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The Large-Scale Synthesis and Asymmetric Hydrosilylations of CuIPhEt, a C2-Symmetric N-Heterocyclic Carbene

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The Large-Scale Synthesis and Asymmetric Hydrosilylations of CuIPhEt, a C2-Symmetric N-Heterocyclic Carbene

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by

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This dissertation is approved for recommendation to the Graduate Council.

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Abstract

CuIPhEt is a C2-symmetric N-heterocyclic carbene catalyst used in the asymmetric hydrosilylation of a variety of prochiral ketones with good yields and selectivities. The large-scale, five-step synthesis of this carbene has been devised. The second step of the synthetic plan includes a double asymmetric hydrogenation of a 1,1-diaryl alkene—a traditionally difficult transformation. The procedure for the use of CuIPhEt in asymmetric hydrosilylations has been optimized and used on both the originally published substrate scope and new compounds. This protocol for the hydrosilylation has been applied in a 10 g reduction to create an intermediate for use toward the total synthesis of antascomicin B. A class of 2-ketoazoles was synthesized for use in asymmetric hydrosilylations, but only poor selectivities were observed.

Acknowledgements

The further I proceed in my studies, the more I realize how indebted I am to an immense support system. Left to my own devices, none of this research would have come to fruition.

Firstly, I wish to thank Dr. Gawley for dreaming up this project. He was an excellent mentor, whose organization, work ethic, and chemical knowledge are unmatched. I have never met anyone so efficient and motivating.

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A special thanks goes to past and present lab mates. Abby Albright laid the groundwork for this project and introduced me to the Gawley lab. Barry, Beng, Bill, Scott, Brian, Dharma, Jackie, Alexis, Kola, Sefat, and Maha were all excellent sounding boards and friends in my research career. The highest praise, however, goes to Dr. Juliette Rivero for teaching me nearly

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Introduction

The field of organic synthesis is nearly two centuries old and has provided countless pharmaceuticals, agrochemicals, and various other necessary compounds. Despite the contributions of the field to the everyday lives of people, chemical syntheses are often vilified for depleting natural resources and creating large amounts of waste. [1] Some shortcomings have been addressed as more elegant synthetic methodologies have been developed over time. In order to set a target for which to aim, many efforts have been made to clearly outline a perfect total synthesis.

Hendrickson was one of the first chemists to attempt to explicitly state the parameters of an ideal total synthesis. [2] In a time where organic synthesis was developing quickly, he defined the archetype to be the following:

> "The ideal synthesis creates a complex skeleton … from available small molecules so functionalized as to allow constructions linking them together directly, in a sequence only of successive construction reactions involving no intermediary refunctionalizations, and leading directly to the structure of the target, not only its skeleton but also its correctly placed functionality."

Trost first elaborated on the idea of atom economy, in which an ideal reaction would consist of a simple addition where all other reagents are needed in only catalytic amounts. [3] He notes that cross couplings, cycloadditions, and rearrangements are among some examples of atom economical reactions. Syntheses that require multiple protecting groups, excess equivalents of reagents, and stoichiometric metal catalysts leave room for improvement.

Wender introduced step economy to the total organic syntheses of complex natural products. [4] In one sense, step economy can be implemented by creating new reactions to access the desired complicated targets in fewer total steps. Avoiding functional group additions and, later, removals is an easy target for step economy. Another technique in step economy that is

being used by medicinal chemists with growing frequency is function-oriented synthesis (FOS). The key tenet to FOS is that the desired biological activity of these structures can be mimicked or even improved through scaffold modifications. Simpler targets with similar functionalities or easily accessible derivatives of target compounds can be used in FOS.

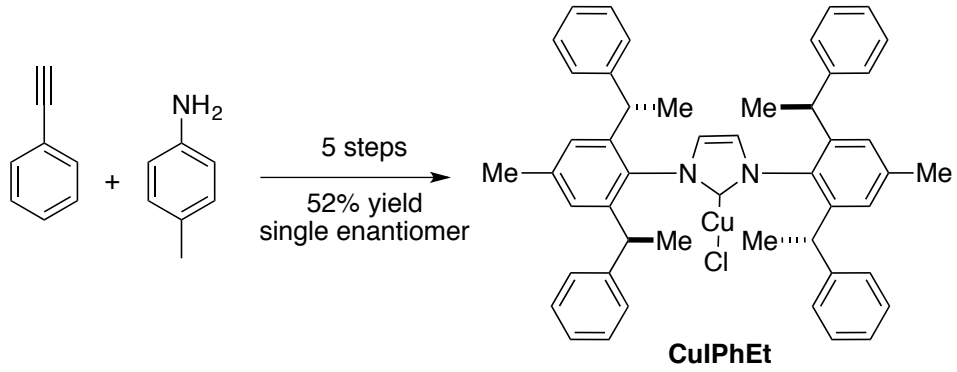
Redox economy, the avoidance of unnecessary refunctionalizations, was familiarized by Baran.[5] It is an effort to reduce the number of corrective or non-strategic (non-scaffold building or stereochemistry setting) oxidation and reduction steps. By fostering the redox economy in a synthetic plan, the overall atom and step economies are often increased as well. Also, traditional redox reactions tend to be difficult to scale up for industrial standards and lack chemoselectivity. Some strategic redox reactions, such as the Noyori hydrogenation, affect molecular scaffolds by installing stereocenters in economical ways and are not considered negative to the redox economy.

In 2010, Baran attempted to combine all of the above goals of an ideal synthesis into one quantifiable statistic.[6] He proposed the equation for the ideality of a synthetic plan to be the number of construction and strategic redox reaction divided by the total number of steps. Construction reactions are those that form the skeletal carbon-carbon and carbon-heteroatom bonds of the target compound. Strategic redox reactions are those that install the stereochemistry of the final molecule. Every other type of reaction, including functional group manipulations and interconversions, would negatively impact the percent ideality.

$$\%\text{ideality} = \frac{[(\#\text{construction reactions}) + (\#\text{strategic redox reactions})]}{(\text{total } \#\text{steps})} \times 100$$

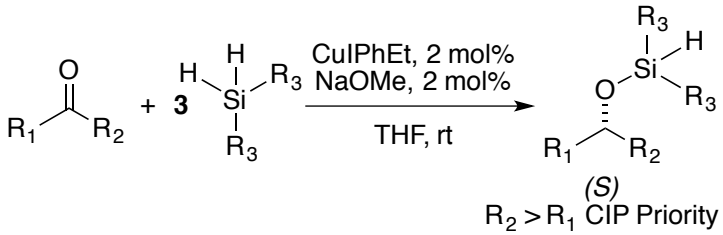
The Gawley lab developed CuIPhEt, an N-heterocyclic copper carbenoid. Before the work in this dissertation, it was synthesized on a small scale in 13% yield, due to a traditional resolution in the second step.[7] Now, a strategic reduction, specifically a double asymmetric

hydrogenation, is employed in lieu of the resolution to give the catalyst on a much larger scale in 52% overall yield (**Scheme 1**). [8] Technically, this new linear synthesis has 100% ideality according to Baran's definition; although, some steps use stoichiometric amounts of reagents that do not contribute to the skeletal structure, which is not completely atom economical.



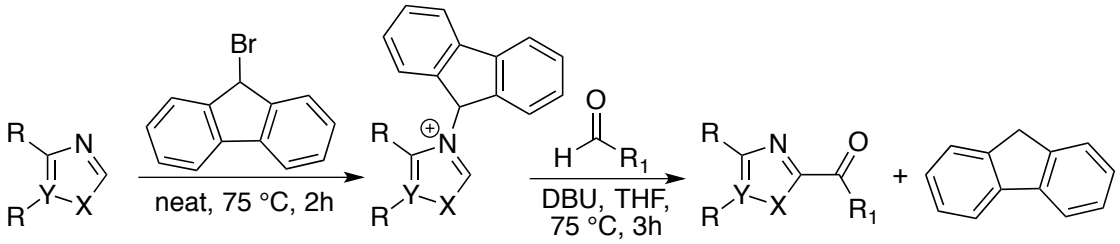
Scheme 1. Synthetic outline of CuIPhEt

CuIPhEt is an asymmetric hydrosilylation catalyst that gives the desired silyl ether in high yields and selectivities (**Scheme 2**). [9] In an asymmetric hydrosilylation, a prochiral ketone is reduced in a stereoselective manner to afford a protected alcohol in one step. While protecting groups are ideally avoided for both atom and step economy, they are often times necessary. This reaction at least eliminates one of the extra steps involved in protecting group manipulations while installing a stereocenter with a strategic reduction reaction. Depending on the silane chosen, the protecting group can often be cleaved upon work-up.



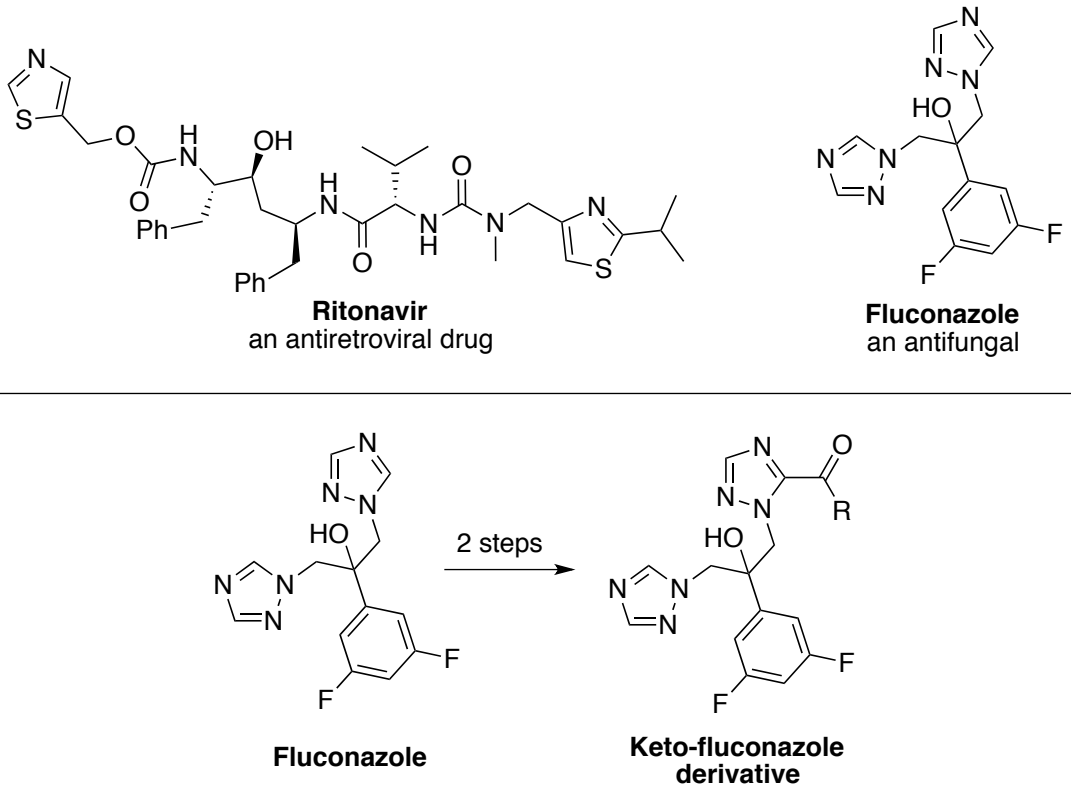
Scheme 2. General hydrosilylation using CuIPhEt

The McIntosh group developed a new strategy for obtaining 2-ketoazoles (**Scheme 3**). [10] The two-step synthesis does employ a fluorenyl leaving group, which despite its large appearance, weighs less than a tosyl group. Procedures do exist for converting the final fluorene byproduct back into the active 9-bromofluorene starting material, which helps increase the atom economy of the system.



Scheme 3. McIntosh two-step formation of azolyl ketones

Many azoles are already recognized as commercially available, biologically relevant compounds. Modifications to these existing scaffolds could create new classes of more effective and/or anti-resistance drugs. Using the chemistry in **Scheme 3**, some of these pharmaceuticals could easily be modified without having to completely reinvent the synthetic plans (**Scheme 4**). In fact, fluconazole, an antifungal, has been modified using this chemistry as an example of a step economical FOS.



Scheme 4. Representative pharmaceutical azoles suitable for McIntosh keto-functionalization

By considering the atom, step, and redox economies as well as the percent yield and ideality, one can begin to evaluate the elegance of a total synthesis. Very few syntheses are the epitome of perfection, but new techniques are allowing for the general improvement of synthetic organic chemistry. The various definitions of organic economies are complementary to each other and prove to be good guidelines for planning and assessing syntheses. While most chemists would agree that striving for these ideals is worthwhile, there will always be debates on the best ways to achieve it. Rarely are completely ideal syntheses attainable in reality. There are some cases in which undesirable reactions cannot be avoided with the current set of available chemical methodologies.

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2. The Asymmetric, Large Scale Synthesis of CuIPhEt

A. Introduction

The importance of the field of *N*-heterocyclic carbene (NHC) catalysis has been established over the past two decades due in large part to the practical synthetic applications in numerous bond forming reactions. [1,2] Many NHCs have proven to be successful organometallic ligands with several attributes in common with phosphine ligands. [3]

A carbene is a neutral divalent carbon atom with two unshared valence electrons. They can exist as triplets with paramagnetic valence electrons or as singlets with spin-paired valence electrons. In general, the triplet or diradical carbene is considered the ground state, whereas the singlet carbene is considered the excited state with greater reactivity. The energy difference of 8 kcal/mol between the two in hydrocarbon carbenes is explained by Hund's rule, which says that high-spin states are of the lowest energies. [4]

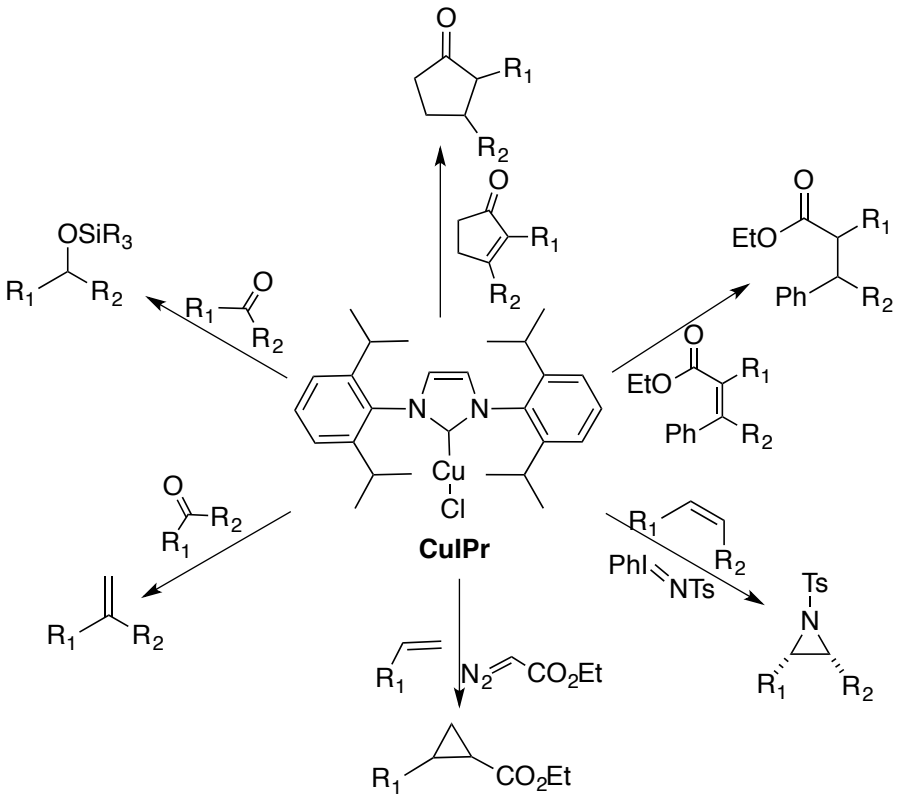
Although carbenes were hypothesized as intermediates by Buchner and Curtius in 1885, [5] their existence was not confirmed until 1968 by Wanzlick and Schönherr and, independently, Öfele. [6,7] When Arduengo synthesized the first isolable and crystalline NHC in 1991, [8] the interest of the scientific community was piqued. This appeal has not yet waned; over the past year, nearly 100 publications regarding NHCs were published in the *Journal of the American Chemical Society* alone.

NHCs are applicable across a wide variety of catalyzed organic reactions. Some of the most successful applications of NHC transition metal catalysis have been Heck and Suzuki type palladium cross couplings, olefin metathesis, arylations, alkylations, hydrogenations, and hydrosilylations.[9]

There are two major classes of imidazole *N*-heterocyclic carbenes—those originating from imidazoliums and those from imidazoliniums. The imidazolium-derived category features a singlet carbene stabilized by two adjacent π-donating nitrogens in an unsaturated, aromatic ring. The carbene p-orbital is therefore available to act as a π-acid and exhibits strong backbonding when coordinated to a metal. The imidazolinium set contains NHCs with saturated rings that lack aromaticity, so the carbene is more likely to exist in the triplet state, which decreases the Lewis acidity of the carbene and making the ligands more labile. [10] The saturated backbone does, however, lend itself to two possible stereocenters, which upon functionalization may create a chiral ligand. Exploitation of the structural and electrical properties inherent to each class allows for efficient catalyst design.

B. Background and Significance

One of the most explored and applied imidazolium NHC ligands is the air stable *N*,*N*'-bis(2,6-diisopropylphenyl)imidazol-2-ylidine (IPr). The CuIPr NHC catalyst has been applied to the catalysis of many reactions including conjugate reductions of α,ß-unsaturated ketones and esters, aziridinations of olefins, cyclopropanations of terminal alkenes, olefinations, and hydrosilylations of ketones (**Scheme 1**). [11]



Scheme 1. Selected applications of the CuIPr NHC catalyst

The X-ray crystal structure of CuIPr **1.1** emphasized the close proximity of the isopropyl methyls of the IPr imidazolium to the copper (3.840 Å) and chlorine (~4.8 Å) atoms. Analysis of **1.1** inspired the design of the IPhEt ligand (I for imidazolium, PhEt for phenethyl) via incorporation of a stereogenic center at the location of the isopropyl methynes to induce a chiral pocket surrounding the catalytic reactive site. If an asymmetric compound could be synthesized to preserve the synthetic flexibility and stability of the achiral CuIPr, it could be a valuable contributor to the field of NHC catalysts. The crowded chiral pocket of CuIPhEt, an NHC organometallic catalyst designed to meet every criterion set above, is apparent in its space-filling model **1.2**. A vast number of C2-symmetric NHCs have been reported throughout the brief history of the field; [12–19] however, before the IPhEt ligand, none contained a stereocenter γ to the imidazolium.

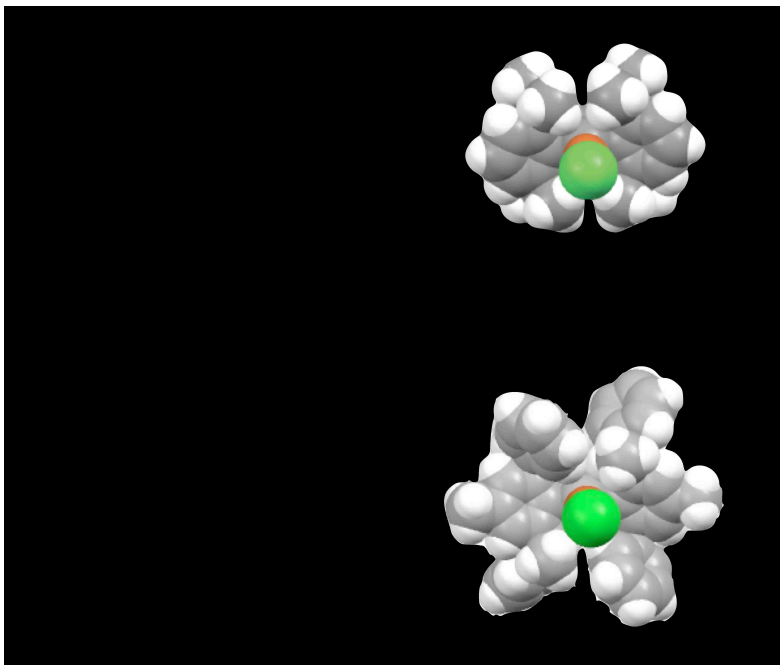
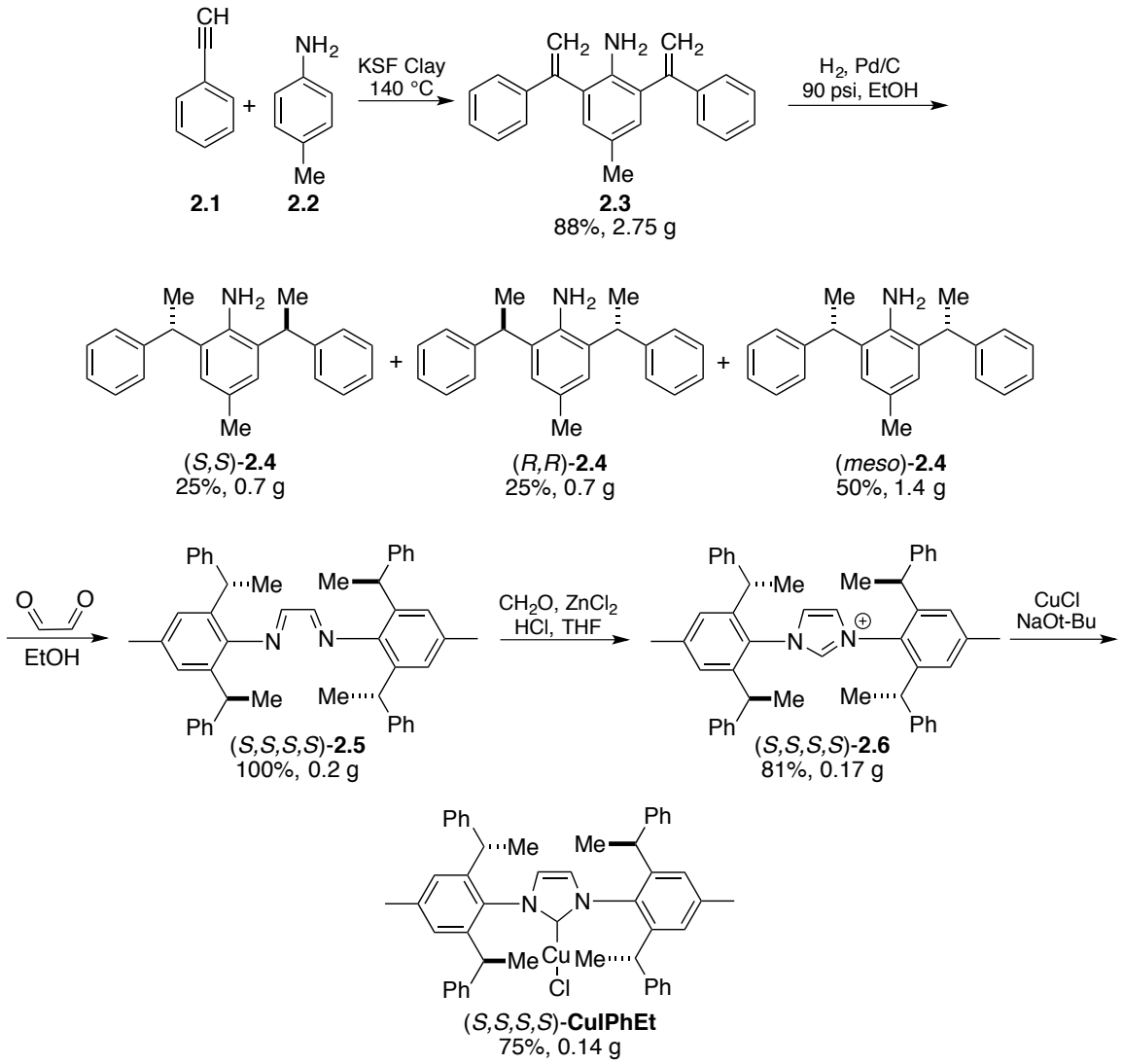


Figure 1. 3D structures of CuIPr and CuIPhEt

The original synthetic route to CuIPhEt was accomplished in five steps (**Scheme 2**).[20] The synthesis begins by employing Friedel-Crafts type chemistry with the dialkylation of toluidine **2.2** with excess phenylacetylene **2.1** originally laid out by Sartori.[21] The resulting diene **2.3** was hydrogenated to give a statistical mixture of racemate and meso-**2.4**. Initially, a variety of asymmetric reductions were attempted, but none proved immediately successful, so the mixture of **2.4** was separated by stacked injection onto a semipreparative chiral stationary phase SFC to give a total of about 200 mg of each stereoisomer. Subsequent condensation of (*S,S*)-**2.4** with glyoxal gave the (*S,S,S,S*)-diimine **2.5** in quantitative yield upon recrystallization of the reaction mother liquor. Slight modifications were made to the Markó procedure for the cyclization to the (*S,S,S,S*)-imidazolium **2.6** with paraformaldehyde and zinc chloride.[22] Finally, deprotonation with an alkoxide base gave the carbene, which was metallated *in situ* to give a single enantiomer of the copper carbenoid CuIPhEt in 13% yield through the linear synthesis.



