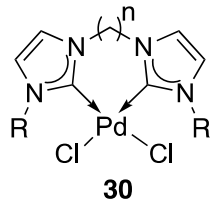
Abstract: Bis(azolium)dichloride Salts are excellent precursors for metal bis(carbenes) as ligands for metal-catalyzed processes such as cross-coupling reactions. However, the synthesis for the formation of such salts is inefficient. New reaction kinetics and mechanistic studies have inspired us to develop a novel method for the improved synthesis of bis(azolium) salts in excellent yields, applicable to a wide-scope of heterocyclic cores. Applications of this method include the synthesis of metal bis(carbenes) in a one-pot reaction directly from imidazoles.

3.1 History and Synthetic Problems of bis(azolium)dichloride Salts

NHCs have been widely used in recent years as an alternative to phosphine ligands for metal catalysis, exhibiting characteristics similar to other strong σ-donating ligands in metal coordination chemistry that have the ability to bind to practically any transition metal. More importantly, these ligands are commonly employed in metal-catalyzed reactions due to their enhanced stability and tolerance of harsh reaction such as high temperatures and moisture. The Nolan group concluded that NHCs "behave as better donors than the best phosphane ligands with the exception of sterically demanding (adamantyl) carbene".[1] Due to their application in C–H functionalization, C–C, C–N, and C–O bond formation, straightforward and high-yielding methods for their synthesis are highly valuable.

While there are many known methods for the synthesis of monodentate NHCs, less is known about the synthesis and application of alkane-bridged chelating bis(carbenes). These chelated carbenes are similarly stable but less explored due to the limited known procedure for variability in alkane bridge length and limited studies of coordination to metal other than palladium and platinum.[2] Recent reports have shown, however, examples of a range of metal coordination to

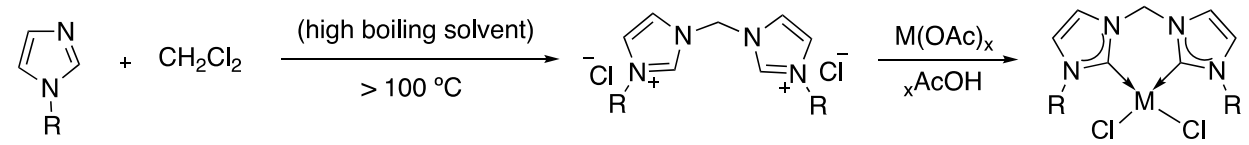
alkane-bridged biscarbene ligands such as rhodium, iridium, and ruthenium. [3] Complex **30** depicts a representative palladium-bound bis(azolium)chloride NHC (Figure 3.1).



30

Figure 3.1: Chelated bisNHC model system

The known methodology for the formation of bridged bisNHC-dichloride complexes involves the use of two equivalents of a heterocyclic core such as 1-methylimidazole as a nucleophilic reagent that preforms two consecutive S_N2 reaction on the selected dichloroalkane of choice, yielding the alkyl-bridged bisimidazoliumdichloride salt. This salt can then coordinate to a metal to produce the corresping metal bis(carbene)dichloride.[4] This reaction also works using dibromomethane and diiodomethane for the synthesis of the resulting dibromo or diiodosalts; however, these salts are much less useful due to the instability of the corresponding metalbis(carbene)dibromide or diiodide complex.[5]