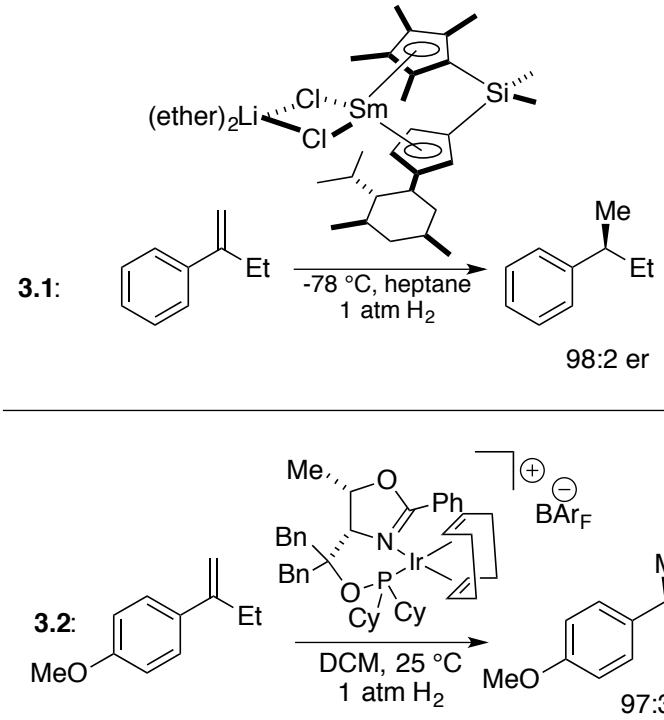
Scheme 2. First synthetic route to CuIPhEt

C. Results and Discussion

While the initial synthesis did afford enantiopure CuIPhEt, it was far from ideal. The hydrogenation in the second step greatly diminished the possible yield of the catalyst by splitting half of the yield to the meso diastereomer, which has no application in asymmetric catalysis. Also, the synthesis was carried out on a fairly small scale.

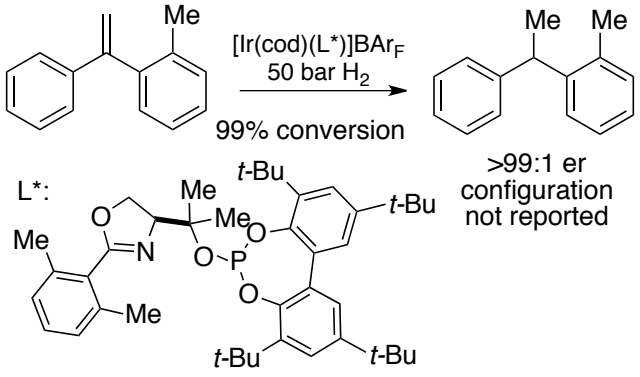
1. Asymmetric Hydrogenation

In order to optimize the reduction of diene **2.3**, an asymmetric hydrogenation method was needed. Disubstituted terminal alkenes are a challenging substrate class for asymmetric hydrogenation compared to the more widely studied trisubstituted olefins.[23–26] Although Marks and coworkers reported the asymmetric hydrogenation of 2-phenyl-1-butene in 98:2 er at –80 °C in 1992, the chiral organosamarium complex they used did not find further application due to the difficult preparation and high sensitivity of this catalyst system (**3.1**).[27,28] Iridium complexes based on chiral P,N ligands provided a more practical solution in this case, as they are less sensitive to air and moisture and are easy to handle. It was found that the enantioselectivity in the hydrogenation of 2-phenyl-1-butene strongly depended on the hydrogen pressure with best results achieved at 1 atm of H_2. Under these conditions a range of 2-aryl-1-butenes was hydrogenated with high enantioselectivites of up to 97:3 er (**3.2**).[29]



Scheme 3. Representative techniques to reduce 2-aryl-1-butenes by Marks (**3.1**) and Pfaltz (**3.2**)

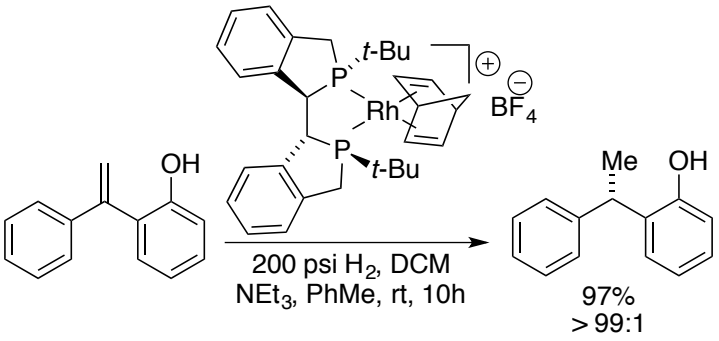
Until recently no examples of asymmetric hydrogenation of diaryl-substituted terminal alkenes were known. However in a combined effort the groups of Börner, Andersson, and Diéguez showed that excellent enantioselectivities could be obtained with substrates of this type, using very sterically demanding phosphite-oxazoline ligands (**Scheme 4**).[30]



Scheme 4. Asymmetric hydrogenation of a 1,1-diarylalkene by Diéguez

While iridium P,N ligand complexes are the catalysts of choice for the asymmetric hydrogenation of olefins lacking any coordinating substituents, rhodium- and ruthenium-

diphosphine complexes perform best with functionalized olefins bearing a coordinating group next to the double bond. A recent example of phenol-directed rhodium-catalyzed asymmetric hydrogenation of 1,1-diarylethenes was reported by Wang and coworkers (**Scheme 5**).[32] By analogy, because the amino group of diene **2.3** is a potential coordinating group, we included a series of rhodium-diphosphine catalysts in our study.



Scheme 5. Asymmetric hydrogenation using DuanPhos

After initial screens with a variety of iridium catalysts with diene **2.3** and the *N*-acylated derivative did not provide both high diastereo- and enantioselectivity, we turned to rhodium based catalysts prepared in situ from bis(norbornadiene)rhodium(I) tetrafluoroborate and the corresponding P,P-chiral ligands (**Figure 2**).[33] The screenings for the double asymmetric hydrogenation were performed at 500 psi overnight with careful exclusion of air in a 96-well microtiter plate.

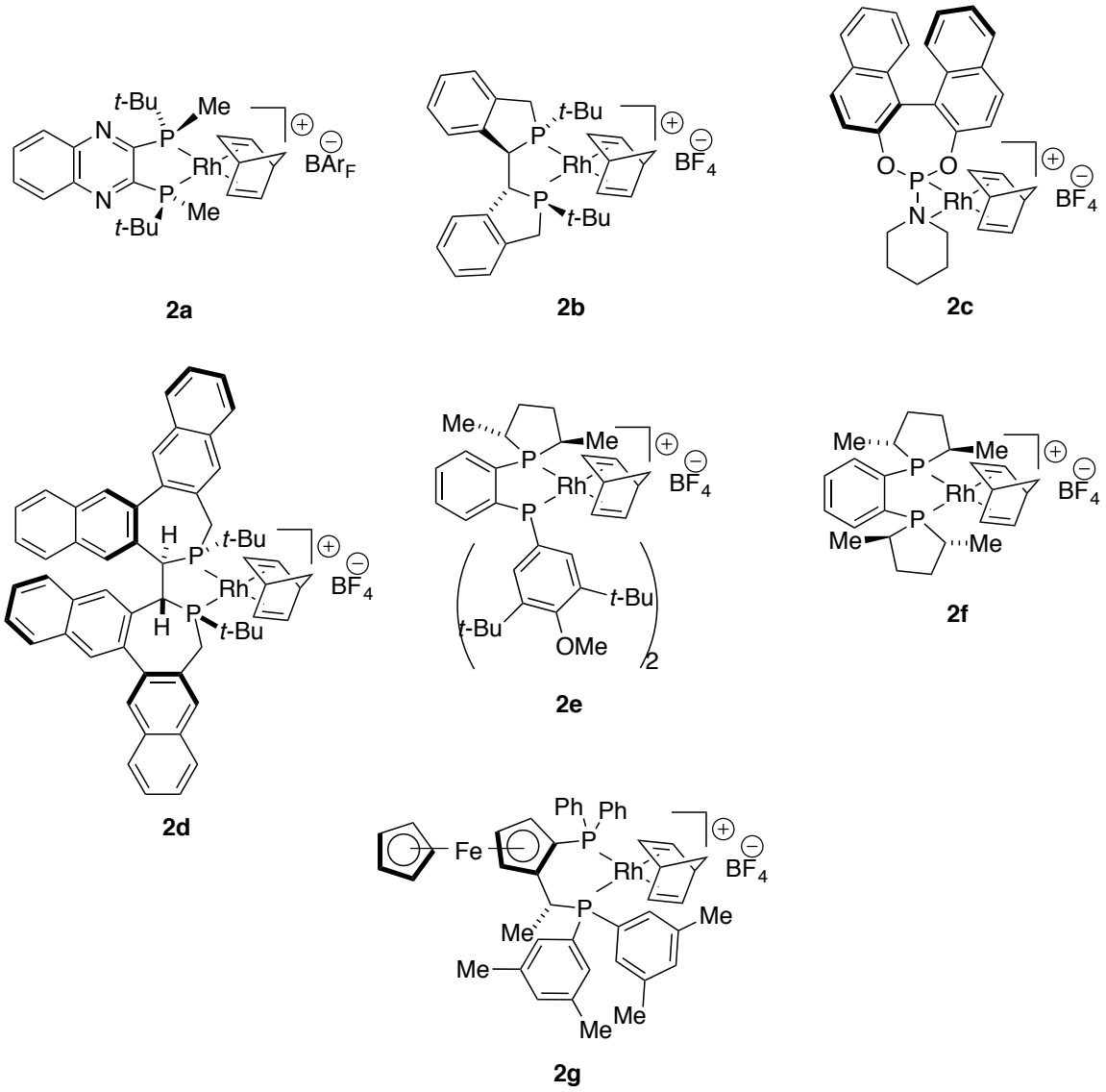
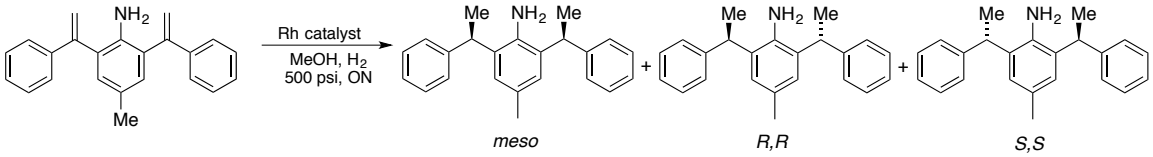


Figure 2. Chiral rhodium catalysts screened for the asymmetric hydrogenation

Catalyst **2b**, based on the diphosphine ligand (R_C-S_P)-DuanPhos developed by Zhang et al., [34] provided the highest dr and er of any system tested (**Table 1**).



Entry	Catalyst	Ligand Name	meso : R,R : S,S
1	**2a**	(*R,R*)-QuinoxP*	3 : 3 : 94
2	**2b**	(R_C,S_P)-DuanPhos	1 : 0 : 99
3	**2c**	(*P*)-PipPhos	6 : 0 : 94
4	**2d**	(*S*)-Binapine	70 : 2 : 28
5	**2e**	(*R,R*)-Me-UCAP-DTBM	20 : 74 : 6
6	**2f**	(*R,R*)-Me-DuPhos	31 : 61 : 8
7	**2g**	SL-J005-1	4 : 0 : 96

Table 1. Results of catalysts screened for diene reduction

Upon identifying the Rh-DuanPhos catalyst **2b** as the most selective system, we optimized the reaction conditions. We began by probing solvent options. Based on solvent studies (**Table 2**), methanol and ethyl acetate proved to be viable candidates for the reaction. We chose to proceed with methanol due to ease of use and solubility of the catalyst. In larger scale-ups, 10 vol% of methylene chloride was employed as a co-solvent to enhance the solubility of the starting materials.

Solvent	meso	R,R	S,S
MeOH	1.2	0.2	98.6
EtOH	5.6	0.3	94.1
iPrOH	13.2	0.6	86.2
TFE	33.1	1.4	65.4
DCE	18.5	0.4	81.0
$PhCF_3$	4.9	0.2	94.9
PhCl	6.1	0.3	93.6
CyH	6.4	0.5	93.1
PhMe	6.5	1.8	91.8
EtOAc	3.3	0.2	96.5
iPrOAc	4.0	0.2	95.7
MEK	2.5	0.1	97.4
THF	5.9	0.3	93.8
MeTHF	6.3	0.3	93.4
CPME	5.5	0.3	94.2
DME	3.8	0.2	96.1

Table 2. Solvent studies with DuanPhos at 500 psi overnight

To further optimize the system, catalyst loading studies were performed on 0.1 M reactions (**Table 3**). Only 0.2% catalyst loading is needed to effectively reduce the starting material in a reaction at 500 psi overnight. Smaller loadings still exhibit high selectivity but conversion to product is attenuated. In practice, a catalyst loading of 0.5% was employed to ensure that potential catalyst poisons in the substrate lot and reaction vessel would not be as likely to affect the reaction.

Load	% Conversion	meso	R,R	S,S
5%	100.0	1.2	0.2	98.6
2%	100.0	3.6	0.3	96.2
1%	100.0	4.8	0.5	94.7
0.5%	100.0	3.6	0.1	96.3
0.3%	99.7	3.1	0.1	96.8
0.2%	99.3	3.7	0.1	96.2
0.1%	23.1	2.5	0.4	97.0
.05%	9.3	2.5	1.4	96.1

Table 3. Loading studies with DuanPhos at 500 psi overnight

The asymmetric hydrogenation has now been conducted on over a six gram scale, with only small amounts of the *meso* diastereomer contaminating the enantiopure product (**Figure 3**). The small amounts of undesired stereoisomers are eliminated during condensation with glyoxal and subsequent crystallizations.

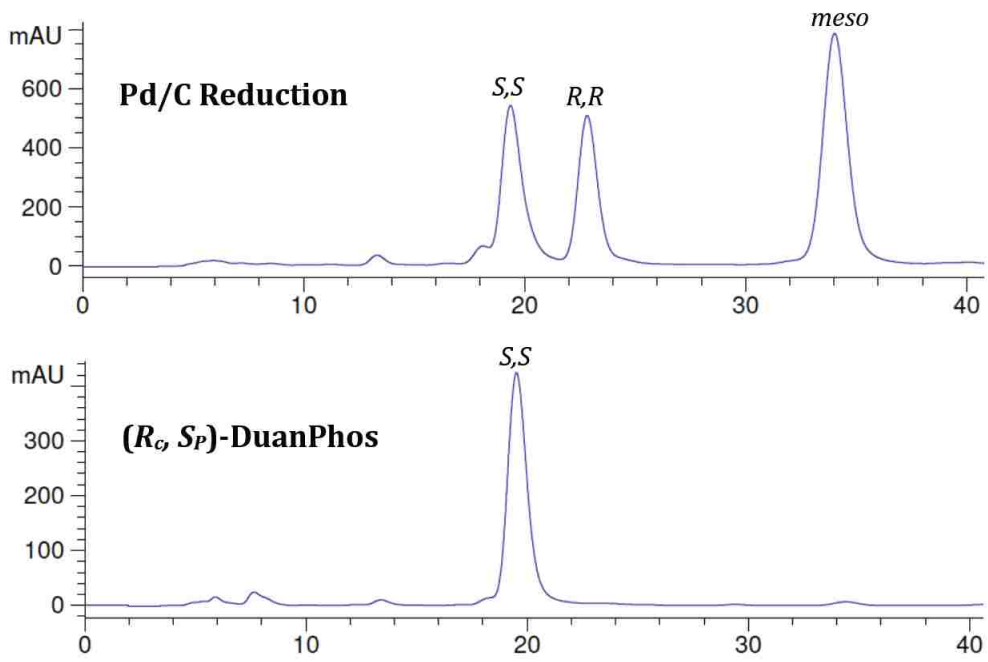


Figure 3. CSP-HPLC racemate/meso mixture and *S,S* enantiomer obtained in gram scale reduction.

2. Large Scale Synthesis of CuIPhEt

To begin the revised synthetic plan, the Friedel-Crafts dialkylation was performed on a larger scale (**Scheme 6**). *P*-Toluidene **6.2** was refluxed in excess phenylacetylene **6.1** in the presence of KSF Montmorillonite, an acidic clay, to give the diene **6.3** in 80% yield. The key to complete conversion to product is the careful cooling of a Dimroth reflux condenser. Aniline **6.3** is purified via column chromatography to give a yellow solid. Multiple attempts to recrystallize the crude reaction mixture did not prove successful.

To attempt to mimic the success of the screening reactions on a larger scale and circumvent the need for a glove box, we modified a Parr 5500 bench top reactor by removing the original gas relief valve and replacing it with Swagelok ® fittings to become a manifold with three needle valves designated as ports for N_2, vacuum, and vent. The vessel was charged with a slurry of diene **6.3** and pre-formed catalyst in solution before quickly sealing the system from the

atmosphere and purging with nitrogen before beginning the hydrogenation. Under this procedure, no conversion to product was observed.

Several potential problems were identified. Firstly, a catalyst poison could be present within the reactor. To remove any potential reactive metal traces from the stainless steel surfaces, 10% nitric acid was boiled in the vessel until the solution remained clear. Still, no conversion was observed. Secondly, the rhodium metal precursor or the DuanPhos chiral ligand could have been oxidized from being stored outside of a glove box. Literature indicates that although the catalyst is bench stable, the chiral ligand is sometimes oxidized. [35] We established that both components of the catalyst were active by using our reagents at Merck facilities successfully, so the problem existed in the procedure. The catalyst and its precursors, while bench stable when isolated, are extremely sensitive to air when in solution.

To accommodate this new knowledge, the Parr reactor was further modified by replacing the cooling loop with a Swagelok ball valve to allow for the injection of the catalyst solution under nitrogen. Using careful syringe techniques, the catalyst could successfully be prepared in an inert round bottom flask and transferred to the reactor.

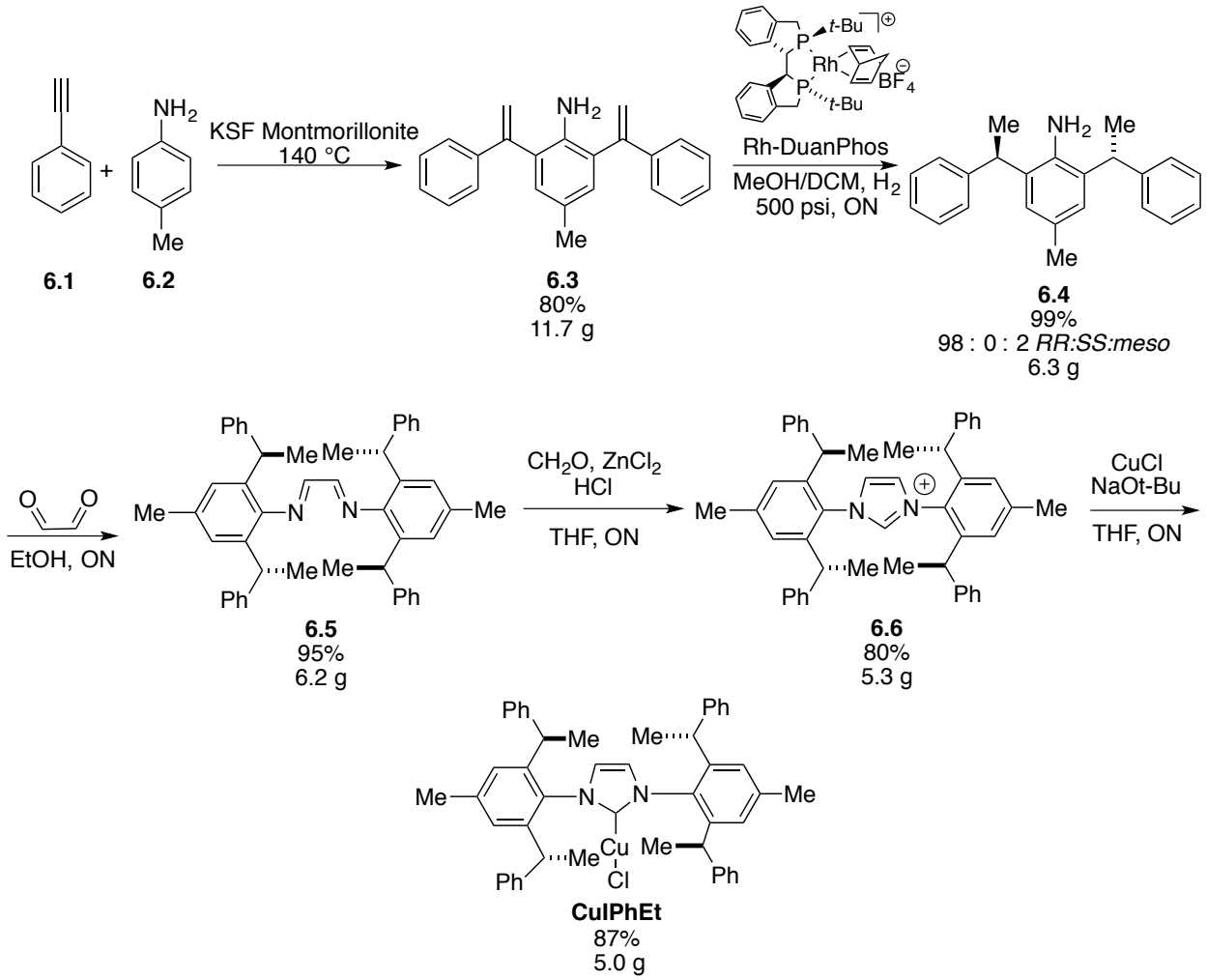
The collected diene **6.3** was approximately divided in half and hydrogenated in two batches to afford aniline **6.4** in near quantitative amounts. In order to maintain similar concentrations to the small scale screening reactions, the hydrogenation is limited to less than ten grams in the high-pressure Parr reactor. Future concentration studies could be attempted to increase this capacity.

Aniline **6.4** was then condensed with glyoxal through overnight sonication to give the solid, bright yellow diimine **6.5** in 95% yield after re-concentrating and washing the filtrate three times. Paraformaldehyde was used in the presence of a zinc chloride and hydrochloric acid

solution give the cyclized imidazolium **6.6**. The yield for these two steps was slightly lower than in the small-scale synthesis.

Finally, deprotonation of C2 with either sodium or potassium *tert*-butoxide and *in situ* metallation with copper (I) chloride gave CuIPhEt in 87% yield. The key to increasing the yield of this step was careful purification of the copper (I) chloride, which is easily oxidized to copper (II) chloride on the benchtop—evident by a blue color. Pure, white CuCl is obtained by first dissolving in concentrated hydrochloric acid, then precipitating with water, and rinsing with diethyl ether and cold ethanol.

The overall synthesis took five steps, with column chromatography only required in the first step. Just over five grams of CuIPhEt can be obtained in 52% overall yield. The new synthetic plan gives an overall percent yield four times higher than the original synthesis and affords nearly 36 times as much catalyst.



Scheme 6. Asymmetric synthesis of CuIPhEt

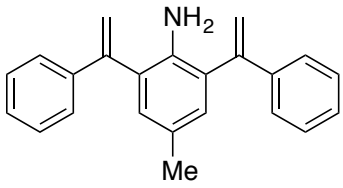
D. Conclusion

CuIPhEt is a novel, asymmetric copper *N*-heterocyclic carbenoid based on the successful, achiral CuIPr catalyst. It was originally synthesized on a milligram scale utilizing a chiral resolution after a non-selective hydrogenation.

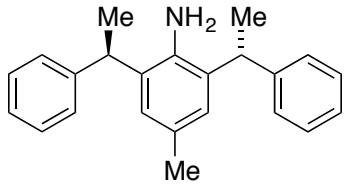
The asymmetric hydrogenation of 1,1-diaryl-substituted terminal olefins is a challenge and a highly selective double asymmetric hydrogenation of functionalized dienes of this type are rare. We found that the Rh-DuanPhos catalyst is highly selective in reducing 2,6-di-(1-phenylethenyl)-4-methyl aniline to provide a key intermediate in the synthesis of the NHC

carbenoid CuIPhEt. Through this discovery, CuIPhEt is now attainable on a five gram scale through a five step synthesis in 53% overall yield.

E. Experimental



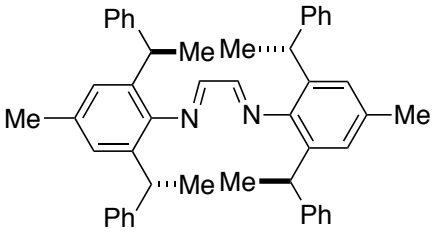
4-Methyl-2,6-bis(1-phenylvinyl)benzenamine: A 50 mL round bottom flask equipped with a stir bar was charged with toluidine (5.0 g, 47 mmol), KSF Montmorillonite (5.25 g), and phenylacetylene (20.6 mL, 187 mmol). The round bottom flask was fitted with a reflux condenser and the heterogeneous slurry was refluxed with vigorous stirring at 140 °C for 6 h. The reaction vessel was allowed to cool to room temperature before dilution with ethyl acetate and filtration. The solvent was removed from the mother liquor under reduced pressure and the resultant red oil was purified via column chromatography with 95:5 hexanes: ethyl acetate. The product was obtained as a light yellow solid in 80% yield (11.6 g, 37 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.3 (s, 3H), 3.4 (s, 2H), 5.4 and 5.8 (dd, 4H), 6.9 (s, 2H), 7.2-7.4 (m, 10H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 20.5, 116.2, 126.5, 127.8, 128.3, 128.7, 131.0, 139.3, 139.9, 147.5.



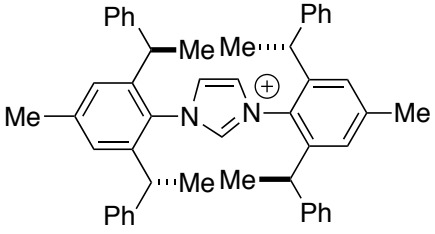
4-Methyl-2,6-bis((R,R)-1-phenylethyl)benzenamine: All asymmetric hydrogenations carried out in Parr 5500 compact mini bench top reactor with the following modifications. The cooling loop was removed and replaced on one side with a Swagelok ball valve with septum and on the other side with a stainless steel plug. The original gas relief valve was modified with Swagelok fittings to become a manifold with three needle valves. The needle valves were designated as ports for N_2, vacuum, or vent. The lower guide bearing that formerly braced the impeller shaft to the cooling loop was reconnected to the dip

tube. A 1L Parr High Pressure Buret was connected to the reactor with a high-pressure hose. This buret was fitted with valves so that it can be sealed off from both the hydrogen supply cylinder and the reactor. Reactions were performed in a glass insert inside of the stainless steel reactor.

A 25 mL round-bottom flask containing bis(norbornadiene)-rhodium(I) tetrafluoroborate (38 mg, 100 μmol; 0.5 mol % loading) and (S_C, R_P)-DuanPhos (47 mg, 120 μmol) was sealed with a septum and purged with anhydrous nitrogen. Dichloromethane distilled from CaH_2 (5 mL) was added, and the solution was allowed to stir for 15 min. Aniline diene **6.3** (6.3 g, 20 mmol) and methanol dried over $MgSO_4$ (60 mL, ~0.25 M solution) were stirred in a round bottomed flask with stir bar to form a well-distributed slurry before addition to the glass insert for the Parr reactor. The hydrogenation chamber was assembled and then evacuated and flushed five times with nitrogen. The catalyst solution was introduced to the reactor under slight positive pressure of nitrogen via syringe through the ball valve. Upon filling three times and venting the system with hydrogen, the system was pressurized to 500 psi; the buret was closed to the hydrogen cylinder to minimize hydrogen loss in the event of a leak. After vigorously stirring overnight, the reactor was closed to the hydrogen buret, then vented and disassembled. The reaction mixture was filtered through a plug of silica gel (4 Å, ~1.5 cm) and concentrated to yield an orange solid in 95% yield (6.3 g, 19 mmol). The product mixture was analyzed by chiral stationary phase HPLC (Chiralpak OJ-RH 150 Å~ 2.1 mm, 5 μm, 0.1 mL/min isocratic, 65% CH_3CN/35% 0.1% aq H_3PO_4) indicating complete conversion to a 98:0.2:1.8 mixture of R,R:S,S:meso products. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.6 (d, 6H), 2.4 (s, 3H), 3.1-3.4 (bs, 2H), 4.0 (q, J = 65, 2H), 7.1 (s, 2H), 7.2-7.3 (m, 10H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 20.5, 116.2, 126.5, 127.8, 128.3, 128.7, 131.0, 139.3, 139.9, 147.5.

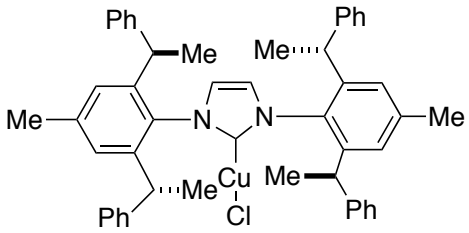


N,N'-Bis-[4-methyl-2,6-bis((R,R)-1-phenylethyl)phenyl]-ethane-1,2-diylidenediimine: To a 25 mL round bottom flask was added aniline **6.4** (6.3 g, 19 mmol) in 10 mL absolute EtOH. To this was added 40% glyoxal (2.2 mL, 19 mmol) and one drop of formic acid. The reaction mixture was sonicated overnight at room temperature. The contents were then filtered to give a bright yellow solid. The mother liquor was concentrated and recrystallized from ethanol. These combined batches yielded the product diimine in 95% yield (6.2 g, 9 mmol) as a single diastereomer. ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.5 (d, J = 6.3, 12H), 2.3 (s, 6H), 4.0 (q, J = 6.5, 4H), 6.9 (s, 4H), 7.1-7.3 (m, 20H), 7.7 (s, 2H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 21.4, 22.1, 39.1, 125.9, 126.2, 127.8, 128.6, 134.5, 146.6, 164.0.



1,3-Bis-[2,6-(R,R)-(1-phenyl-ethyl)-phenyl]-1H-imidazolium chloride: A solution of zinc (II) chloride and paraformaldehyde in concentrated hydrochloric acid was prepared ($ZnCl_2$:p-formaldehyde:HCl=1:1:2). A tube with a screw cap was charged with the diimine **6.5** (6.2 g, 9.5 mmol) in freshly distilled THF (40 mL) under inert atmosphere and was treated with the acid solution (11.4 mmol paraformaldehyde, 1.2 equiv). The reaction solution was then heated to 70 °C in a sealed tube for 1h before cooling to room temperature and removal of the solvent *en vacuo*. The resultant residue was then dissolved in dichloromethane and thrice washed with water and saturated $NaHCO_3$ before drying over $MgSO_4$, filtration and removal of the solvent *en vacuo*. The off white solid was then

recrystallized from diethyl ether and dichloromethane (5.3 g, 7.6 mmol, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.4 (d, J = 6.7, 6H), 1.6 (d, J = 6.7, 6H), 2.3 (s, 6H), 3.75 (q, J = 6.6, 2H), 3.85 (q, J = 6.6, 2H), 6.5 (s, 2H), 6.7 (d, J = 7.5, 4H), 6.9 (s, 2H), 7.0-7.5 (m, 18H), 12.1 (s, 1H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 21.8, 21.85, 22.7, 38.5, 40.0, 124.3, 126.5, 126.8, 127.1, 127.6, 127.8, 128.3, 128.5, 129.1, 141.3, 141.9, 142.8, 143.5, 145.6.



Copper carbenoid (R,R,R,R)-CuIPhEt: A 25mL round bottom flask equipped with a stir bar was charged with purified Cu(I)Cl (0.75 g, 7.6 mmol) and sodium tert-butoxide (0.72 g, 7.6 mmol). The reaction vessel was sealed under inert atmosphere and a solution of **6.6** (5.3 g, 7.6 mmol) in freshly distilled THF (25 mL) was added. The reaction was stirred overnight at room temperature before being filtered through a plug of celite. The celite was rinsed with dichloromethane and the combined organic layers were concentrated *en vacuo*. The resulting beige solid was recrystallized from dichlormethane and hexanes to give CuIPhEt as an off-white solid (5 g, 6.6 mmol, 87%). ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.4 (d, J = 8.0, 6H), 1.6 (d, J = 8.0, 6H), 2.35 (s, 6H); 3.85 (overlapping quartets, J = 5.3, 4H); 6.5 (s, 2H), 6.9 (d, J = 4.0, 4H), 7.1-7.4 (m, 20H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 21.7, 21.9, 22.7, 38.0, 39.6, 123.0, 126.0, 126.5, 127.0, 127.5, 128.0, 129.1, 133.2, 140.5, 142.3, 144.0, 144.3, 145.9, 181.2.

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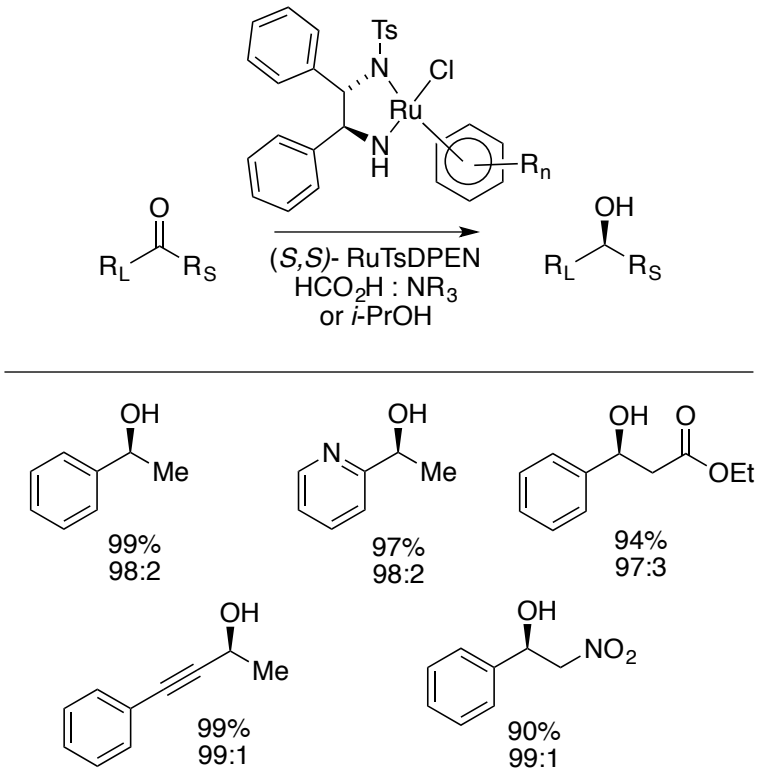
3. Developing a Reproducible Procedure for Asymmetric Hydrosilylations

A. Introduction

Modified aluminum hydrides, borohydrides, boranes, and transition metal catalysts have been applied to the asymmetric reduction of carbonyls in an ongoing effort of over 50 years. [1–3] Highly stereoselective and chemoselective Noyori-type transition metal catalyzed hydrogenations of ketones can be achieved; however, these reactions sometimes require harsh conditions of high temperatures, pressures, and reaction times. [4,5] The substrate scope of this method is also somewhat limited. Some classes of ketones, such as dialkyl ketones, are reduced with only moderate to low selectivities.

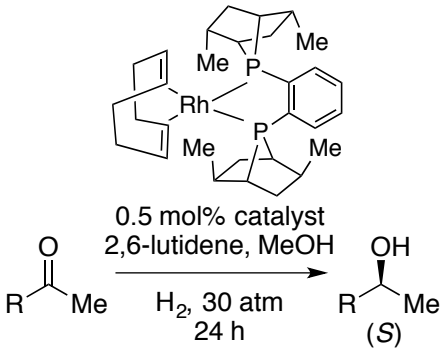
1. Asymmetric Transfer Hydrogenations

Asymmetric transfer hydrogenations (ATH) have met success as the field has developed over the past two decades. [6,7] In an ATH of a ketone, the equivalent of a molecule of hydrogen from a donor is added to a prochiral face of the carbonyl acceptor, in the presence of a metal catalyst, to give an enantioenriched alcohol. Its conditions are milder than traditional hydrogenations. The field began growing rapidly with Noyori's work in 1995 that found a ruthenium-BINAP catalyst in the presence of a protic diamine donor and potassium hydroxide allowed for the efficient enantioselective reduction of acetophenone, which lacks a heteroatom for anchoring the metal. [8] Since this initial effort, Noyori's lab has developed a novel class of ruthenium (II) catalysts that now dominates the field. Combined with the either enantiomer of the TsDPEN ligand in isopropanol or formic acid and trialkylamine mixtures, the system provides high enantioselectivies in the ATH of a variety of ketones, often in the presence of other reducible moieties (**Scheme 1**).[7,9–13]



Scheme 1. Asymmetric transfer hydrogenation of ketones with Ru-TsDPEN

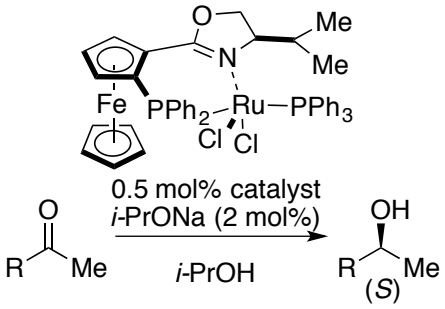
While the Noyori ATH conditions worked for many ketones, they did not provide high enantioselectivities for simple dialkyl ketones. Zhang et al. developed a rhodium-PennPhos catalyst that proved effective for the reduction of alkyl-aryl and alkyl-methyl ketones. [14] The dialkyl ketones were reduced with higher enantioselectivity as the steric bulk difference between the alkyl and methyl groups increased; however the highest selectivity with *tert*-butyl methyl ketone came at the cost of the yield (**Scheme 2**).



R	Yield (%)	er
n-butyl	96	88:12
isopropyl	99	92:8
isobutyl	66	93:7
t-butyl	51	97:3

Scheme 2. The ATH of dialkyl ketones with Rh-PennPhos

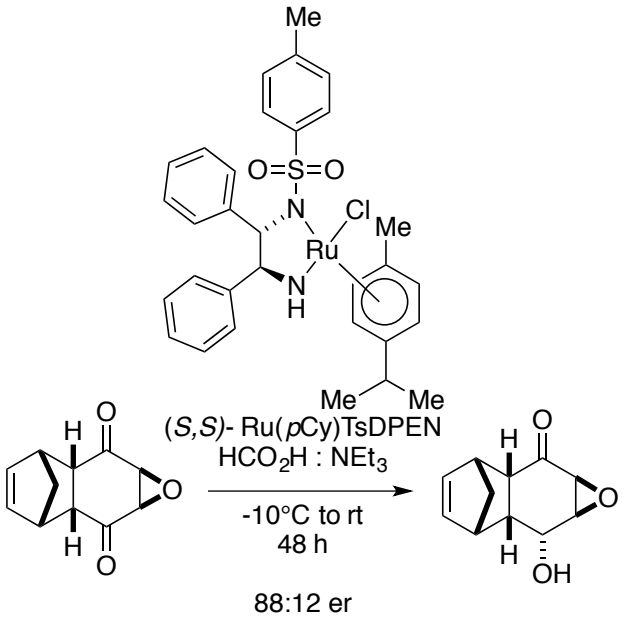
The Hidai group found similar results with their ruthenium (II) catalyst equipped with an oxazolinylferrocenylphosphine ligand (**Scheme 3**).[15] Simple, straight chain substituents did not afford high selectivities. As the steric size of one group increased, so did the er.



R	Yield (%)	er
n-hexyl	99	63:37
c-hexyl	68	76:24
t-butyl	81	99:1

Scheme 3. The ATH of dialkyl ketones with Ru-oxazolinylferrocenylphosphine

Most recently, the McIntosh group was able to affect the asymmetric reduction of a dialkyl ketone on a multigram scale (**Scheme 4**). [16] Using the Noyori Ru(*p*-cymene)[(*S,S*)-TsDPEN] as the catalyst and formic acid/triethylamine as the stoichiometric reductant, they identified the intrinsic selectivity of the reaction to be 88:12. However, upon long reaction times, a highly enantiopure product (>99:1 er) could be obtained in 44% yield through a kinetic resolution of the minor enantiomer.



Scheme 4. Noyori-type desymmetrization of a *meso*-diketone

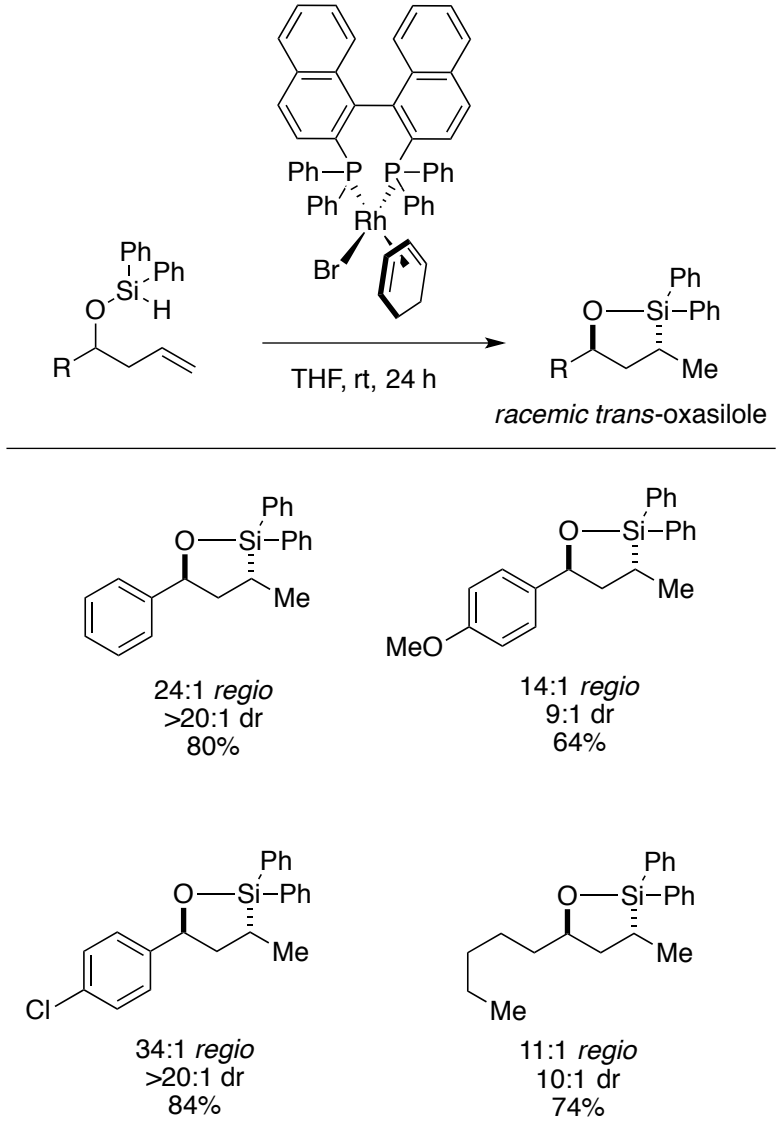
2. Hydrosilylations

Another mild reduction alternative to high-pressure hydrogenations is hydrosilylations. The field of hydrosilylations has grown with the use of silanes as protecting groups for alcohols. The ideal asymmetric hydrosilylation of a ketone would afford an enantiopure, protected alcohol in one step. Both phosphine and NHC ligands are suitable choices in building a hydrosilylation catalyst due to the highly tunable electronic and steric properties.[17,18]

Aside from serving as protecting groups for alcohols, silyl ethers can also participate in the intramolecular hydrosilylation or silylation of C_{sp2} bonds. [19–27] The resulting oxasilole can undergo a variety of functionalizations to C-C, C-O, or C-X bonds.[19,20]

The Jeon group has contributed much to the field of intramolecular hydrosilylations. [24–28] Using a racemic rhodium (I) BINAP catalyst, they developed a method to obtain a *trans*-selective hydrosilylation of β,γ-unsaturated silylethers to give a variety of 1,3-*anti*-oxasiloles

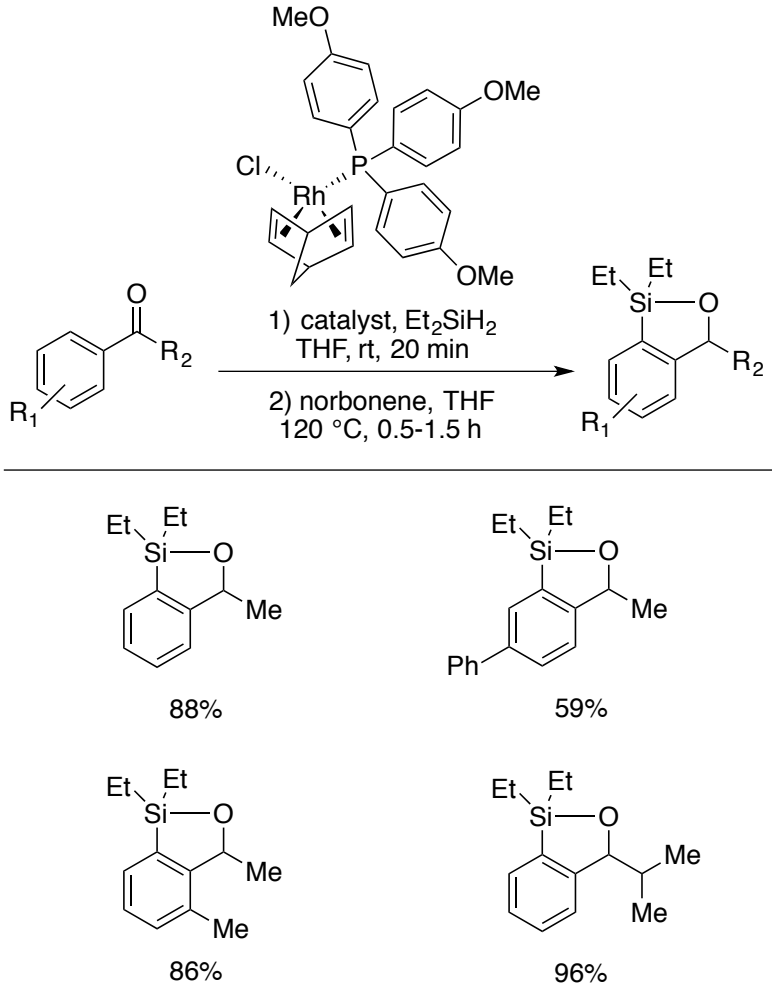
(**Scheme 5**). [24,25] The BINAP ligand provided high regioselectivity for the formation of an oxasilacyclopentane through hydrosilylation of the internal position of the alkene.