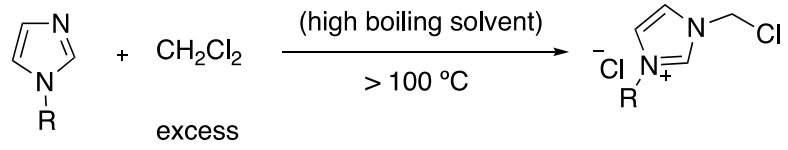


2 equiv 1 equiv **< 65%**

Scheme 3.1: Reaction system for the formation of bis(azolium)chloride salts

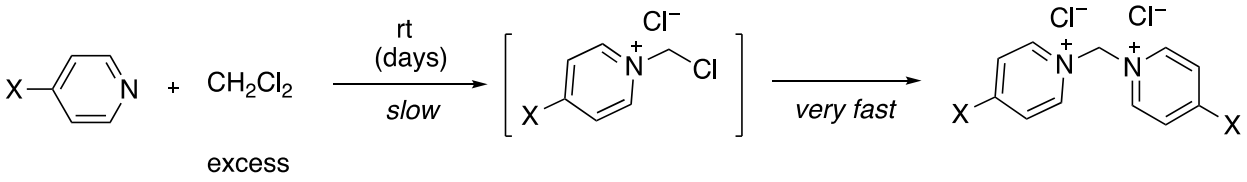
While this synthetic route does afford the desired product, notable problems exist in the efficiency of this reaction with CH_2Cl_2. The use of high temperatures for a prolonged period of time in combination with the use of volatile reactants such as CH_2Cl_2 can result in the loss of reagent equivalents and the ensuing lower yield. Previous literature studies suggest that only one

equivalent of chloroalkane should be used in fear of the reaction stopping at the undesired monosubstituted intermediate.



Scheme 3.2: Proposed undesired monosubstituted product using excess CH_2Cl_2 as reagent

This aforementioned hypothesis relies on the assumption that both of the S_N2 steps to furnish the bis(azolium) salt are proceeding at the same rate, in which it would make chemical sense that the reaction would stop at the monosubstituted intermediate. However, a recent report by the Wamser group studied the reaction kinetics of dichloromethane with pyridine derivatives and determined different reaction kinetics of the two substitution steps. They report second-order rate constants of 2.56(±0.06) for the first substitution and 4.29(±0.01) for the second substitution step,[6] indicating that the second S_N2 step is much faster than the first. The report goes on to clarify that the monosubstitution product of the reaction could not be isolated or detected in any instance during the reaction.



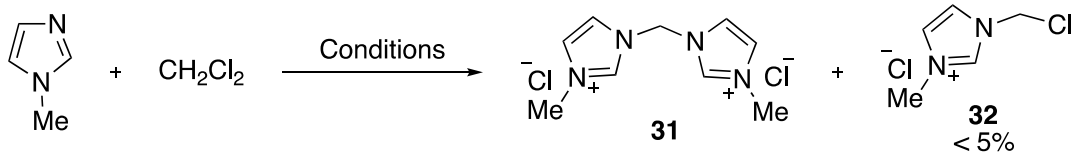
Scheme 3.3: Literature reaction kinetic studies of pyridine and excess CH_2Cl_2

3.2 Methodology development of bis(azolium) Salts for Metal Catalysis

Due to the similar nucleophilicities of pyridine (N=12.0) and imidazole derivatives (N=11.90), we hypothesized that similar kinetics would be true for the nucleophilic reaction of imidazole with excess CH_2Cl_2 that would allow for an optimized methodology to improve yields

for the formation of such bisimidazolium chloride salts. Initial reaction optimization studied began with 1-methylimidazole as the imidazole core model with large excesses of CH_2Cl_2 as the dichloroalkane at 70°C for a period of 24 hours, performed in a sealed microwave reaction vial (work of Kyle Penn). A screen of co-solvents showed that DMSO demonstrated slightly improved yields, presumably due to its high polarity, allowing improved stabilization of the S_N2 transition state. When the temperature was steadily increased, so did the yield, maximizing to an impressive 92% yield at high concentration. This yield was produced in conditions containing three equivalents of CH_2Cl_2 in a 4.0M concentration with DMSO as the co-solvent (Table 3.1). This study helped to validate the hypothesis that an excess of dichloromethane can be used without the reaction stopping at the monosubstituted intermediate **32**.[6]

Table 3.1: Optimization studies for the formation of bisimidazolium chloride complex