Scheme 5. Formation of 1,3-*anti*-oxasiloles by Jeon

Jeon continued working by developing a one-pot ketone hydrosilylation followed by an intramolecular aromatic C-H silylation (**Scheme 6**). [26,27] An *in situ* formed rhodium (I) catalyst with a monodentate phosphine ligand provides the hydridosilyl ether, which upon heating forms the oxasilole. A negative influence on the yield was observed when *para*-substituents were

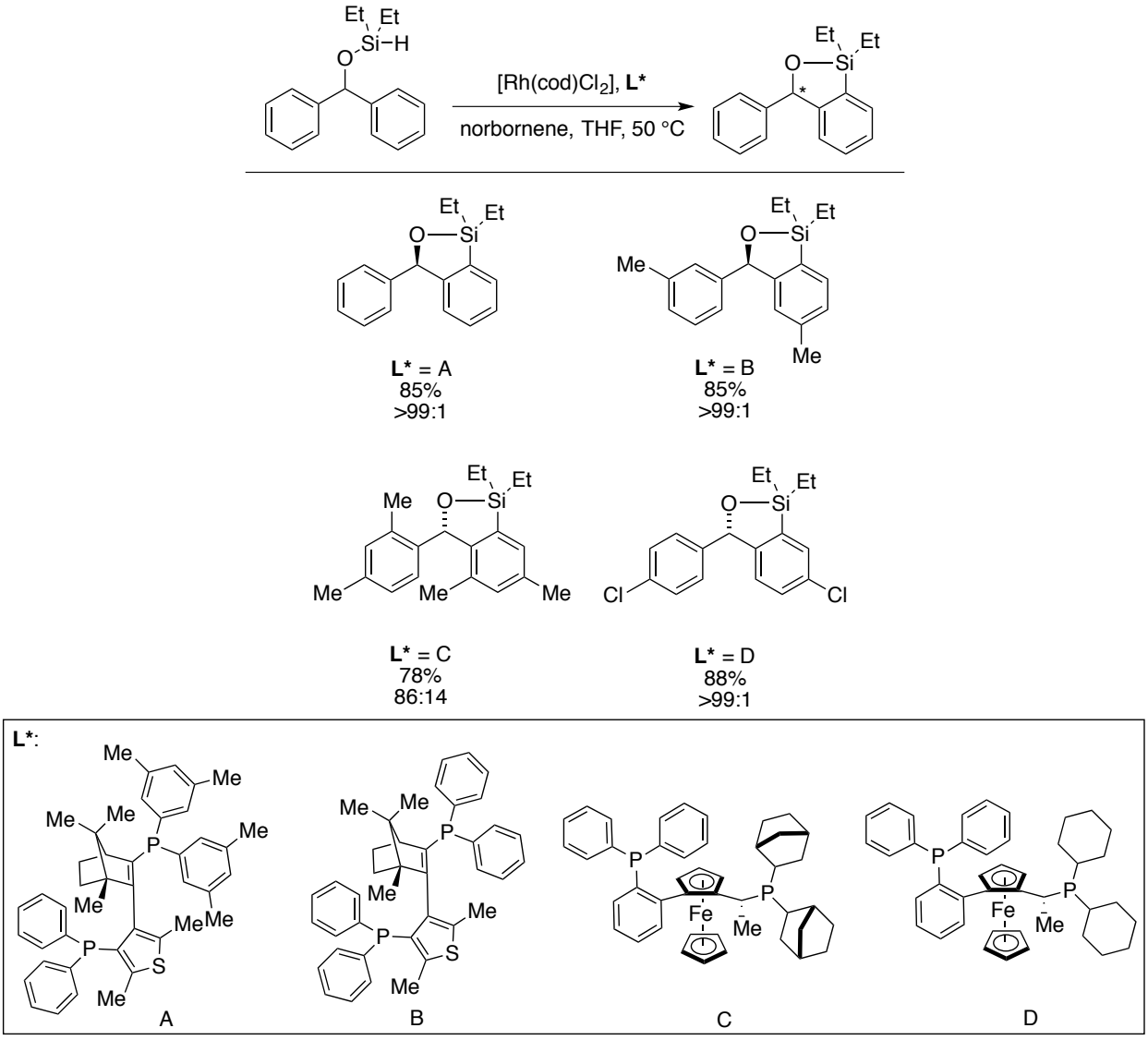
employed. More sterically hindered systems such as *ortho*-substituted arenes and the isopropyl ketone gave excellent yield.



Scheme 6. Ketone hydrosilylation and subsequent arene C-H silylation by Jeon

Hartwig reported an enantioselective application for hydrosilylated ketones.[20] His group was able to desymmetrize racemic hydridosilyl ethers through the use of a rhodium (I) catalyst with a variety of chiral ligands to silylate the *ortho*-position of an adjacent aromatic ring (**Scheme 7**). Unsubstituted and alkyl-substituted benzophenone derivatives containing *meta* and *para* substituents gave the oxasilole in good yields and selectivities through the use of the catASium family of ligands. Substrates exhibiting *ortho*-substituents provided lower yields and

selectivities and were reacted at higher temperatures in the presence of a Walphos ligand. The Walphos ligand family was used on compounds bearing a variety of electronic properties. Electron withdrawing substituents such as chloro groups were well tolerated.



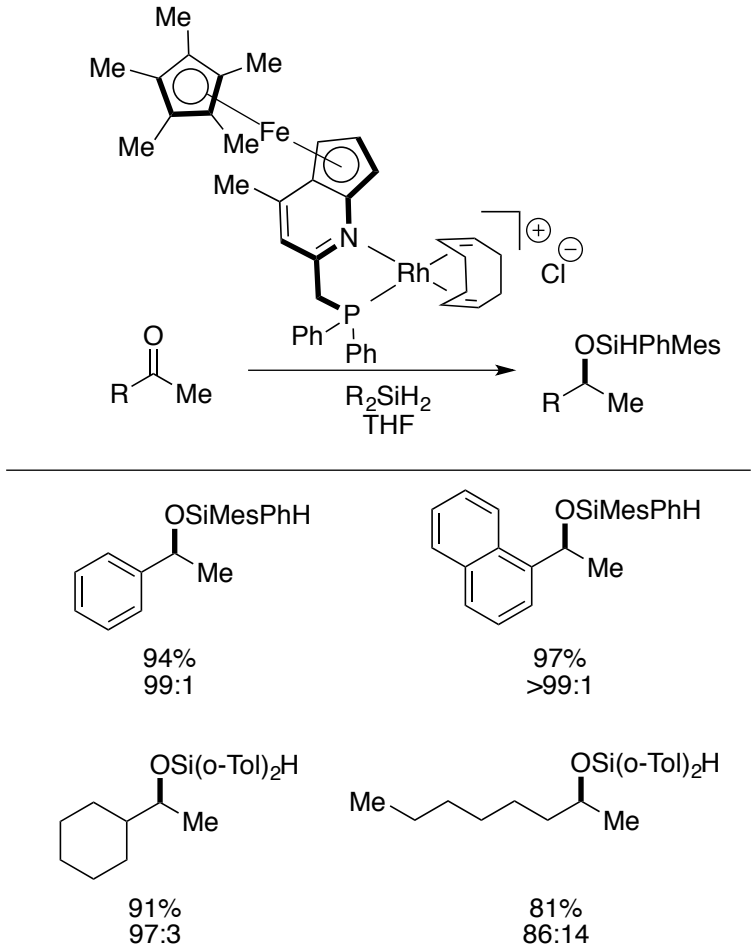
Scheme 7. Hartwig asymmetric arene silylation employing chiral rhodium catalysts

B. Background and Significance

1. Asymmetric Hydrosilylations with Ru and Rh Catalysts

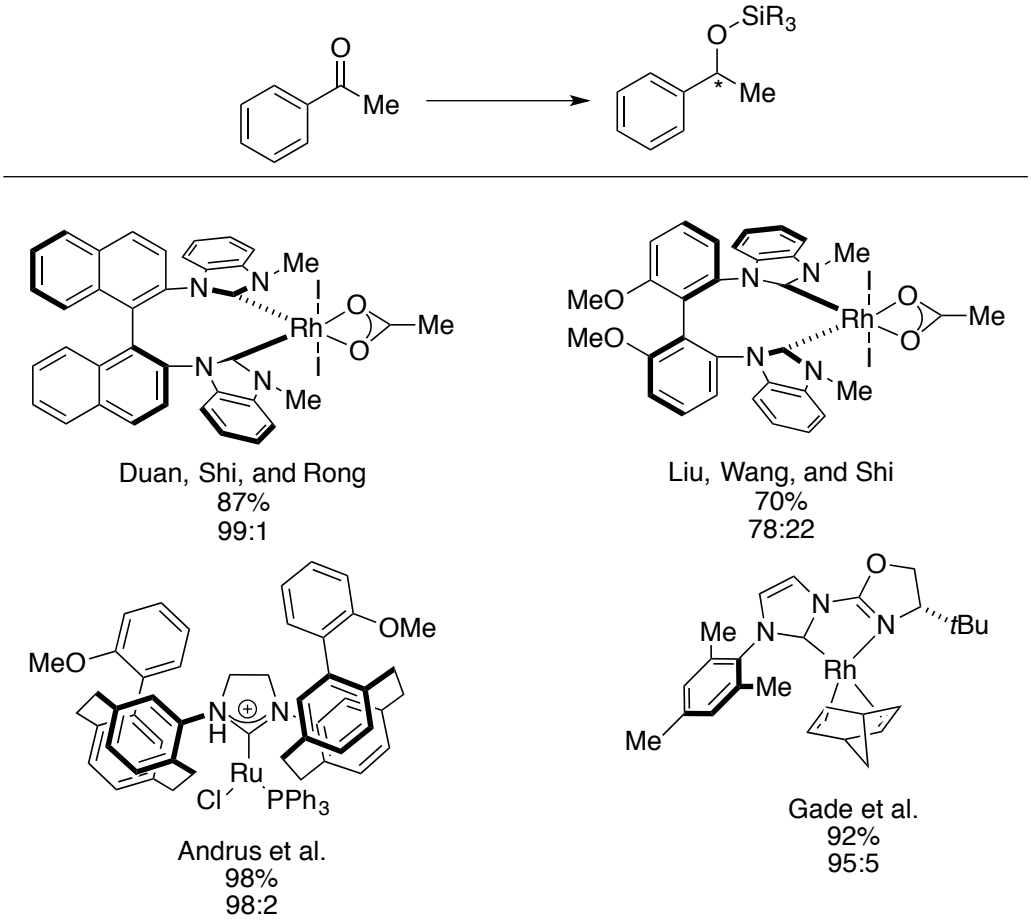
Nishiyama pioneered the field of asymmetric hydrosilylations with a series of rhodium (III) bis(oxazolinylpyridine) (Rh-PYBOX) catalysts reducing alkyl aryl ketones. Acetophenone was hydrosilylated in 90% yield with a 97:3 er.[29] More recently, Fu and Tao employed the use

of a rhodium (II) planar-chiral ferrocenyl P,N-ligand to achieve high selectivities in the hydrosilylation of a variety of dialkyl and alkyl-aryl ketones (**Scheme 8**).[30]



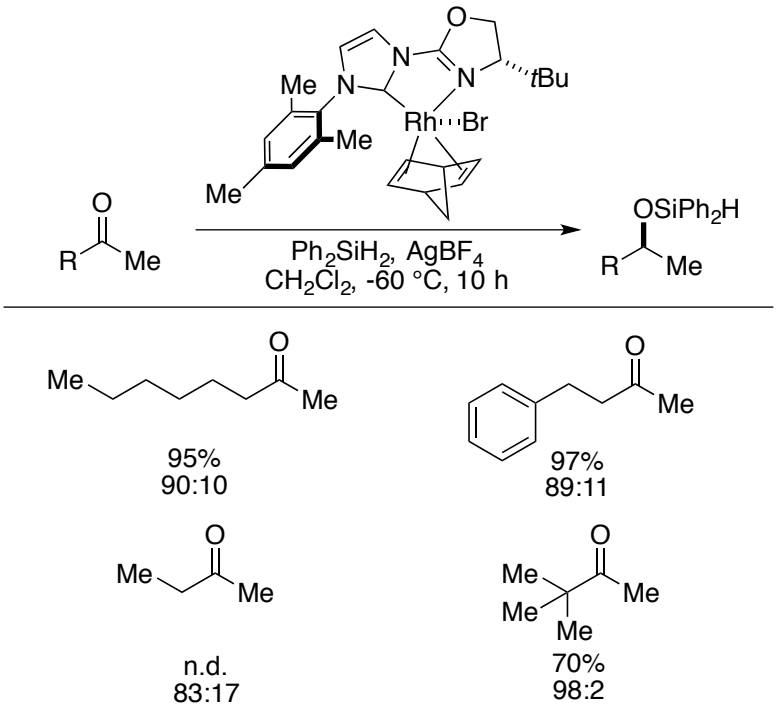
Scheme 8. Representative product scope of Fu and Tao

In addition to amine and phosphine ligands, a few chiral N-heterocyclic carbene (NHC) catalysts have been employed successfully in asymmetric hydrosilylations.[31–35] The four examples highlighted (**Scheme 9**) were able to reduce acetophenone with good to high selectivities.



Scheme 9. NHC catalysts applied to the hydrosilylation of acetophenone

While all examples above were able to reduce alkyl-aryl ketones with good selectivities, only Gade's catalyst was able to facilitate the asymmetric hydrosilylation of dialkyl ketones (**Scheme 10**). The rhodium complex reduced 2-octanone with a 90:10 selectivity; however, the hydrosilylation of 2-butanone proceeded with only 83:17 er.[34,35]

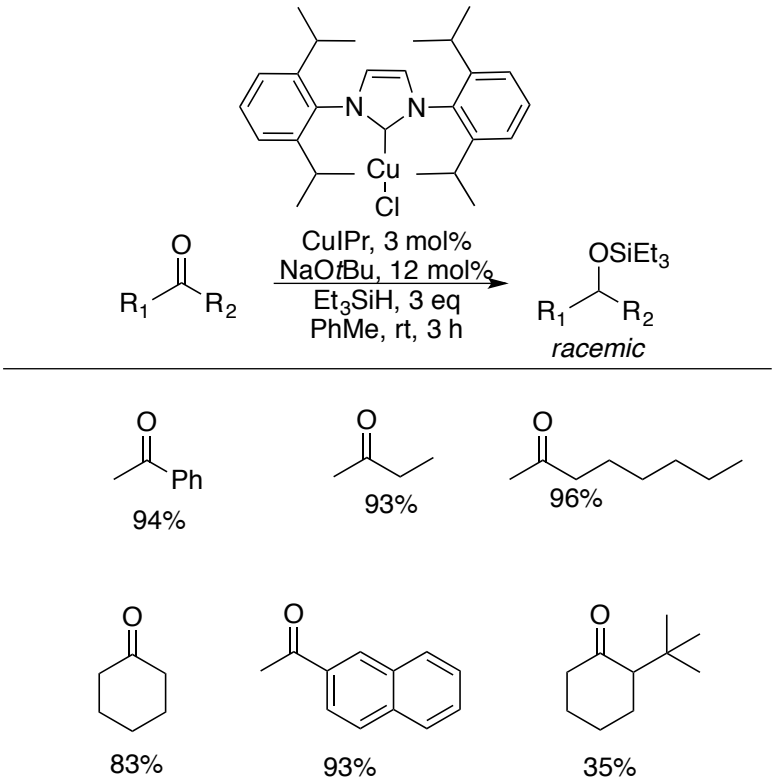


Scheme 10. Representative dialkyl ketones used by Gade

2. Copper Catalyzed Hydrosilylations

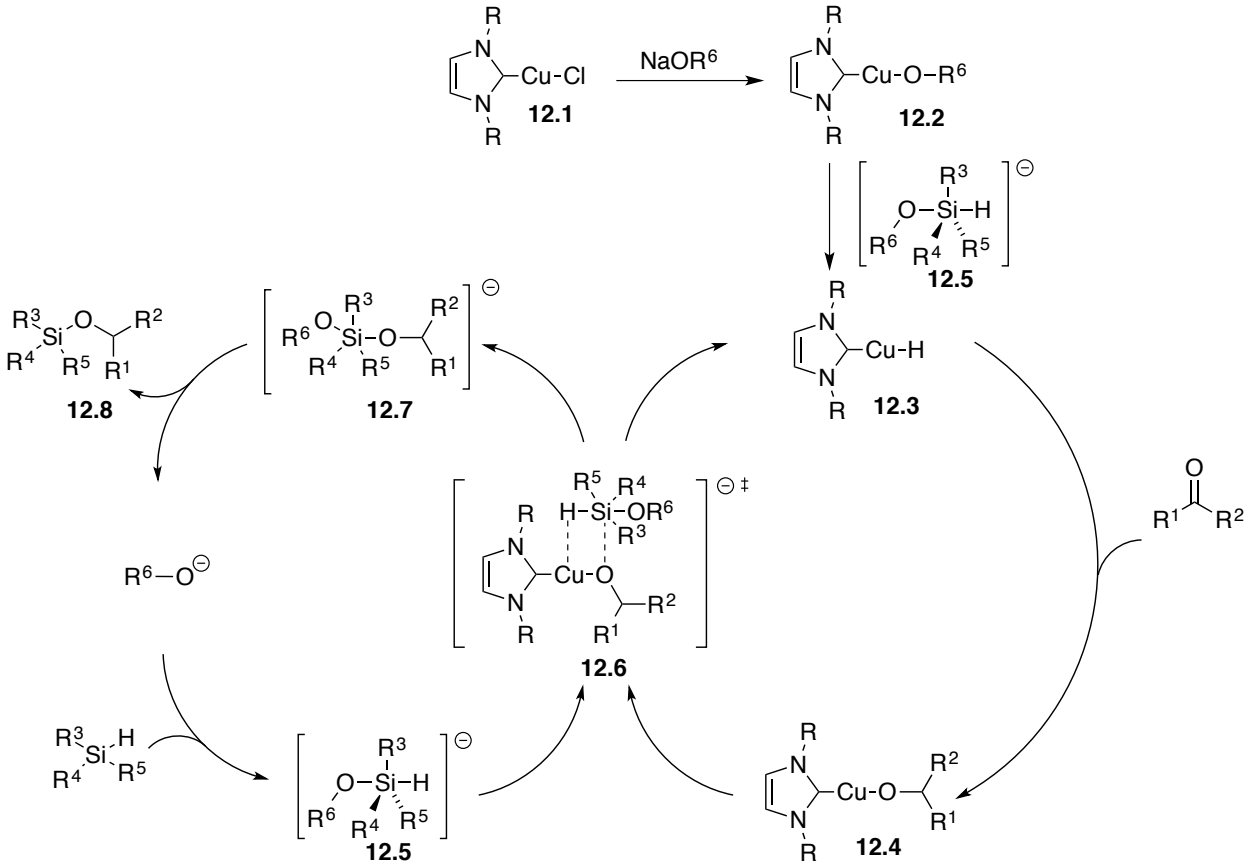
As seen in all of the examples listed thus far, transition metal catalyzed hydrosilylations are most frequently developed from complexes of group 8 and 9 metals such as ruthenium, rhodium, and iridium, but recently there have been reports of using group 11 metals as less expensive, yet effective, alternatives. [36]

Specifically, copper hydride sources are powerful reducing agents for many reactions, including the hydrosilylation of ketones. [37–41] The well-established CuIPr NHC complex was shown to be an efficient hydrosilylation catalyst of both dialkyl and alkyl aryl ketones (**Scheme 11**).[42]



Scheme 11. Representative ketone scope for the hydrosilylation using CuIPr

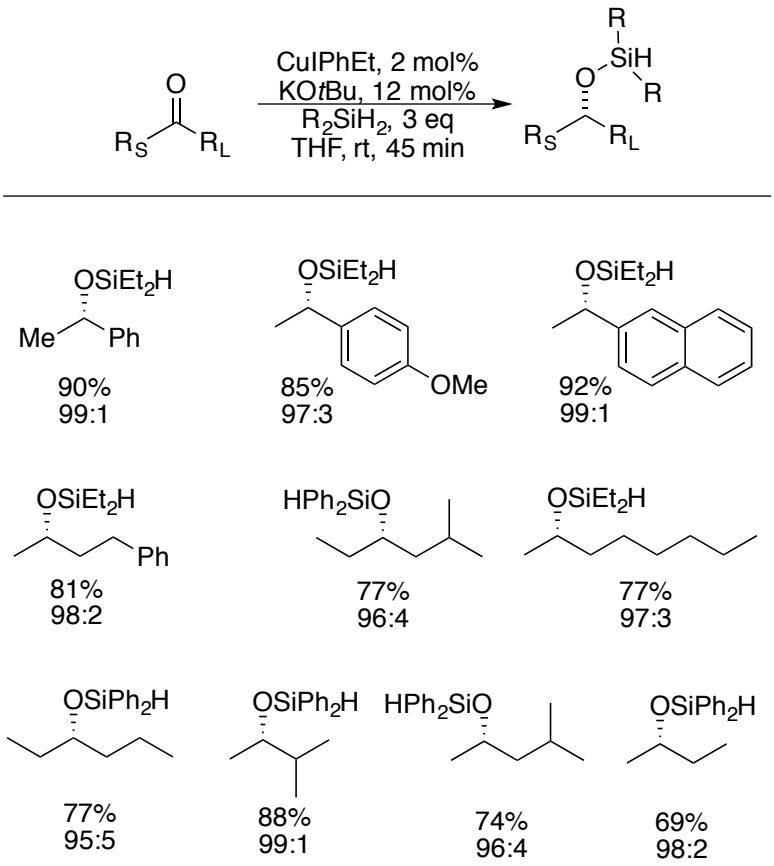
The catalytic cycle for hydrosilylations using copper NHCs proposed by Leyssens et al.[43] His group employed kinetic and computational DFT studies to validate their proposed mechanism. **Scheme 12** begins with the NHC copper chloride **12.1** undergoing a ligand exchange with a Lewis base, usually sodium or potassium *tert*-butoxide, to give the copper alkoxide **12.2**. A σ-bond metathesis of **12.2** with the Lewis base activated silane **12.5** gives the active copper hydride **12.3**. The copper hydride coordinates to a ketone in the rate-limiting step to give copper alkoxide **12.4**. The pentavalent hydridosilicate **12.5**, formed by simple nucleophilic attack of the alkoxide base to the silane reagent, and intermediate **12.4** proceed through the four-center transition state **12.6**. Another σ-bond metathesis regenerates the active copper hydride **12.3** and produces the hypervalent silicon species **12.7**, which quickly reforms the original alkoxide base and the desired hydrosilylated product **12.8**.



Scheme 12. The catalytic cycle for copper NHC catalyzed hydrosilylations

3. CuIPhEt Hydrosilylations

Because of the success of Cu-NHCs in the field of hydrosilylations, [42] the Gawley group applied CuIPhEt toward the reduction of an assortment of ketones. In the initial paper regarding the scope of CuIPhEt, ten examples are reported with good yields and excellent enantioselectivities (**Scheme 13**). [44] In the presence of CuIPhEt, the hydrosilylation of acetophenone, the benchmark test for catalysts in this category, gives a 99:1 er in 90% yield after 45 minutes at room temperature. The hydrosilylation of 2-butanone occurred with a 98:2 er—meaning the chiral pocket of CuIPhEt can differentiate between a methyl and ethyl substituent. The record hydrosilylation on this substrate before this application was achieved with Gade's bisoxazoline rhodium catalyst giving an 83:17 er (**Scheme 10**).[34]



Scheme 13. Silyl ethers formed from the asymmetric hydrosilylation with CuIPhEt

There is no other asymmetric hydrosilylation catalyst as of yet that can match CuIPhEt in its enantioselectivity when reacting with dialkyl ketones. A typical CuIPhEt reaction is performed under mild conditions at room temperature in THF for less than 60 minutes with only 2 mol% catalyst loading. [44] Gawley proposed that the reaction times are shorter than CuIPr (3-4 hours) due to the increased steric bulk around the copper and decreased propensity to dimerize.

To develop a *post hoc* rationale for the selectivities observed, DFT calculations (B3LYP 3-21g-d) were performed. The copper-coordinated ketone intermediate had a 3.6 kcal/mol difference between the energies of the orientation of acetophenone in the configuration shown and the orientation with the methyl (S) and phenyl (L) reversed (**Figure 1**). Because of the symmetry in the catalyst, the hydride should always be delivered to the *Re* face of prochiral

ketones in which the larger substituent is oriented in the quadrant away from the (*R,R,R,R*)-CuIPhEt phenyl substituent.

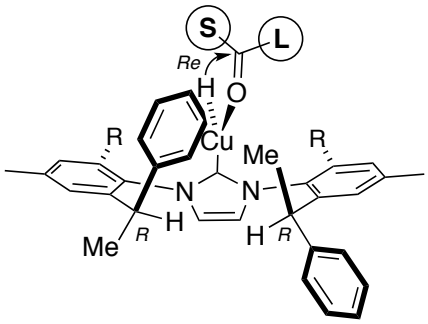
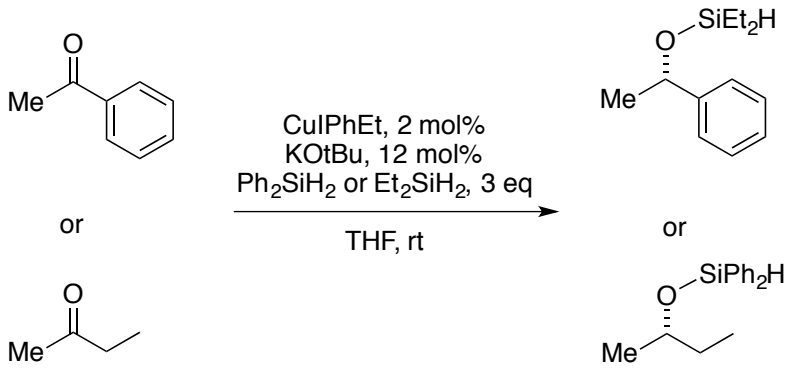


Figure 1. 3D model showing the delivery of the hydride to the Re face of a prochiral ketone by (*R,R,R,R*)-CuIPhEt

C. Results and Discussion

1. Finding a Reproducible Procedure

Reproducing previous work involving the hydrosilylation of alkyl-alkyl and alkyl-aryl ketones using CuIPhEt proved to be a challenge. Initial efforts focused on both acetophenone and butanone (**Table 1**). As seen in the first two entries, following the published procedure did not reliably give either hydrosilylation product. Distilling the silane and subliming the potassium tert-butoxide immediately before the reaction or use of fresh reagents also did not afford the desired products regularly (entries 3-6). Interestingly, one attempt (entry 3) did provide the product in excellent yield; however none of the other attempts in entries 3 and 4 gave any product.

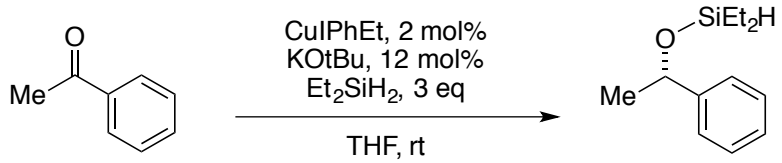


Entry	Substrate	Conditions	Attempts	Results
1	acetophenone	Published procedure [45]	4	Complex mixture
2	butanone	Published procedure	3	First attempt gave some product, the other two decomposed
3	acetophenone	Purified all reagents immediately before reaction	3	One attempt gave product, the other two decomposed
4	butanone	Purified all reagents immediately before reaction	3	Complex mixture
5	acetophenone	New silane, base, and ketone	2	Complex mixture
6	butanone	New silane, base, and ketone	1	Complex mixture

Table 1. Attempts to reproduce hydrosilylations using CuIPhEt and check the reagents

These tests led us to believe that the reagents were not the source of failure, so the issue must remain within the procedure. Also, the volatility of butanone made it difficult to tell if starting material was indeed consumed, so we switched our focus to solely to acetophenone. In the published procedure for hydrosilylations, CuIPhEt and the base are dissolved in THF and stirred for five minutes before the addition of the silane. This is designed to allow for the ligand exchange of the chloride and alkoxide and the subsequent formation of the active copper hydride

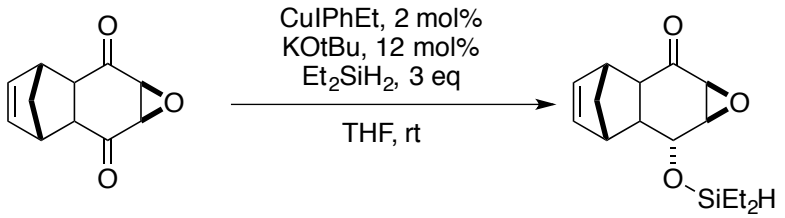
(**Scheme 12**). After ten more minutes of stirring, the ketone is finally introduced. Modifying the time scale of the additions did not provide a route to a more reproducible procedure (**Table 2**). Eliminating any gaps in the addition only accelerated the reaction failure (entry 1). Increasing the stirring time between additions did not hamper the decomposition.



Entry	Conditions	Results
1	Did not wait between reagent additions	Complex mixture
2	Waited one hour between additions	Complex mixture
3	Waited 6 hours between base and silane additions	Complex mixture
4	Used PhMe as solvent	Complex mixture

Table 2. Attempts to modify the procedure of CuIPhEt hydrosilylations

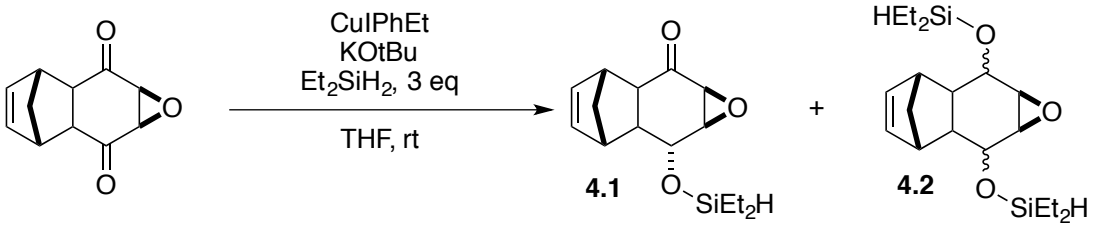
After the previous attempts, an average reaction success rate of 5% was achieved. We feared that the benzylic position of the carbonyl and eventual siloxane in the acetophenone reductions could be the source of further complications. At this point, we changed to the *meso*-diketone used in an ATH by the McIntosh lab (**Scheme 4**). While this ketone did not immediately give good results, it did give cleaner reactions, so we chose to proceed with it.



Entry	Conditions	Attempts	Results
1	Published Procedure	3	Complex mixture
2	Purified all reagents immediately before reaction	3	Complex mixture

Table 3. Attempts to reduce the *meso*-diketone with CuIPhEt

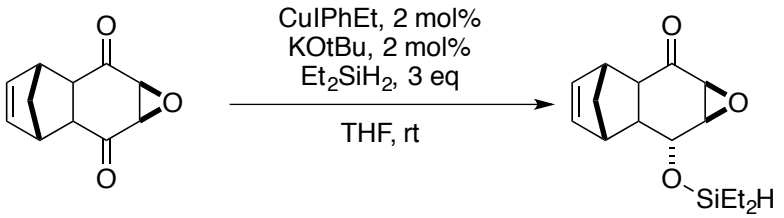
Efforts were then focused on the catalyst and base loading of the reaction (**Table 4**). Decreasing the catalyst loading did not clean up the complex mixture of the reaction. Increasing the amount of catalyst caused over-reduction in one case. Decreasing the base loading still afforded an inseparable mixture of products; however, the ^{1}H-NMR analysis of the crude reaction showed fewer byproducts. Decreasing the base loading further (entry 4) provided the desired product once and allowed for the recovery of the starting material in the other two trials.



Entry	Conditions	Attempts	Results
1	Catalyst loading 1%	1	Complex mixture
2	Catalyst loading 3%	2	Over-reduced ketone **4.2** obtained once, complex mixture in other
3	Base loading 6%	3	Mixture
4	Base loading 2%	3	Reaction worked once, starting material not consumed in others

Table 4. Catalyst and base loading studies

Suspecting that atmospheric oxygen could be the culprit, the reactions were performed in a glove box with oxygen levels well below 0.3 ppm (**Table 5**). No product was ever detected under these careful conditions. The reaction would only work, on occasion, when performed in the hood under nitrogen (entry 3). Any intentional introduction of air greater than 3 μL caused immediate reaction failure, but reaction success was not guaranteed below those levels.



Entry	Conditions	Attempts	Results
1	Entire reaction and work up in glovebox	1	Starting material not consumed
2	Reaction in glovebox, work up in hood	2	Starting material not consumed
3	Set up in glovebox, reaction and work up in hood	5	Reaction worked once
4	Injected 1 μL air	1	Complex mixture
5	Injected 2 μL air	1	Reaction succeeded
6	Injected 3 μL air	1	Complex mixture
7	Injected 5 μL air	1	Complex mixture

Table 5. Modifying the atmospheric conditions

A conversation with Don Watson brought to light a possible source for the limited reproducibility of the hydrosilylations. He suggested that moisture, not air could be the crucial component to the reaction. We hypothesized that the base, potassium *tert*-butoxide, is actually too bulky to perform the ligand exchange with the chloride on CuIPhEt as its suggested role in the catalytic cycle. In the original reports, our group used sublimated KOtBu stored in a bench-top desiccator. Due to the extreme hydroscopic nature of the base, it likely converted at least partially to KOH upon brief exposure to the atmosphere. This much smaller hydroxide could potentially allow for proper hydrosilylation catalysis. It was suggested to perform an *in situ* exchange of the *tert*-butoxide for a smaller alkoxide such as a methoxide or ethoxide through the

use of the corresponding alcohol as a co-solvent. This particular method was not successful, but the thought process proved to be fruitful.

Initially, solid sodium methoxide stored in the glovebox was used. Reproducibility was still somewhat limited due to difficulties in weighing milligram quantities of a fine powder in a static filled environment. Often times, the over-reduced disilane **4.2** was produced. Changing to a 0.5 M solution of sodium methoxide in methanol provided a way to both accurately measure the base loading and circumvent the need for a glovebox. To get consistent results, the base loading was decreased to a 1:1 ratio with the catalyst (**Figure 2**). The silane was cleaved to afford the alcohol with a 97:3 er in 93% yield.

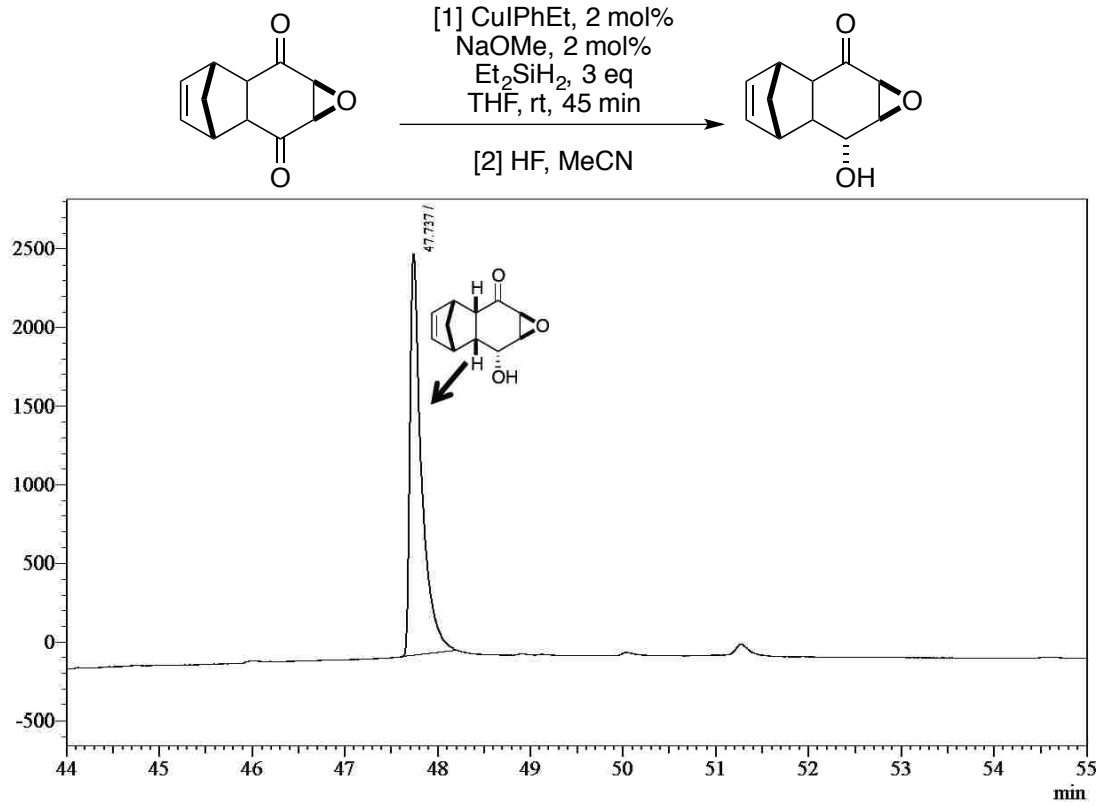


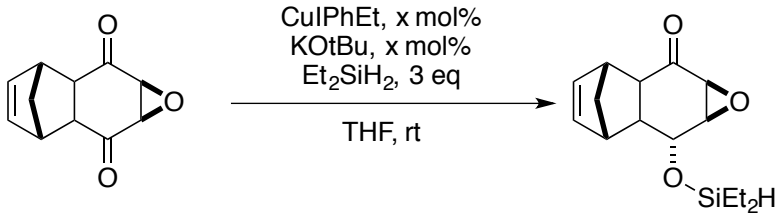
Figure 2. The asymmetric reduction of a *meso*-diketone with CuIPhEt

2. The Large-Scale Reduction of a *meso*-Diketone

When compared to the original McIntosh method (**Scheme 4**), the CuIPhEt hydrosilylation of the *meso*-diketone time is much faster, the yield is greater, and the selectivity is much improved.

Larger scale reactions went smoothly with only small changes necessary to the procedure (**Table 6**). As we began multiplying the amount of starting material from 200 mg to 1 g, a noticeable exotherm was observed. The heat generated in the reaction seemed to accelerate the reaction rate, thus giving more disilylated product in the 45 minute reaction time. We decided to begin simultaneously decreasing the catalyst loading while increasing the substrate loading. This worked well giving high yields and selectivities all close to 97:3 er. In typical small-scale reactions, the ketone is added last to a mixture of the catalyst, base, and silane. On reactions

larger than 4 g, better yields were achieved when this order of addition was reversed and the catalyst, base, and silane were slowly cannulated into the dissolved ketone. This did slightly increase reaction times (to two hours), but it completely eliminated any disilylated byproducts. Attempting to cool the reaction mixture did not improve selectivity and decreased the yield.



Entry	Catalyst Loading (mol%)	Amount *meso*-diketone (g)	Yield (%)
1	2	0.2	93
2	2	1	60
3	1	2	90
4	0.5	4	90
5	0.25	7.5	93
6	0.24	10	93

Table 6. Scaling up the hydrosilylation of a meso-diketone

3. Further Expanding the Substrate Scope

To prove the hydrosilylation procedure is now fully optimized and reproducible, the original published substrate scope of CuIPhEt hydrosilylations was revisited. The new protocol was used to effectively reduce 2-octanone (**Figure 3**). The product was recovered in 95% yield and with over 99:1 selectivity. This is both higher yields and selectivity than the previously published Gawley method.

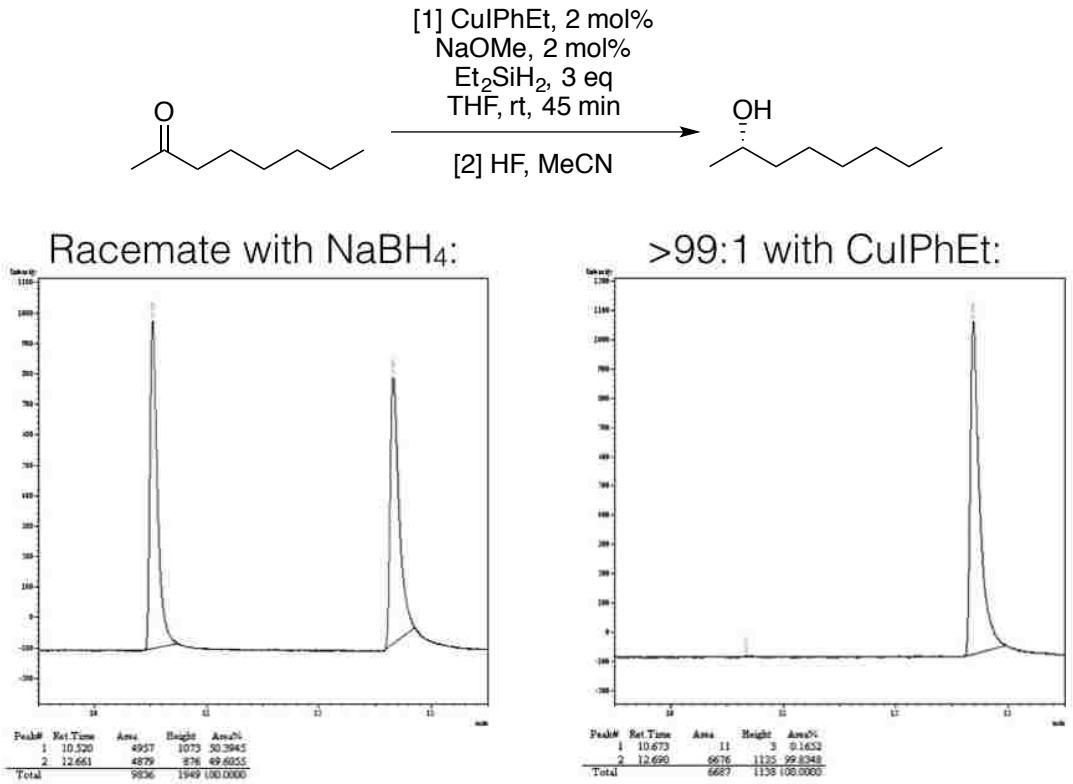
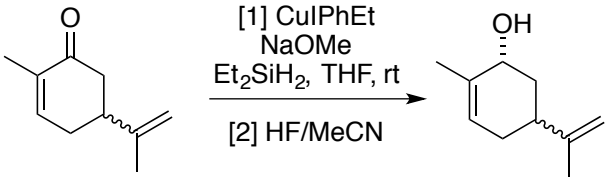


Figure 3. The asymmetric reduction of 2-octanone with CuIPhEt

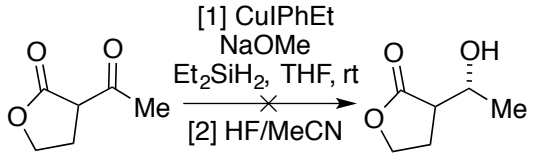
In an effort to expand the substrate scope of CuIPhEt hydrosilylation beyond simple ketones, we began investigating α,β-unsaturated ketones—specifically carvones. This class of ketones is interesting because both 1,2 and 1,4-reductions are possibilities. Buchwald observed 1,4 reductions on both α,β-unsaturated cyclic ketones and acyclic esters using the achiral NHC CuIPr. [46] Regrettably, no conditions were found to afford a clean reaction (**Table 7**). Inseparable, complex mixtures were obtained even at decreased catalyst loading. GC/MS of the reaction mixture indicated the starting material was likely silylated at multiple positions.



Entry	Conditions	Results
1	R-Carvone, 2 mol% loading	Complex mixture
2	S-Carvone, 2 mol% loading	Complex mixture
3	R-Carvone, 1 mol% loading	Complex mixture
4	S-Carvone, 1 mol% loading	Complex mixture

Table 7. Attempts to hydrosilylate carvone

We next investigated 2-acetylburtyolactone, an interesting substrate to test both the chemoselectivity of CuIPhEt and to explore the possibility of a dynamic kinetic resolution with the stereocenter α to the carbonyl. Despite longer reaction times and higher catalyst loading, no conversion of the starting material was ever observed (**Table 8**).

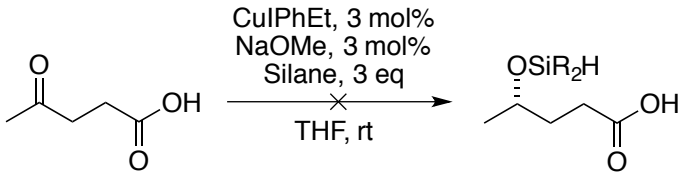


Entry	Conditions	Results
1	1 mol% loading, 1 hr	Starting material recovered
2	1 mol% loading, 19 hr	Starting material recovered
3	2 mol% loading, 19 hr	Starting material recovered
4	4 mol% loading, 19 hr	Starting material recovered

Table 8. Attempts to hydrosilylate 2-acetylbutryolactone

We next turned our attention to the commodity chemical levulinic acid, a keto acid used as a precursor for many cosmetics, pharmaceuticals, and herbicides.[47] This substrate would test

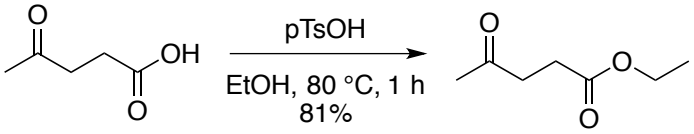
the ability of CuIPhEt to reduce a carbonyl in the presence of a carboxylic acid. Once asymmetrically reduced, a lactonization could occur to give a single enantiomer of γ-valerolactone, which costs over $80 per 100 mg from Sigma Aldrich. Attempts to reduce the unprotected keto acid resulted in no recovered compounds except for CuIPhEt regardless of which silane was used (**Table 9**).



Entry	Silane	Results
1	Diethyl silane	Nothing recovered
2	Diphenyl silane	Nothing recovered

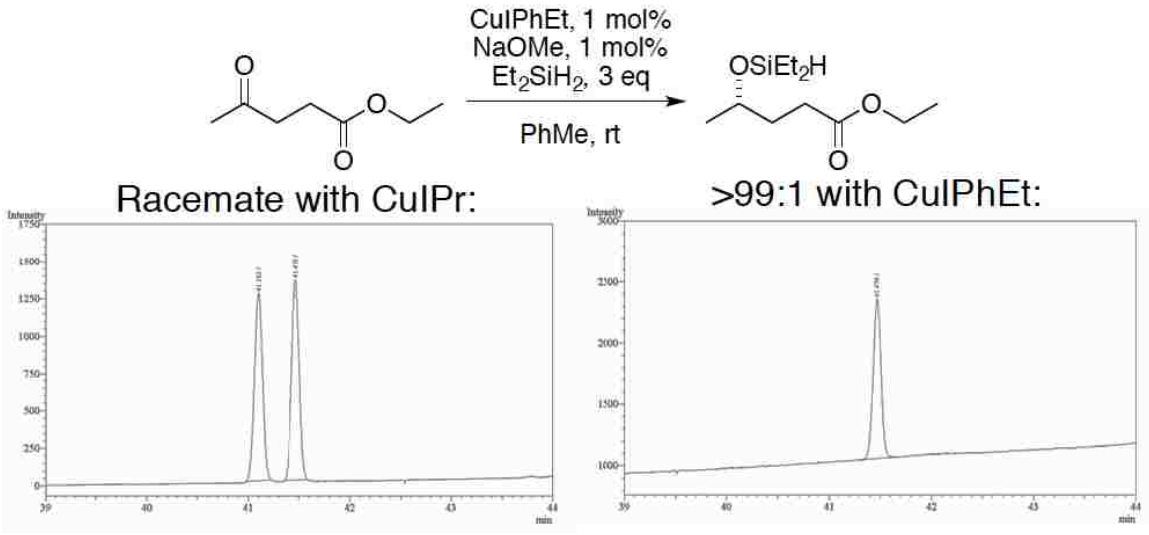
Table 9. Attempts to reduce unprotected levulinic acid

We then converted the carboxylic acid (**Scheme 14**) into an ester via a Fisher esterification. Heating the acid in absolute ethanol at reflux in the presence of *p*-toluenesulfonic acid gave the ethyl ester quickly and in good yields.



Scheme 14. Esterification of levulinic acid

Once the ethyl ester was formed, the CuIPhEt hydrosilylation was attempted. Through minor reaction modifications, the optimized conditions were found to be 1 mol% catalyst and base loading in toluene (**Scheme 15**). The reaction proceeded smoothly with good yields and excellent enantioselectivity.