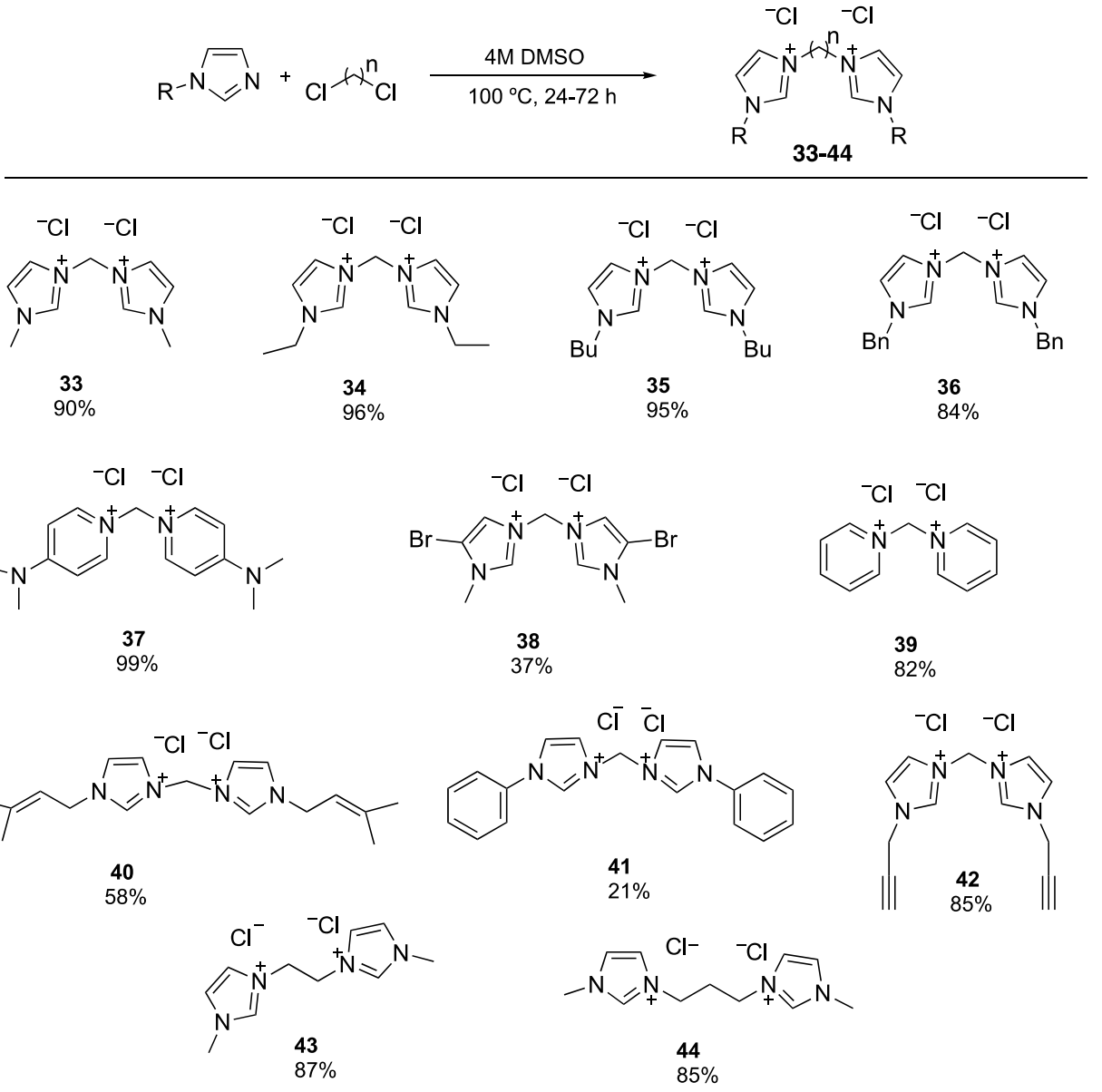


Entry	Temp (°C)	DCM equiv (mL)	Conc. (M)	Co-Solvent (mL)	NMR yield (%)
1	70	7.8 (5)	2.0	-	14
2	70	3.0 (0.38)	2.0	Tol (3.1)	2
3	70	3.0 (0.38)	2.0	Et_2O	3.5
4	70	3.0 (0.38)	2.0	DMSO	16
5	90	3.0 (0.38)	2.0	DMSO	55
6	90	3.0 (0.77)	3.0	DMSO	76
7	90	3.0 (0.77)	4.0	DMSO	84
8	100	3.0 (0.77)	4.0	DMSO	92

3.3 The Synthesis of bis(azolium) salts: Scope Expansion

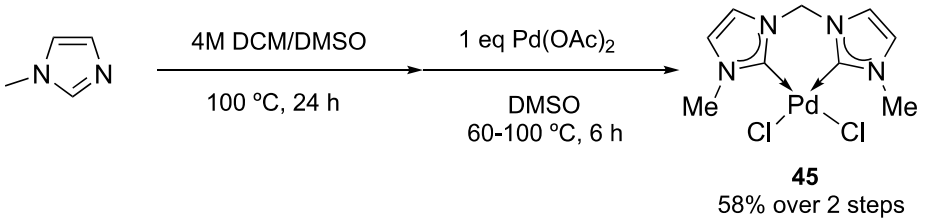
After determination of an improved methodology for the formation of the model bisimidazoliumdichloride salt **31**, we expanded the optimized reaction conditions to a variety of substitution patterns of imidazole cores as well as examining a diverse array of *N*-heterocycles. Gratifyingly, similar improved yields were observed for our scope expansion with various alkyl-functionalized imidazoles (**34**-**36**) and other common *N*-heterocycles (Scheme 3.4). Compounds such as **38** and **41** were synthesized in noticably lower yield due to lower nucleophilicity of the imidazole precursor. In addition to imidazole cores, pyridine derivatives **37** and **39** are produced in excellent yields. Exteneded alkane bridge lengths **43** and **44** to two and three-carbon chains were also synthesized in good yields using dichloroethane and 1,3-dichloropropane as the dichloroalkane reagents.

Scheme 3.4: Scope study of optimized reaction methodology toward diverse *N*-heterocycles.



To fully apply this chemistry, we proposed that we could synthesize the bisNHC-palladium-chloride complex **45** in a one-pot reaction by utilizing the chemistry developed so far. Indeed, the formation of metal bis(carbene) complexes is reported to be effective in DMSO at high temperature, similar to our conditions for the bis(azolium)dichloride salts from imidazole.[4] This could allow for the synthesis of metal bis(carbenes) to be made directly from the imidazole starting

material, an efficient and greatly improved reaction application. With inspiration from previous literature reports of the synthesis of the bisNHC-palladiumdichloride complexes starting from the alkane-bridged bisimidazoles,[4] we were able to produce the palladium(biscarbene) in one-pot starting from 1-methylimidazole and CH_2Cl_2 (Scheme 3.5).



Scheme 3.5: One-pot formation of metal(biscarbene) directly from imidazole

3.4 Conclusions

We report an improved and convenient methodology for the synthesis of bis(imidazolium)dichloride salts using an excess of dichloroalkanes without the formation of the undesired monosubstituted intermediate. This methodology can be applied to a diverse array of *N*-heterocycles with varying substitution and alkane bridge length. Moreover, we have demonstrated a one-pot synthesis of bisNHC-palladium complex directly from 1-methylimidazole applying the same reaction conditions. Future work will involve expanding our scope to additional *N*-heterocycles as well as developing additional one-pot reactions for the formation of metal bis(carbenes) with other metals such as copper, nickel, and iron.

3.5 Experimental Section

General: Unless stated otherwise, all non-aqueous reactions were performed in oven-dried glassware sealed with rubber septa under a nitrogen atmosphere and were stirred with Teflon-