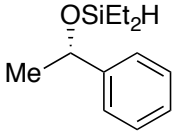
Scheme 15. The asymmetric hydrosilylation of levulinic ethyl ester

D. Conclusion

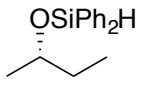
The asymmetric reduction of ketones has been a recurrent theme in organic chemistry. Noyori-type hydrogenations and asymmetric transfer hydrogenations have been the golden standard for the past two decades. *N*-Heterocyclic carbenes have been successfully employed in the asymmetric hydrosilylations of various ketones. CuIPhEt was reported to be an efficient hydrosilylation catalyst of both alkyl-aryl and dialkyl ketones. Reproducing the work on the original substrate scope, however, proved to be a challenge. Through modifying the procedure to include a less sterically hindered base at lower loadings, excellent yields and selectivities have been achieved on 2-octanone, a ketone from the original scope, and on a *meso*-diketone, a new application for CuIPhEt. The *meso*-diketone is an early stage intermediate in the McIntosh synthesis of a natural product, so the reduction was carried out on a 10 g scale to prove its feasibility in total synthetic endeavors. The ethyl ester of levulinic acid, a commodity chemical, was also asymmetrically reduced using CuIPhEt.

E. Experimental

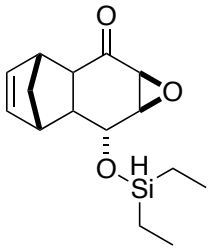
General Procedure for CuIPhEt Hydrosilylation: To an oven dried round bottom flask fitted with a septum was added CuIPhEt (2 mol%, 0.02 mmol, 15.3 mg). The flask was evacuated and flushed with N_2 three times. Dry THF (2 mL) was added and stirred until the CuIPhEt dissolved. NaOMe in MeOH (0.5 M, 2 mol%, 40 μL) was added and stirred for 5 min. Freshly distilled silane (3 eq, 3 mmol) was added. An immediate color change to bright yellow was observed and the reaction was stirred for an additional 5 min before addition of the ketone (1 eq, 1.0 mmol, in concentrated THF solution if solid). The reaction progress was monitored using TLC. If the silane was cleaved, 2 mL 5% HF/MeCN was injected and stirred for 5 minutes. Upon completion the reaction solution was concentrated under reduced pressure. The residue was purified via Kugelrohr distillation.



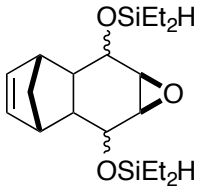
((*S*)-1-phenylethoxy)triethylsilane: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (q, J = 7.84 Hz, 2.35 Hz, 4H), 0.95 (t, J = 7.87 Hz, 3H), 1.03 (t, J = 7.87 Hz, 3H), 1.51 (d, J = 6.41 Hz, 3H), 4.47 (q, J = 2.44 Hz, 1H), 4.92 (q, J = 6.44 Hz, 1H), 7.23-7.41 (m, 5H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 5.46, 6.70, 26.43, 72.44, 125.37, 127.00, 128.18, 145.94.



((S)-sec-butoxy)diphenylsilane: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, J = 7.52 Hz, 3H), 1.11 (d, J = 6.49 Hz, 3H), 1.46 (m, 2H), 3.82 (sextet, J = 5.92 Hz, 1H), 5.38 (s, 1H), 7.25-7.37 (m, 6H,), 7.51-7.61 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.11, 22.75, 32.02, 72.34, 127.95, 130.16, 134.68, 134.70.



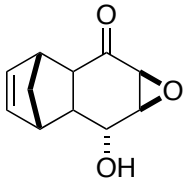
Mono-hydrosilylated epoxyketoalcohol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69 (m, 4H), 0.97 (m, 6H), 1.21 (d, J = 8.24 Hz, 1H), 1.34 (d, J = 8.17 Hz, 1H), 2.87 (m, 2H), 3.03 (br s, 1H), 3.09 (br s, 1H), 3.22 (d J = 4.36 Hz, 1H), 3.42 (dd, J = 4.28 Hz, 3.36 Hz, 1H), 4.45 (s, 1H), 4.66 (m, 1H), 5.99 (ddd, J = 2.60 Hz, 5.03 Hz, 16.21 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 5.37, 6.78, 42.75, 43.62, 45.26, 49.15, 50.91, 54.72, 59.29, 68.50, 132.59, 136.34, 208.7.



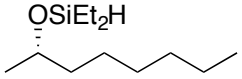
Di-hydrosilylated epoxyketoalcohol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (m, 8H), 0.99 (m, 12H), 1.21 (d, J = 8.24 Hz, 1H), 2.29 (s, 3H), 2.84 (s, 2H), 3.40 (p, J = 2.58 Hz, 2H), 4.73 (s, 2H), 6.00 (7, J = 1.92 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 5.25, 6.48, 42.71, 50.54, 54.72, 59.29, 68.76, 134.59.

Large-Scale CuIPhEt Hydrosilylation: To an oven dried round bottom flask fitted with a septum was added CuIPhEt (0.24 mol%, 0.13 mmol, 99.7 mg). The flask was evacuated and flushed with N_2 three times. Dry THF (2 mL) was added and stirred until the CuIPhEt dissolved. NaOMe in MeOH (0.5 M, 0.16 mol, 0.31 mL) was added and stirred for 5 min. Freshly distilled diethylsilane (3 eq, 156 mmol, 20.2 mL) was added. An immediate color change to bright yellow was observed and the mixture was cannulated into the *meso*-diketone (1 eq, 54 mmol, 10.4 g) dissolved in THF (~100 mL). The reaction progress was monitored using TLC. After 2 hours, 5% HF/MeCN (75 mL) was injected and stirred for 5 minutes. Upon completion the reaction

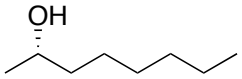
solution was concentrated under reduced pressure. The residue was purified via recrystallization in hexanes/Et_2O.



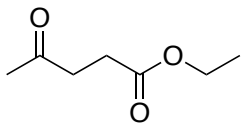
Epoxyketoalcohol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, J = 9.54 Hz, 1H), 1.31 (d, J = 8.38 Hz, 1H), 1.45 (dt, J = 8.39 Hz, 1.88 Hz, 1H), 2.97 (ddd, J = 11.20, 5.75, 3.21, 1H), 3.03 (br s, 1H), 3.09 (br s, 1H), 3.17 (dd J = 11.0 Hz, 3.43 Hz, 1H), 3.29 (d, J = 4.36, 1H), 3.57 (m, 1H), 4.65 (ddd, J = 9.35 Hz, 5.73 Hz, 3.39 Hz, 1H), 6.22 (ddd, J = 3.05 Hz, 5.53 Hz, 16.55 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 42.60, 44.88, 45.06, 49.58, 51.44, 54.75, 59.59, 67.47, 135.51, 136.15, 208.1.



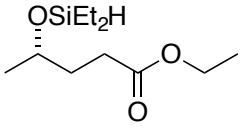
((S)-octan-2-yloxy)diethylsilane: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (q, J = 7.9 Hz, 4H), 0.90 (3H, m), 1.01 (t, J = 7.39 Hz, 6H), 1.18 (d, J = 6.59 Hz, 3H), 1.23-1.51 (m, 10H), 3.80 (sextet, J = 5.75 Hz, 1H), 4.44 (p, J = 2.34 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 5.58, 6.724, 14.09, 22.64, 23.41, 25.75, 29.32, 31.87, 39.40, 70.57.



(S)-2-octanol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J = 7.21 Hz, 3H), 1.18 (d, J = 6.35 Hz, 3H), 1.20-1.58 (10H, m), 3.85 (sextet, J = 5.75, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.09, 21.99, 23.61, 25.25, 29.01, 31.23, 39.90, 69.87.



Levulinic acid ethyl ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1, 3H), 2.20 (s, 3H), 2.57 (t, J = 6.6, 2H), 2.75 (t, J = 6.5, 2H), 4.13 (q, J = 7.1, 2H), ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.18, 28.03, 29.91, 37.97, 60.65, 172.77, 208.15.



((S)-ethyl γ-valeryloxy)diethyl silane : ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (m, 4H), 0.99 (t, J = 7.7 Hz, 6H), 1.19 (d, J = 6.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 2H), 1.78 (m, 2H), 2.39 (m, 2H), 3.85 (p, J = 6.1 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 4.42 (p, J = 2.3 Hz, 1H) ^{13}C NMR (400 MHz, $CDCl_3$) δ 5.89, 6.68, 14.24, 23.26, 30.52, 34.15, 60.27, 69.37, 207.56.

$[\alpha]_D^{25} = -5.6$ (c = 2.5, $CHCl_3$)

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4. Literature Review: The Radical Formation of Azolyl Ketones

A. Introduction

Carbon-hydrogen bonds are ubiquitous within organic molecules. The archetypal, targeted approach to functionalization of these "un-functional" groups would allow for a flexible synthetic plan and would create much less waste and fewer byproducts—ideally only hydrogen gas. The abundance of carbon-hydrogen bonds that are energetically similar and the strong bond dissociation energy have historically limited the applicability of the reaction. While the field of C-H activations is not new, it has certainly gained in popularity within the last few decades possibly due to improvements on the bond selectivity and to innovative bond forming reactions. [1]

In general, the term C-H functionalization (and especially C-H activation) implies the use of an organometallic complex due to huge contributions from the field. [2] More recently, advances have been made to include selected metal-free C-H functionalization techniques.

B. Background and Significance

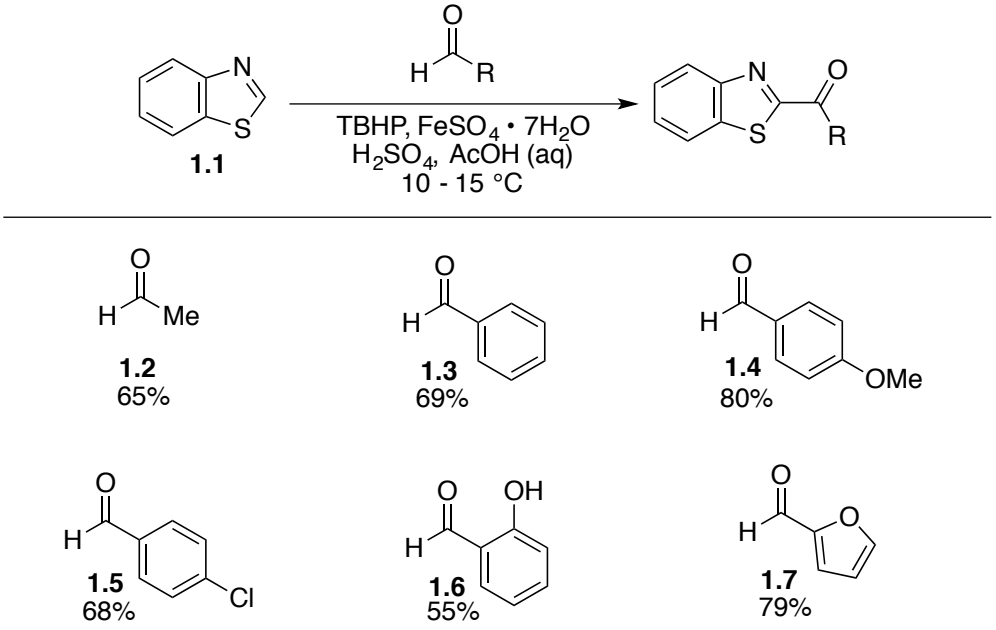
Charles Friedel and James Crafts first described the acylation of aromatic rings, a specific example of a C-H functionalization, in 1877. [3] An electron-rich aromatic ring reacts with the electrophile formed by an acyl chloride or acid anhydride and a Lewis acid. Because a double bond in the arene acts as the nucleophile, deactivated aromatic compounds are not tolerated within this system. Despite multiple advances in the field, heteroaromatic rings are not often employed in Friedel-Crafts acylations. [4] Unprotected nitrogens, oxygens, and sulfurs are often more reactive than the C-C double bond, resulting in the competing acylation of heteroatoms.

Acyl derivatives of heteroarenes, especially azoles, are useful synthetic targets. Azoles are central components in numerous natural products, medicines, and biologically relevant

compounds.[5] Described below is the direct access to acylated azoles through efficient and functional group tolerant pathways.

C. Minisci Reaction

Minisci reported the first direct acylation of a thiazole ring in 1969 through umpolung reactivity of the Friedel-Crafts reaction.[6] He observed the regioselective radical C-H functionalization of benzothiazole **1.1**. A threefold excess of the aldehyde was employed under acidic conditions in the presence of two stoichiometric equivalents of *tert*-butyl hydroperoxide (TBHP) and iron (II) sulfate radical initiators (**Scheme 1**).[7] Simple aliphatic aldehydes, such as acetaldehyde **1.2**, gave moderate yields. Benzaldehyde **1.3** gave slightly higher yields presumably due to the increased stability of the acyl radical due to resonance. Electron donating groups in the para position on the phenyl ring increased the nucleophilic character of the subsequently formed radical and consequently increased the yields, as seen with *p*-anisaldehyde **1.4**. Electron withdrawing substituents like *p*-chlorobenzaldehyde **1.5** had little effect on the yield. The use of salicylaldehyde **1.6**, however, resulted in a decrease in conversion to product. Heteroaromatic aldehydes, such as 2-furaldehyde **1.7** were well tolerated.



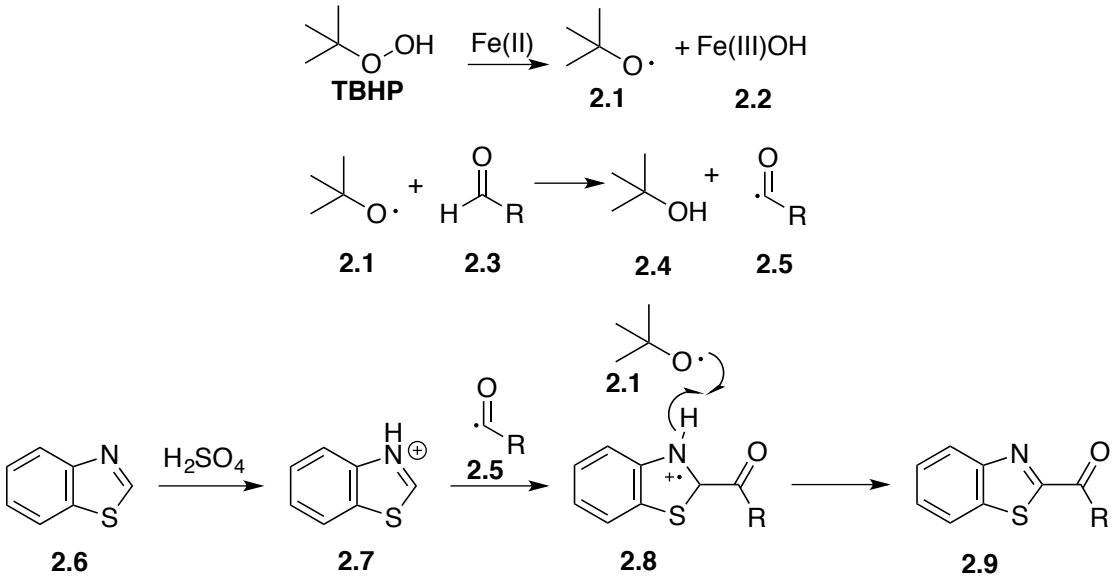
Scheme 1. Homolytic acylation of benzothiazoles described by Minisci

Although yields were not reported, Minisci claims similar results for quinoline, pyridine, acridine, isoquinoline, pyrazine, pyrimidine, and quinoxaline. The use of secondary and tertiary aliphatic aldehydes with any of the tested azoles resulted in decarbonylation of the aldehydes and successive alkylation, rather than acylation, of the heteroarene.

The rate of the acetylation of 6-nitrobenzothiazole in this system was double that of the benzothiazole indicating that electron deficient heteroarenes are more reactive to the nucleophilic acyl radical. Minisci noted this reaction is opposite to traditional Friedel-Crafts acylation both in reactivity and regioselectivity.

This Minisci reaction likely proceeds through a radical mechanism (**Scheme 2**). The TBHP oxidizes the iron sulfate to give the tert-butoxy radical **2.1** and iron (III) hydroxide **2.2**. The tert-butoxy radical **2.1** can then abstract a hydrogen atom from the aldehyde **2.3** to give tert-butanol **2.4** and the acyl radical **2.5**. Benzothiazole **2.6** is likely protonated by the acidic solution to give the thiazolium **2.7**, which reacts with radical **2.5** to give the radical cation **2.8**. A

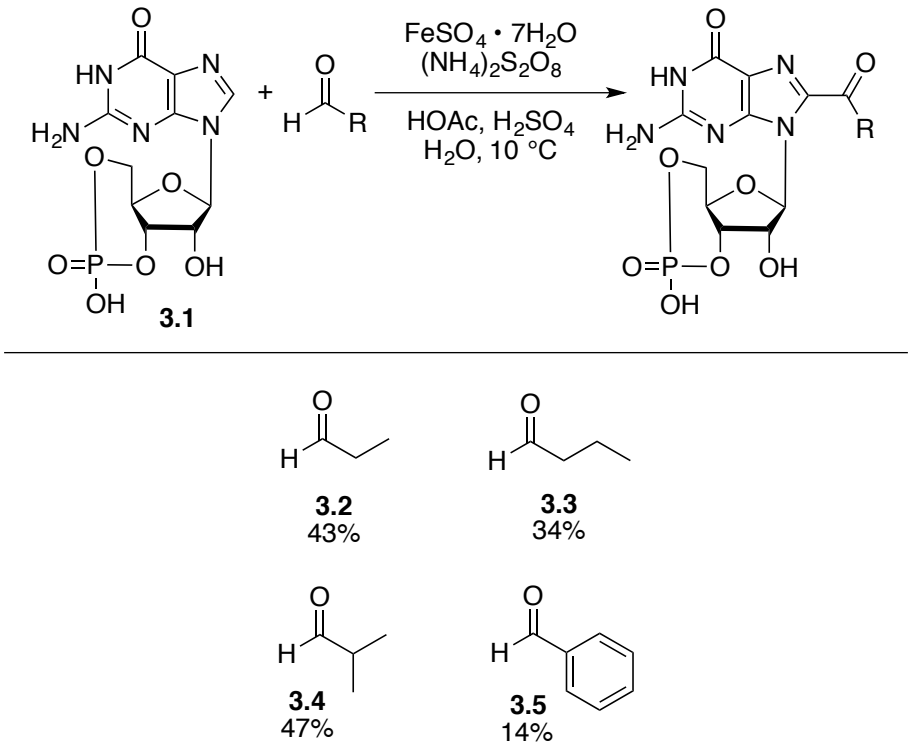
subsequent hydrogen atom abstraction rearomatizes the compound giving the 2-ketobenzothiazole **2.9**.



Scheme 2. The proposed mechanism of the Minisci Reaction

Christensen et al. acylated cyclic guanosine monophosphate (cGMP) **3.1** in low to moderate yields after modifying the Minisci conditions (**Scheme 3**).[8] Initially, the iron (II) sulfate and TBHP system described above was tested, but 8-methylguanosine 3',5'-cyclic phosphate was isolated due to the decomposition of the TBHP to a methyl radical. In order to circumvent alkylation competing with hydrogen atom abstraction from the aldehyde, the radical source was changed to ammonium persulfate. In these reactions, cGMP is dissolved in an acidic solution before the introduction of over forty equivalents of the aldehyde and nine equivalents of the iron sulfate and ammonium persulfate. The straight chain aliphatic aldehyde, propionaldehyde **3.2**, gave moderate yields. Increasing the chain length, as seen with butyraldehyde **3.3**, caused a decrease in yield. The branched chain isobutyrylaldehyde **3.4** had high yields; however, 8-isopropyl cGMP was also formed in 22% yield due to the decarbonylation of the aldehyde. Aromatic benzaldehyde **3.5** gave the lowest reported yield.

Attempts to acylate cyclic adenosine monophosphate (cAMP) did not provide any detectable conversion to products. Cyclic inosine monophosphate (cIMP) did afford acylated derivatives but in very low yields. Christensen found that the library of acylated cGMP derivatives showed high affinity for a cGMP-dependent protein kinase and were not hydrolyzed by phosphodiesterase. This indicated that the compounds might be exploited to study biological responses concerning cGMP.

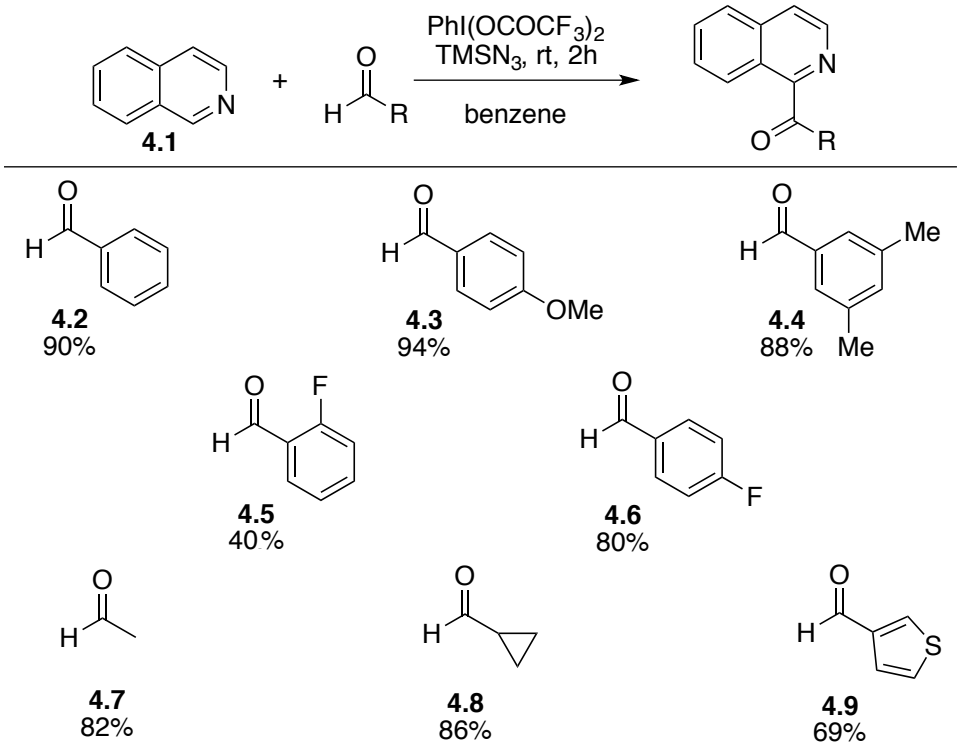


Scheme 3. Christensen's acylation of cGMP

D. Metal-Free Acylation Techniques

Matcha and Antonchick developed a metal-free strategy employing hypervalent iodine and trimethylsilyl azide at ambient temperature to acylate a variety of N-heterocycles.[9] In order to investigate the scope of the reaction, they began reacting isoquinoline **4.1** with various aldehydes (**Scheme 4**). Benzaldehyde **4.2** was used to optimize the oxidant and additive choices

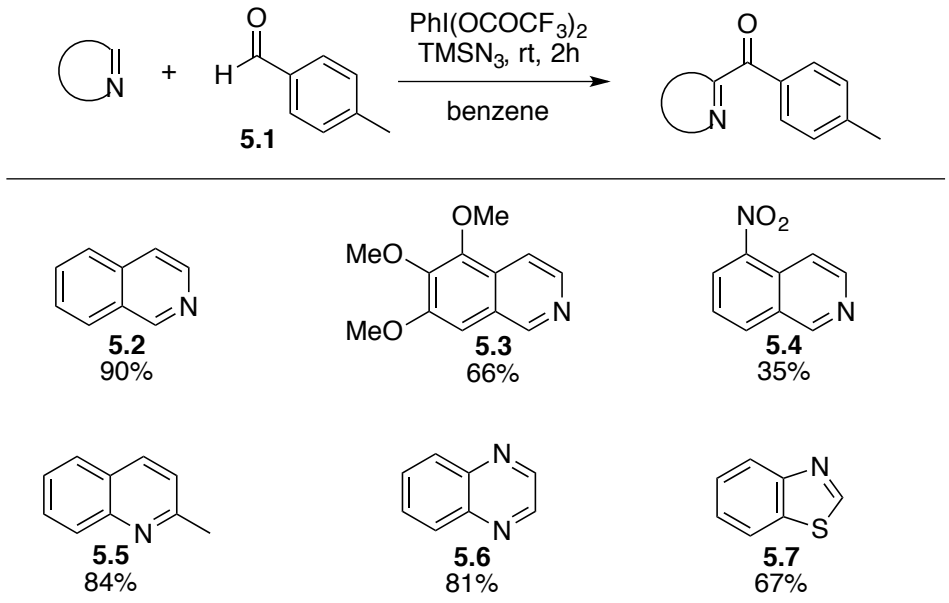
to [bis(trifluoroacetoxy)iodo]benzene and azidotrimethylsilane, respectively. The position of an electron donating substituent on the phenyl ring of the aldehyde had no noticeable effect on the yields, as seen with *p*-anisaldehyde **4.3**. Electron withdrawing substituents, however, give the best results when at the *para* position (**4.5**-**4.6**). Multiple substituents did not affect the yield (**4.4**), signifying that steric effects had little influence in this system. Aliphatic aldehydes, such as acetaldehyde **4.7**, worked as well. In fact, **4.7** was successfully used in a gram scale reaction in an open flask. More sensitive aldehydes were also tested in the system. Cyclopropanecarboxaldehyde **4.8** gave high yields of product with no noticeable decomposition. Thiophenecarboxaldehyde **4.9** was converted in good yield to product without any over-oxidation to a sulfoxide or sulfone.