coated magnetic stir bars. Liquid reagents and solvents were transferred by syringe using standard Schlenk techniques. Tetrahydrofuran (THF), toluene (PhMe), acetonitrile (MeCN), Dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), chloroform ($CHCl_3$), and methanol (MeOH) were dried by passage over a column of activated alumina (solvent filtration system). 1,2-dichloroethane (DCE) was obtained in a Sure Seal bottle from Aldrich. All other solvents and reagents were used as received unless otherwise noted. Thin layer chromatography was performed using Silicycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde, potassium permanganate, or iodine stain. Sorbent silica gel (particle size 40-63 μm) was used for flash chromatography of the indicated solvent system according to standard techniques. Nuclear magnetic resonance (NMR) spectra (^1H, ^{13}C) were recorded on Bruker spectrometers operating at 700 MHz for ^1H and ^{13}C experiments, or using Varient spectrometers at 300 MHz for ^1H. Chemical shifts (δ) for ^1H NMR spectra are recorded in parts per million with the solvent resonance as the internal standard (dimethylsulfoxide, δ 2.54 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), coupling constant in Hz, and integration. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million using the central peak of deuterochloroform (δ 77.16 ppm) as the internal standard. All spectra were obtained with complete proton decoupling. Only select ^1H and ^{13}C spectra are reported. Infrared (IR) spectra were collected on a Thermo Scientific Nicolet iS5 instrument using attenuated total reflectance (ATR) mode and signals are reported in reciprocal centimeters (cm^{-1}). Only selected IR frequencies are reported. Low and high-resolution mass spectral data were obtained from the North Carolina State University Mass Spectral Facility, using a *Thermo Fisher Scientific Exactive Plus MS*, a benchtop full-scan Orbitrap™ mass spectrometer.

Reagents: NMI, N-butylimidazole, N-ethylimidazole, DMAP, 5-bromo-1-methylimidazole, pyridine, N-benzylimidazole, DCE, propyl bromide, and dichloropropane were purchased from commercial sources and used without further purification.

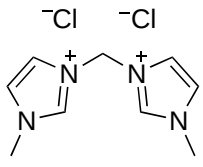
GENERAL PROCEDURE A: Synthesis of bis(azolium) salts 33-45.

33-44

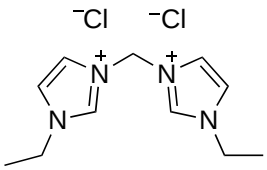
A flame-dried 5 mL microwave vial was equipped with a magnetic stirbar was charged with the imidazole reagent (4.0 mmol, 1.0 equiv), capped with a microwave cap and flushed with N_2. The anhydrous dichloroalkane (0.77 mL, 12.0 mmol, 3.0 equiv) and DMSO (0.23 mL) were added under N_2, and the resulting mixture was stirred at 100 °C for 24 h. The reaction mixture was then slowly allowed to cool to room temperature and to the resulting mixture was added Et_2O (3 x 10 mL) and filtered over celite with excess Et_2O. The organic product was then dissolved with MeOH (100 mL) over celite, collected and concentrated under vacuum to give the pure bis(azolium) product.

Specific procedures and characterization data of 33-45

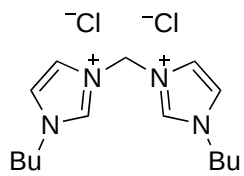
3,3'-methylenebis(1-methyl-1*H*-imidazol-3-ium) chloride (33). General procedure A for the



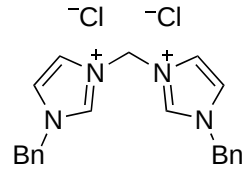
synthesis of bis(azolium) salts was followed, starting with 1-methylimidazole (0.320 mL, 4.0 mmol, 1.0 equiv), DCM (0.77 mL, 12.0 mmol, 3.0 equiv) in DMSO (0.23 mL) at 100 °C for 24 h, affording salt **33** (450.8 mg, 90% yield) as a white solid. All analyses were consistent with previously reported data.[4]



3,3'-methylenebis(1-ethyl-1*H*-imidazol-3-ium) chloride (34). General procedure A for the synthesis of bis(azolium) salts was followed, starting with 1-ethylimidazole (0.386 mL, 4.0 mmol, 1.0 equiv), DCM (0.77 mL, 12.0 mmol, 3.0 equiv) in DMSO (0.23 mL) at 100 °C for 24 h, affording salt **34** (532.8 mg, 96% yield) as a white solid. **^{1}H NMR** (700 MHz, DMSO-d_6) δ 9.81 (s, 2H), 8.18 (s, 2H), 7.92 (app t, J = 1.8 Hz, 2H), 6.78 (s, 2H), 4.26 (q, J = 7.3 Hz, 4H), 1.45 (t, J = 7.3 Hz, 6H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ 137.87, 123.21, 122.72, 58.34, 45.18, 15.19. **IR** (neat) 3051, 1581, 1352, 1215, 764, 647, 623. **HRMS** (EI$^+$) calcd for $[C_{11}H_{18}N_4]^{2+}$: *m/z*, 103.07602 found 103.07586.