Scheme 4. Characteristic scope of aldehydes used with isoquinoline by Matcha and Antonchick

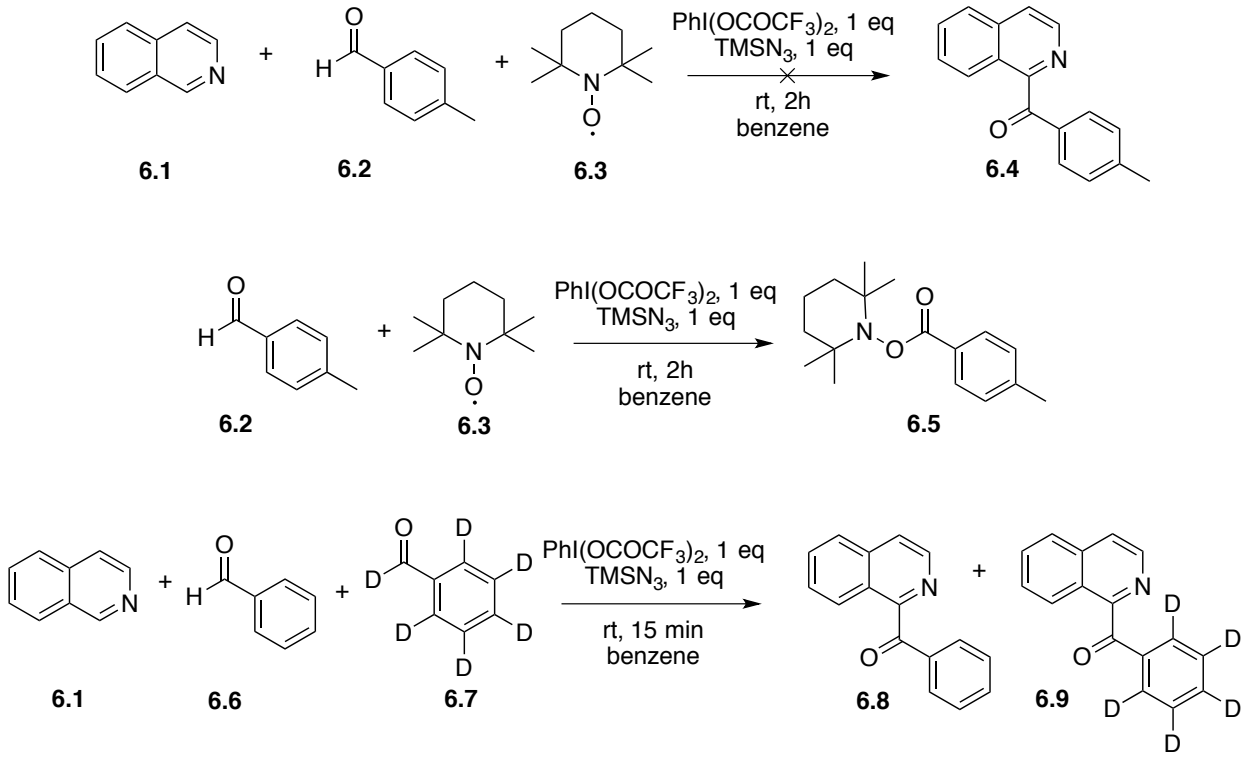
Equipped with a scope of compatible aldehydes, Matcha and Antonchick explored the range of N-heterocycles with *p*-tolualdehyde **5.1** (**Scheme 5**). Isoquinoline **5.2** gave the product

in high yield. The addition of electron donating groups, as seen in 5,6,7-trimethoxyisoquinoline **5.3**, seemingly did not decrease the electrophilic character of the N-heterocycle or the yield. The presence of a strongly withdrawing group in 5-nitroisoquinoline **5.4**, however, did decrease the yield. Quinoline afforded a mixture of mono- and disubstituted products, but blocking the 2-position with a substituent as in quinaldine **5.5** avoided this problem. A variety of other heterocycles, such as quinoxaline **5.6** and benzothiazole **5.7**, also gave good yields.



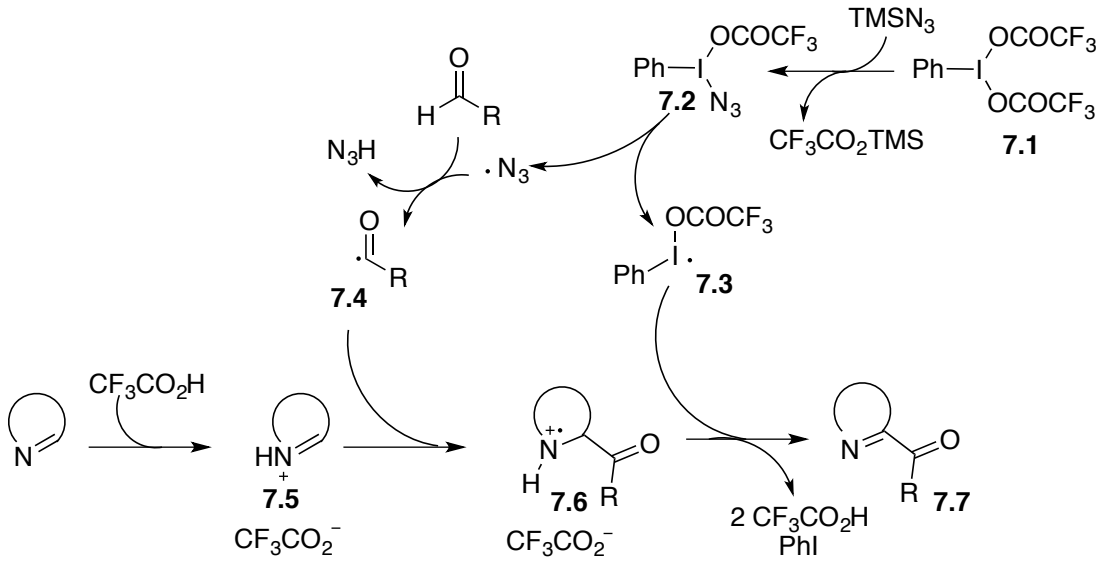
Scheme 5. Representative scope of N-heterocycles used by Matcha and Antonchick

A series of experiments were undertaken to investigate the mechanism (**Scheme 6**). When isoquinoline **6.1** and *p*-tolylbenzaldehyde **6.2** were reacted in the presence of the TEMPO radical trap **6.3**, no desired product was formed. Just mixing the aldehyde **6.2** and TEMPO **6.3** under the reaction conditions gave the isolable adduct **6.5** confirming the formation of an acyl radical *in situ*. The kinetic isotope effect was measured to be 5.7 by using [D_6]-benzaldehyde **6.7** in a competition experiment with benzaldehyde **6.6**—possibly indicating the rate limiting step is the formation of the acyl radical.



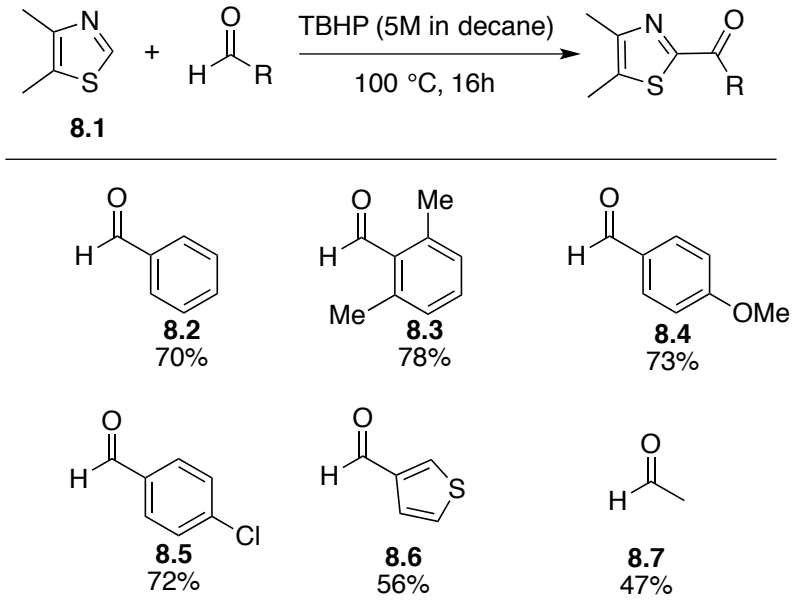
Scheme 6. Experiments to probe the reaction mechanism by Matcha and Antonchick

The proposed mechanism (**Scheme 7**) involves the formation of intermediate **7.2** from the ligand exchange between [bis(trifluoroacetoxy)iodo]benzene **7.1** and azidotrimethylsilane. The weak I-N bond in intermediate **7.2** experiences thermal homolytic cleavage to yield the trifluoroacetoxy iodobenze radical **7.3** and an azide radical. The azide radical abstracts a hydrogen atom from the aldehyde to give the acyl radical **7.4**. The radical **7.4** attacks the electrophilic position of the protonated N-heterocycle **7.5** to give the radical cation intermediate **7.6** under thermodynamic control. A subsequent hydrogen atom abstraction and rearomatization produces the final product **7.7**.



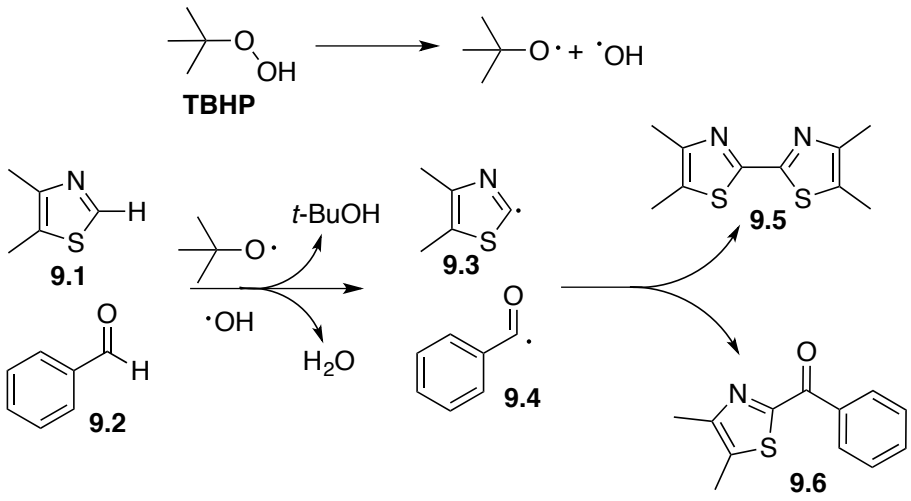
Scheme 7. Matcha and Antonchick's proposed mechanism for acylations utilizing hypervalent iodine and trimethylsilyl azide

Khemnar and Bhanage were able to acylate 4,5-dimethylthiazole **8.1** with a variety of aldehydes in a reaction heating with tert-butyl hydroperoxide (TBHP) at 100 °C (**Scheme 8**).[10] The reaction was optimized using four equivalents of both benzaldehyde **8.2** and TBHP in open air to give the desired product in 70% yield. Adding steric bulk near the aldehyde, as seen with 2,6-dimethylbenzaldehyde **8.3**, did not negatively impact the reaction. Both electron-rich *p*-anisaldehyde **8.4** and electron-poor *p*-chlorobenzaldehyde **8.5** were well tolerated. The use of heteroaromatic thiophene carboxaldehyde **8.6** succeeded without modifying the procedure, albeit with slightly lower yield. The aliphatic acetaldehyde **8.7** also afforded moderate amounts of the azolyl ketone.



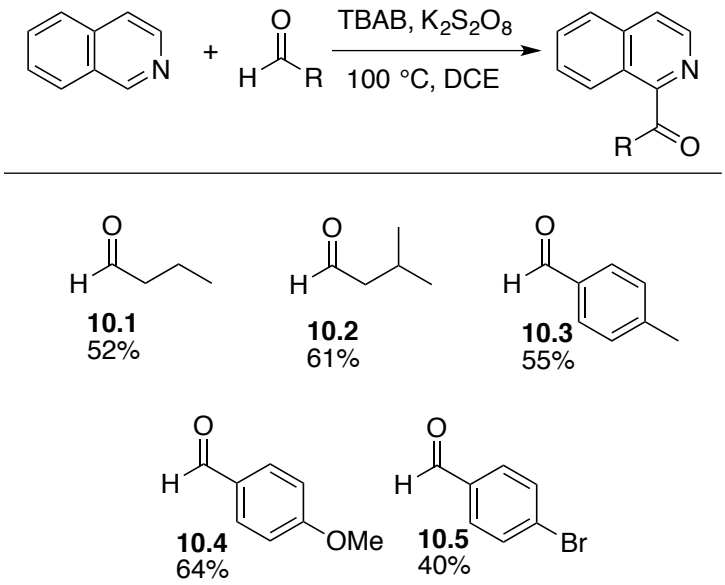
Scheme 8. Acylation of 4,5-dimethylthiazole described by Khemnar and Bhanage

The proposed reaction mechanism is initiated by the homolysis of TBHP. The authors then suggest concomitant hydrogen atom abstraction from both the thiazole **9.1** and aldehyde **9.2** to give the C-2 thiazolyl radical **9.3** and acyl radical **9.4** respectively. Simple recombination of **9.3** with itself yields dimer **9.5**, which was observed in trace amounts. Cross-reaction of the two free radicals would give the desired ketone **9.6**. An alternative, and more plausible, mechanism would be for the reaction to proceed through the Minisci pathway (**Scheme 2**), which circumvents the simultaneous formation of the two higher energy radical intermediates **9.3** and **9.4**.



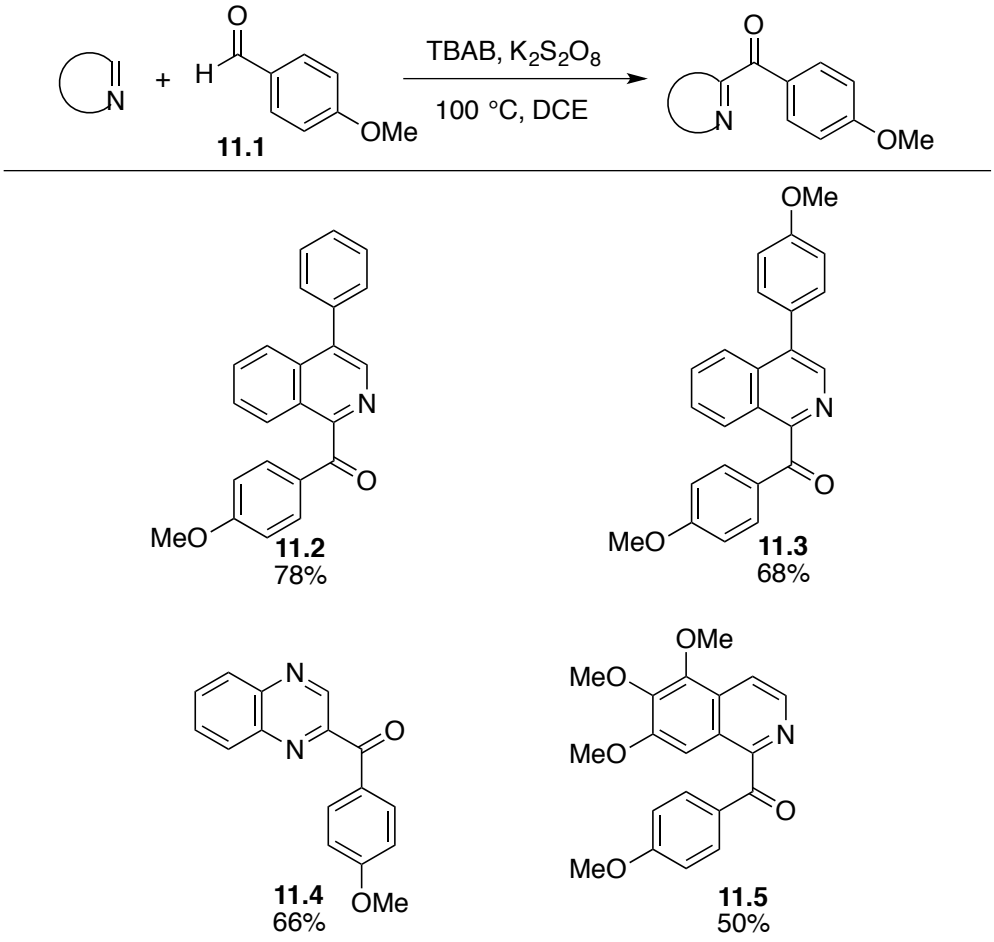
Scheme 9. Proposed mechanism by Khemnar and Bhanage

Prabhu et al. achieved the acylation of a variety of N-heterocycles using potassium persulfate and substoichiometric quantities of tetrabutylammonium bromide (TBAB). [11] The scope of applicable aldehydes is best represented with isoquinoline (**Scheme 10**). These reactions usually proceeded with poor to moderate yields, presumably due to decomposition of isoquinoline under the reaction conditions. Aliphatic aldehydes such as butanal **10.1** and the more bulky isovaleraldehyde **10.2** provided the 1-substituted isoquinoline product. Testing *p*-tolualdehyde **10.3** in the system did not increase the yield. The more electron rich *p*-anisaldehyde **10.4** did perform slightly better, likely due to the increased nucleophilic character of the subsequent radical. This particular example was scaled to using one gram of the isoquinoline with similar yields. Adding an electron-withdrawing group caused a drop in yield (**10.5**).



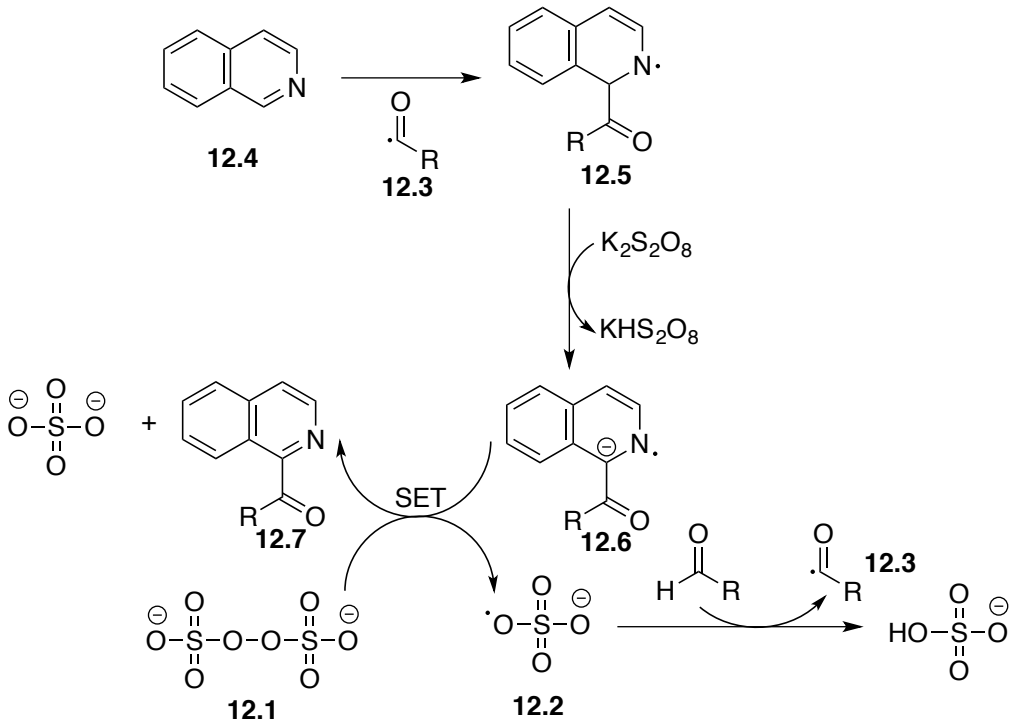
Scheme 10. Representative aldehyde scope for the acylation of isoquinoline by Prabhu

Although the unsubstituted isoquinoline faced decomposition, many 4-substituted isoquinolines were well tolerated under these reaction conditions. Anisaldehyde **11.1** underwent smooth coupling with 4-phenylisoquinoline to give the product **11.2** in good yields. Increasing the electron density of the isoquinoline reduced the yields, which fits with Minisci's original hypothesis that the N-heterocycle is the electrophile in these reactions. The product **11.3** from 4-(4-methoxyphenyl)-isoquinoline was afforded in good yet slightly lower yields. Other heterocycles, such as quinoxaline, were well tolerated (**11.4**). Aldehyde **11.1** reacted well with 5,6,7-trimethoxyisoquinoline to give the natural product thalimicrinone **11.5**, which is isolated from *thalictrum*, or meadow-rue flowers.



Scheme 11. Prabhu's representative N-heterocycle scope using *p*-anisaldehyde

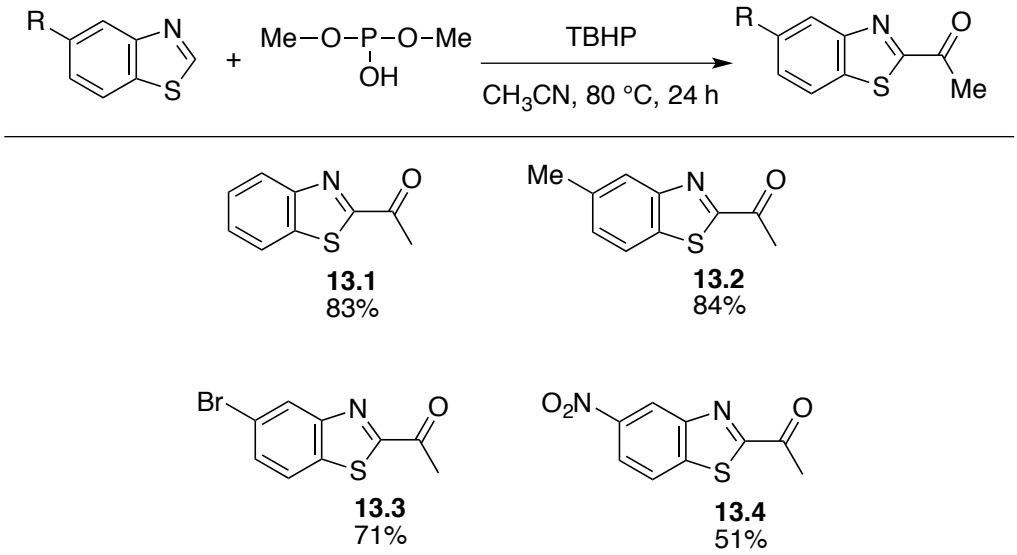
Prabhu et al. propose the following radical mechanism for the metal free acylation (**Scheme 12**). Persulfate **12.1** is known to provide the sulfate radical **12.2** through either a single electron transfer (SET) or through a self-sustaining radical chain mechanism upon heating. Radical **12.2** abstracts a hydrogen atom from the aldehyde to give acyl radical **12.3**. Addition of **12.3** onto the N-heterocycle **12.4** gives the 1-substituted isoquinoline radical **12.5**. Deprotonation at the acidic α-position affords the radical anion **12.6**, which transfers a single electron (SET) to persulfate regenerating **12.2** and giving the product **12.7**. A simpler alternative to this proposed mechanism could include a hydrogen atom abstraction, rather than deprotonation, at the α-position of **12.5** to allow for the rearomatization to the ketoazole **12.7**.