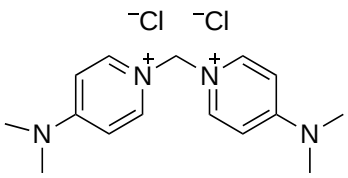


3,3'-methylenebis(1-butyl-1*H*-imidazol-3-ium) chloride (35). General procedure A for the synthesis of bis(azolium) salts was followed, starting with 1-butylimidazole (0.526 mL, 4.0 mmol, 1.0 equiv), DCM (0.77 mL, 12.0 mmol, 3.0 equiv) in DMSO (0.23 mL) at 100 °C for 24 h, affording salt **35** (333.3 mg, 94.8% yield) as a white solid. **^{1}H NMR** (700 MHz, DMSO-d_6) δ 9.93 (s, 2H), 8.25 (t, J = 1.9 Hz, 2H), 7.92 (app t, J = 1.8 Hz, 2H), 6.83 (s, 2H), 4.23 (t, J = 7.3 Hz, 4H), 1.83 – 1.77 (m, 4H), 1.33-1.27 (m, 4H), 0.92 (t, J = 7.4 Hz, 6H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ 138.15, 123.47, 122.76, 58.31, 49.49, 31.53, 19.25, 13.78. **IR** (neat) 3053, 2958, 1579, 1211, 767, 637. **HRMS** (EI$^+$) calcd for $[C_{15}H_{26}N_4]^{2+}$: *m/z*, 131.10732 found 131.10728.

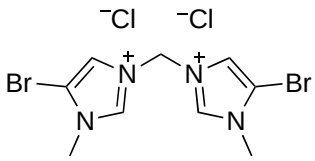


3,3'-methylenebis(1-benzyl-1*H*-imidazol-3-ium) chloride (36). General procedure A for the synthesis of bis(azolium) salts was followed, starting with 1-benzylimidazole (0.632.8 mg, 4.0 mmol, 1.0 equiv), DCM (0.77 mL, 12.0 mmol, 3.0 equiv) in DMSO (0.23 mL) at 100 °C for 24 h, affording salt **36** (401.3 mg, 84%

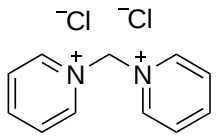
yield) as a white solid. **^{1}H NMR** (700 MHz, DMSO-d_6) δ 9.77 (s, 2H), 8.15 (app t, J = 1.9 Hz, 2H), 7.91 (app t, J = 1.9 Hz, 2H), 7.48 – 7.41 (m, 10H), 6.74 (s, 2H), 5.51 (s, 4H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ 138.31, 134.70, 129.50, 129.40, 129.05, 128.97, 123.64, 123.14, 58.74, 52.78. **IR** (neat) 3026, 1977, 1589, 1497, 1457, 1321, 1163, 709. **HRMS** (EI^+) calcd for $[C_{21}H_{22}N_4]^{2+}$: *m/z*, 165.09167 found 165.09158.



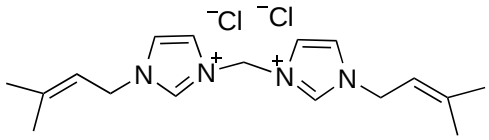
1,1'-methylenebis(4-(dimethylamino)pyridin-1-ium) chloride (37) General procedure A for the synthesis of bis(azolium) salts was followed, starting with DMAP (488.7 mg, 4.0 mmol, 1.0 equiv), DCM (0.77 mL, 12.0 mmol, 3.0 equiv) in DMSO (0.23 mL) at 100 °C for 24 h, affording salt **37** (652.1 mg, 99% yield) as a white solid without Et_2O and MeOH wash. **^{1}H NMR** (700 MHz, DMSO-d_6) δ 8.89 – 8.75 (m, 4H), 7.22 – 7.09 (m, 4H), 6.60 (s, 2H), 3.23 (s, 12H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ 156.95, 141.85, 108.72, 71.75, 40.91, 40.58. **IR** (neat) 3362, 2982, 1635, 1574, 1245, 809, 563. **HRMS** (EI^+) calcd for $[C_{15}H_{22}N_4]^{2+}$: *m/z*, 129.09167 found 129.09158.



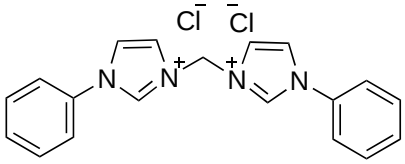
3,3'-methylenebis(5-bromo-1-methyl-1*H*-imidazol-3-ium) chloride (38). General procedure A for the synthesis of bis(azolium) salts was followed, starting with 5-bromo-1-methylimidazole (644 mg, 4.00 mmol, 1.0 equiv), DCM (0.770 mL, 12.0 mmol, 3.0 equiv) in DMSO (0.23 mL) at 100 °C for 48 h, affording crude product. Salt **38** (300.7 mg, 37% yield) was produced as a white solid after recrystallization in hot MeOH without Et_2O and MeOH wash. All analyses were consistent with previously reported data. **^{1}H NMR** (700 MHz, DMSO-d_6) δ 9.62 (s, 2H), 8.27 (s, 2H), 6.72 (s, 2H), 3.86 (s, 6H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ 139.97, 139.38, 127.84, 122.85, 109.89, 104.33, 58.91, 35.97, 33.12. **IR** (neat) 3007.29, 1562.71, 1025.16, 776.16, 613.74.



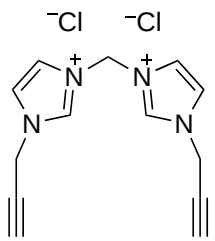
1,1'-methylenebis(pyridin-1-ium) chloride (39). General procedure A for the synthesis of bis(azolium) salts was followed, starting with pyridine (0.323 mL, 4.0 mmol, 1.0 equiv), DCM (0.77 mL, 12.0 mmol, 3.0 equiv) in DMSO (0.23 mL) at 100 °C for 48 h, affording salt **39** (328.2 mg, 60.5% yield) as a white solid without Et_2O and MeOH wash. All analyses were consistent with previously reported data.[5]



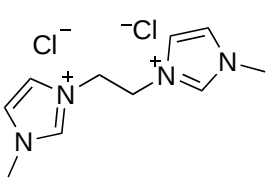
3,3'-methylenebis(1-(3-methylbut-2-en-1-yl)-1*H*-imidazol-3-ium) chloride (40) General procedure A for the synthesis of bis(azolium) salts was followed, starting with 1-(3-methylbut-2-en-1-yl)-1*H*-imidazole (544.8 mg, 4.0 mmol, 1.0 equiv), DCM (0.77 mL, 12.0 mmol, 3.0 equiv) in DMSO (0.23 mL) at 100 °C for 48 h, affording salt **40** (356.2 mg, 60.5% yield) as a white solid. **^{1}H NMR** (700 MHz, DMSO-*d*) δ 9.76 (s, 2H), 8.19 (app t, *J* = 1.9 Hz, 2H), 7.80 (s, 2H), 6.77 (s, 2H), 5.42 (t, *J* = 7.2, 3.5 Hz, 2H), 4.84 (d, *J* = 7.5 Hz, 4H), 1.78 (d, *J* = 5.0 Hz, 12H). **^{13}C NMR** (176 MHz, DMSO-*d*) δ 142.13, 123.94, 123.37, 117.52, 58.90, 47.99, 26.47, 19.07. **IR** (neat) 3037.65, 2968.19, 1547.14, 1438.61, 1162.19, 861.86, 776.86, 617.16



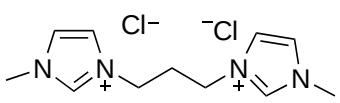
3,3'-methylenebis(1-phenyl-1*H*-imidazol-3-ium) chloride (41). General procedure A for the synthesis of bis(azolium) salts was followed, starting with 1-phenylimidazole synthesized according to literature procedure[7] (432.0 mg, 3.0 mmol, 1.0 equiv), DCM (0.058 mL, 9.0 mmol, 3.0 equiv) in DMSO (0.016 mL) at 100 °C for 24 h, affording salt **41** (152.6 mg, 20.5% yield) as a white solid. All analyses were consistent with previously reported data.[7]



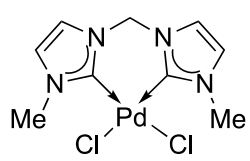
3,3'-methylenebis(1-(prop-2-yn-1-yl)-1*H*-imidazol-3-ium) chloride (42). General procedure A for the synthesis of bis(azolium) salts was followed, starting with 1-(prop-2-yn-1-yl)-1*H*-imidazole (0.424.2 mg, 4.0 mmol, 1.0 equiv), DCM (0.77 mL, 12.0 mmol, 3.0 equiv) in DMSO (0.23 mL) at 100 °C for 24 h, affording salt **42** (384.6 mg, 85% yield) as a white-gray solid. **^{1}H NMR** (700 MHz, DMSO-d_6) δ 9.93 (s, 2H), 8.40 – 8.25 (m, 2H), 8.01 – 7.87 (m, 2H), 6.90 (s, 2H), 5.30 (d, J = 2.6 Hz, 5H), 3.96 (t, J = 2.5 Hz, 2H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ 138.31, 123.35, 123.20, 80.16, 76.08, 58.52, 39.57. **IR** (neat) 3213.86, 3092.54, 2901.34, 1515.68, 775.97.



3,3'-(ethane-1,2-diyl)bis(1-methyl-1*H*-imidazol-3-ium) chloride (43). General procedure A for the synthesis of bis(azolium) salts was followed, starting with 1-methylimidazole (0.320 mL, 4.0 mmol, 2.0 equiv), DCE (0.158 mL, 2.0 mmol, 1.0 equiv) in DMSO (0.842 mL) at 100 °C for 24 h, affording salt **43** (457.1 mg, 87% yield) as a white solid. All analyses were consistent with previously reported data.[4]



3,3'-(propane-1,3-diyl)bis(1-methyl-1*H*-imidazol-3-ium) chloride (44). General procedure A for the synthesis of bis(azolium) salts was followed, starting with 1-methylimidazole (0.320 mL, 4.0 mmol, 2.0 equiv), 1,3-dichloropropane (0.189 mL, 2.0 mmol, 1.0 equiv) in DMSO (0.810 mL) at 100 °C for 24 h, affording salt **44** (470.8 mg, 85% yield) as a white solid after purification of crude solid by suspension in Et_2O (20 mL), followed by sonication for 1 min, and filtering suspension over cotton with Et_2O (50mL) then MeOH (100 mL), where combined organic products were concentrated under vacuum to give the pure product. All analyses were consistent with previously reported data.[4]



1,1-Dimethyl-3,3-methylenediimidazoline-2,2-diylidenepalladium-(II)dichloride (45) General procedure A for the synthesis of bis(azolium) salts was followed, starting with 1-methylimidazole (0.320 mL, 4.0 mmol, 1.0 equiv), DCM (0.77 mL, 12.0 mmol, 3.0 equiv) in DMSO (0.23 mL) at 100 °C for 24 h. The reaction mixture was then allowed to cool to room temperature. $Pd(OAc)_2$ (449 mg, 2.0 mmol, 1.0 equiv), in a N_2-purged vial, was dissolved in 3 mL DMSO and added directly to the reaction mixture and heated at 60 °C for 2 h. Reaction mixture was then heated to 80 °C for 2 h, then 100 °C for 2 h. Crude product was concentrated under and vacuum, then washed with MeOH (2 x 4 mL) and filtered on a Büchner funnel. Compound **45** (488.3 mg, 58% yield over two steps) was obtained as a white solid. All analyses were consistent with previously reported data.[4]

3.6 References

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