Scheme 12. Proposed mechanism for the acylation of isoquinoline in the presence of potassium persulfate and TBAB by Prabhu et al.

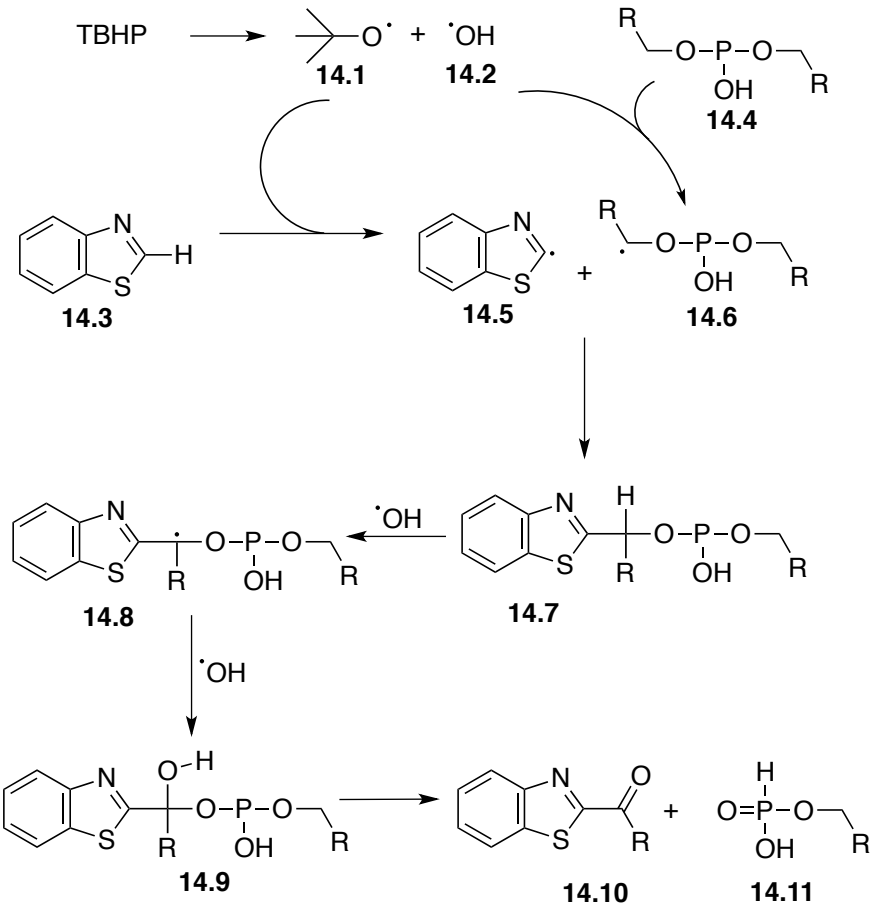
Chen et al. discovered a method for the preparation of either acylated benzothiazoles or phosphonated benzothiazoles depending on the radical initiator used. [12] For the scope of this chapter, only the use of TBHP, which led to 2-acylbenzothiazoles, will be discussed. Several dialkyl phosphites were employed to generate the desired products, although the yields slightly decreased with the length of the carbon chain. Many substituted benzothiazoles were also tested in the system (**Scheme 13**). Benzothiazole and dimethylphosphite gave product **13.1** in good yields. Adding electron-donating groups to the benzothiazole gave higher yields (**13.2**) in comparison to the unsubstituted benzothiazole. Weakly electron-withdrawing groups, such as a bromo group, gave the resulting 2-acetyl product **13.3** in reduced yields. Introducing a nitro substituent, a strongly withdrawing group, dramatically reduced the amount of product **13.4**

recovered. In fact, only dimethyl phosphite afforded any product at all with this starting material. Thiazole and benzoxazole did not produce any desired ketoazoles in this system.



Scheme 13. Chen's representative scope of benzothiazoles with dimethyl phosphite

The proposed mechanism is depicted below (**Scheme 14**). TBHP undergoes homolysis to give the *tert*-butoxide radical **14.1** and hydroxide radical **14.2**, which subsequently abstract hydrogen atoms from both the C-2 of the benzothiazole **14.3** and the α-carbon of the phosphite **14.4** to give the heteroaryl radical **14.5** and phosphite radical **14.6**, respectively. Radical recombination affords **14.7**, and subsequent hydrogen atom abstraction gives the tertiary radical **14.8**. Coupling of **14.8** with hydroxyl radical **14.2** provides the hemiacetal **14.9**, which quickly undergoes an energetically favorable elimination to yield the acylated product **14.10** and alkyl hydrogen phosphonate **14.11**. The simultaneous formation of the two high-energy radicals **14.5** and **14.6** is implausible and unnecessary. Instead, the reaction might proceed more similarly to the Minisci mechanism (**Scheme 2**) and phosphite radical **14.6** could add directly to benzothiazole **14.3**.



Scheme 14. Proposed reaction mechanism of benzothiazole with dialkyl phosphite and TBHP by Chen et al.

E. Conclusion

This literature review describes the various methods used for the C-H functionalization N-heteroarenes with acyl radicals. The groundwork laid by Minisci in the late 1960s was an alternative approach to traditional Friedel-Crafts methods that did not succeed for azoles. All of the reported conditions avoid strong bases and cryogenic temperatures, which allows for high functional group tolerance within the azoles and acyl sources. Also, the evaluated literature employs commercially available azoles, aldehydes, and other reagents in these transformations, making the large library of possible products easily accessible to most chemists. Recent efforts have even progressed toward completely metal free conditions by using alternative radical

initiators and/or heat in the reactions. Overall, the radical acylation of azoles provides a clear pathway to aromatic ketones and, thus, a variety of biologically relevant molecules.

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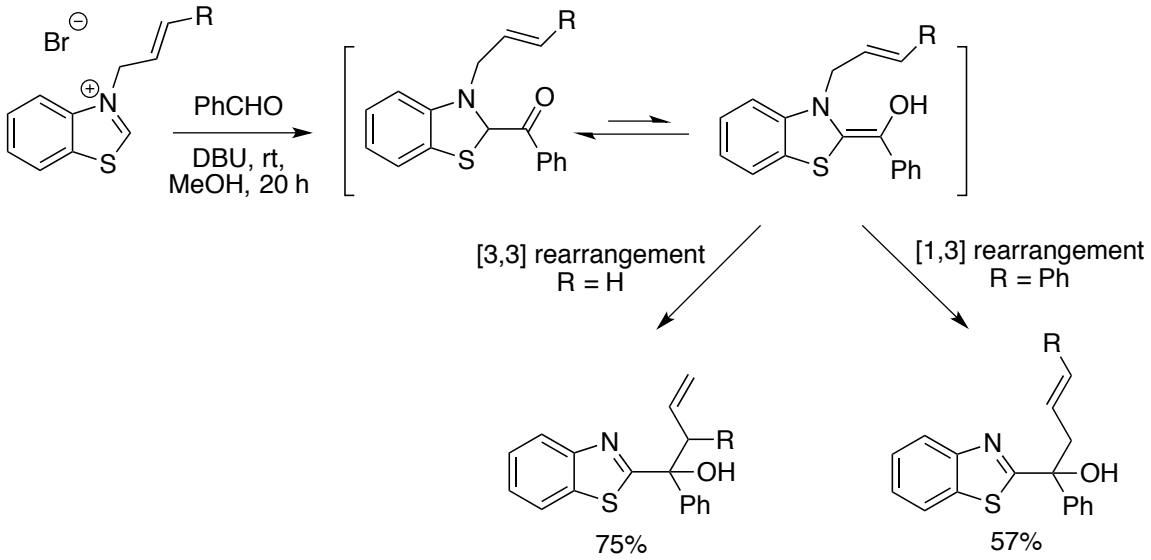
5. The Formation and Reduction of Aryl Thiazolyl Ketones

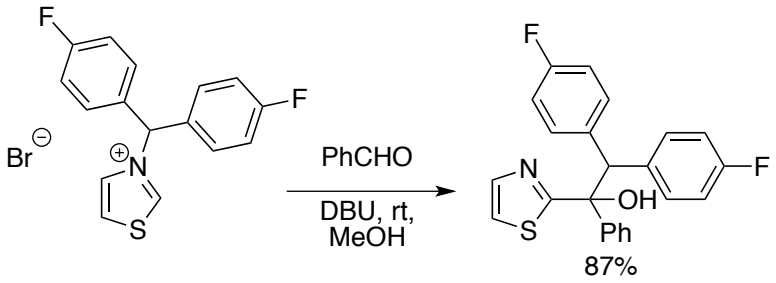
A. Introduction

The McIntosh lab has reported the [3,3] Claisen rearrangement of Breslow intermediates formed from *N*-allyl benzothiazolium bromide and aromatic aldehydes.[1] When the same reaction conditions were applied to *N*-cinnamyl benzothiazolium salts, the major product resulted from a [1,3] stepwise rearrangement (**Scheme 1**).[2]



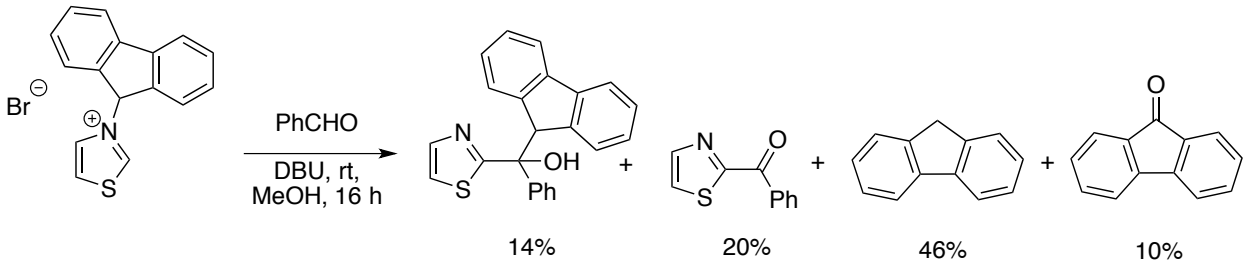
Scheme 1. N-Substituent effects on the rearrangement of benzothiazoles

In order to exploit this new reaction pathway and exclude the chance of [3,3] rearrangement products, non-allylic *N*-substituents were explored. Benzaldehyde and 4,4'-difluorodiphenylmethyl thiazolium bromide were reacted in the presence of DBU in methanol to give good yields of the [1,3] product.[3] It was hypothesized that this rearrangement was proceeding through a radical mechanism.



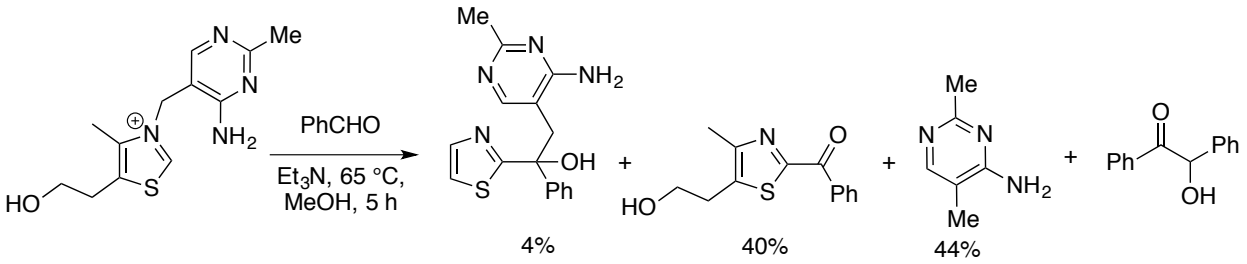
Scheme 2. [1,3] Rearrangement of 4,4'-difluorodiphenylmethyl thiazolium bromide with benzaldehyde

The radical-stabilizing fluorenyl group was then tested as an *N*-substituent. When *N*-fluorenyl thiazolium bromide was subjected to benzaldehyde under the aforementioned reaction conditions, the [1,3] product precipitated albeit at lower yields. Column chromatography of the remaining mixture gave the phenyl thiazolyl ketone, fluorene, and fluorenone.



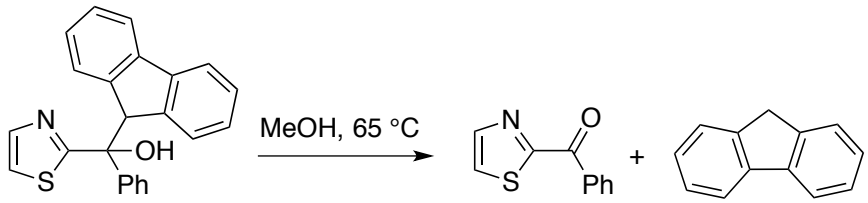
Scheme 3. McIntosh observed products formed from N-fluorenyl thiazolium bromide and benzaldehyde

Oka et al. observed similar fragmentation patterns in 1970 with thiamine and benzaldehyde in the presence of triethylamine.[4] Low yields of the [1,3] rearrangement product were observed with higher yields of the ketone, pyrimidine, and benzoin. Oka proposed a questionable mechanism for the transformation,[5] but despite that, the fragmentation products remained consistent with the McIntosh findings.



Scheme 4. Products observed by Oka from thiamine and benzaldehyde

Efforts to optimize the *N*-fluorenyl thiazolium system for the formation of the [1,3] product never consistently gave more than moderate yields. Heating the product in refluxing methanol confirmed that it was indeed unstable under the reaction conditions because it gave fluorene and the diaryl ketone. [6]



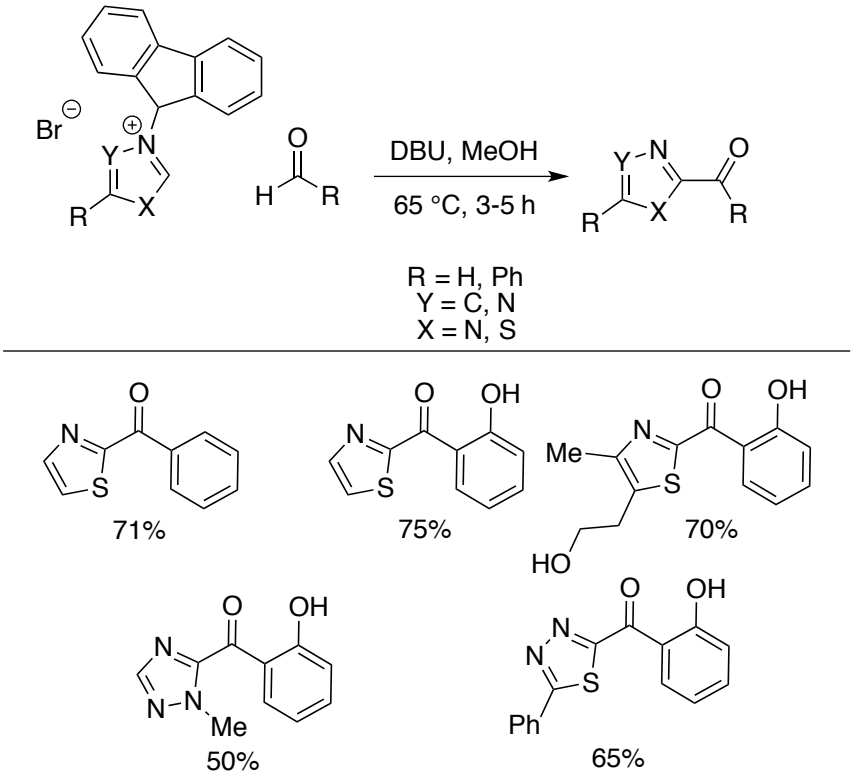
Scheme 5. Decomposition of the [1,3] rearrangement product to the thiazolyl ketone and fluorene

B. Background and Significance

These attempts led to a simple two-step streamlined procedure for access to a wide variety of aryl azolyl ketones. After studying a variety of bases (DBU, Cs_2CO_3, K_2CO_3, TMG, and Et_3N) and solvents (MeOH, DMF, THF and MeCN), the optimal reaction conditions were found to involve adding 1.2 eq of the DBU to a mixture of the salt and 1.2 eq aldehyde in either 0.15 M MeOH or THF at 65 °C for 3-5 hours. [6]

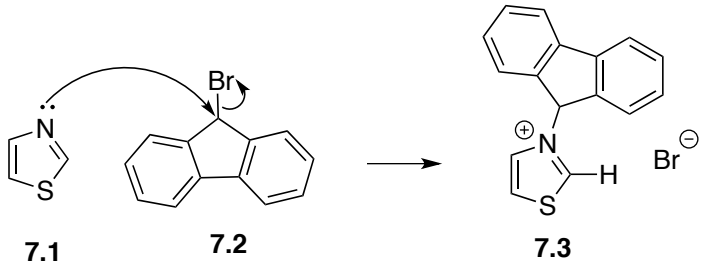
Thiazole, triazole, thiadiazole, and thiamine thiazoles were all successfully alkylated with bromoflorene to provide N-fluorenyl salts. These salts were then reacted with a variety of aromatic and aliphatic aldehydes to give the desired 2-ketoazoles (**Scheme 6**). The gentle reaction conditions are highlighted through the tolerance of unprotected hydroxyl groups on both

the aldehyde and the azole. A wide variety of electron donating and withdrawing substituents also gave good results.



Scheme 6. Representative product scope of various thiazole salts with aromatic aldehydes

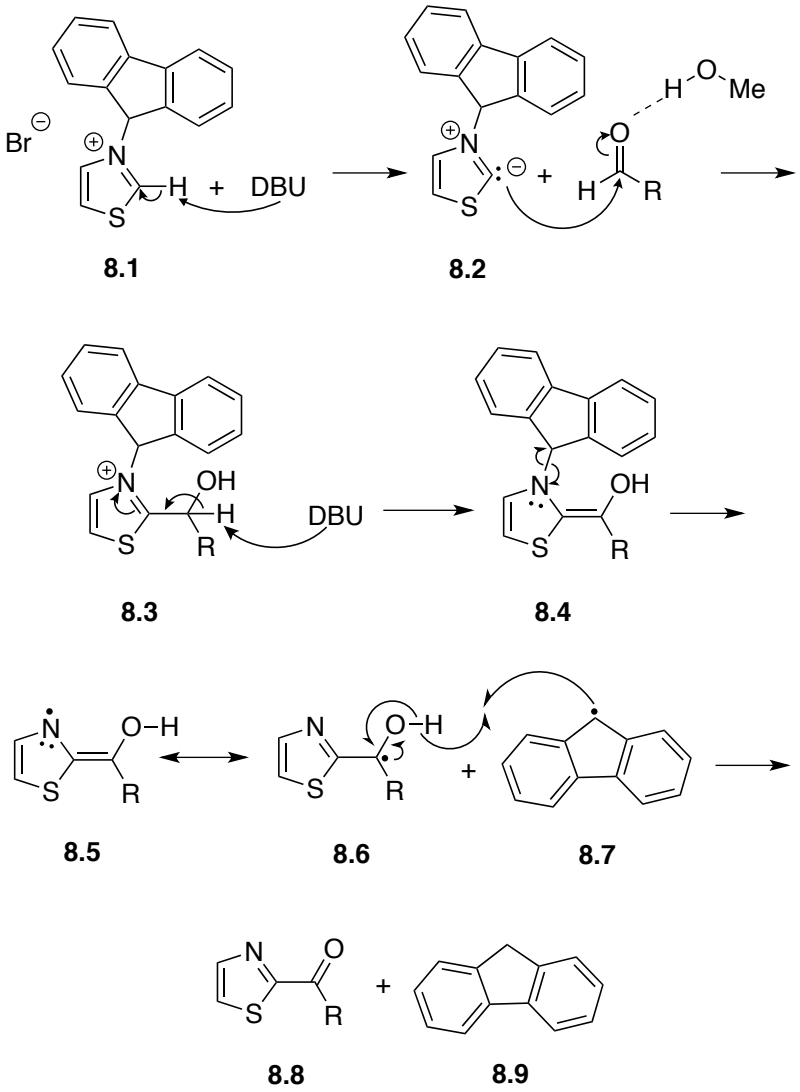
In the proposed mechanism (**Scheme 7**), *N*-fluorenyl thiazolium bromide **7.3** is formed from a simple S_N2 attack of thiazole **7.1** on 9-bromofluorene **7.2**.



Scheme 7. Proposed SN2 mechanism for the formation of N-fluorenylthiazolium bromide

Following the generally accepted mechanism for the reaction of NHCs and aldehydes (**Scheme 8**), deprotonation of **8.1** by DBU gives the carbene **8.2**, which subsequently attacks the

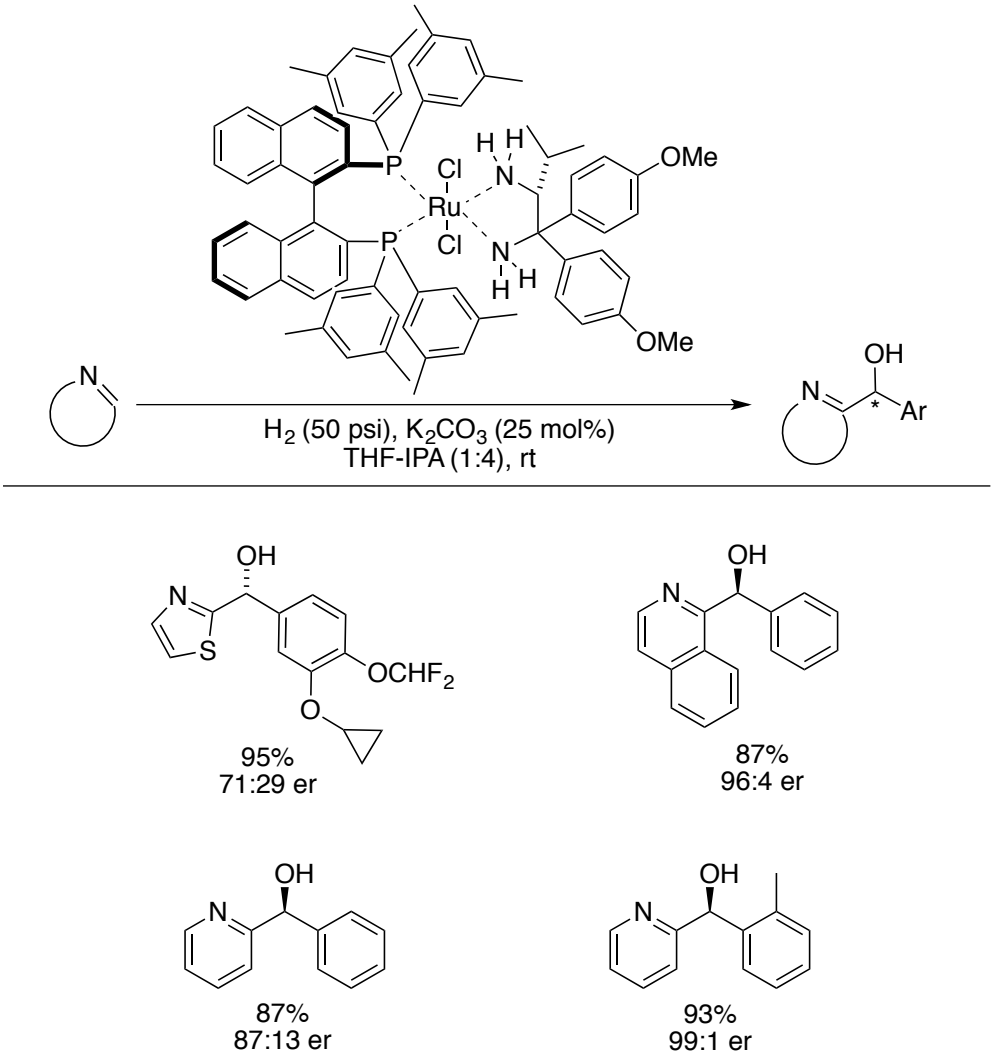
aldehyde to give adduct **8.3**. Another deprotonation gives the Breslow intermediate **8.4**. Homolysis of the *N*-fluorenyl bond gives stable radical intermediates **8.5** and **8.7**. DFT calculations (B3LYP/6-31g*) predict the ΔH for the C-N bond homolysis to be 8.3 kcal/mol. EPR experiments support the radical pathway. Hydrogen atom abstraction from the alcohol **8.6**, which is the resonance form of **8.5**, gives the two major products **8.8** and **8.9**. If instead a simple radical recombination occurred, then the [1,3] product would be obtained.



Scheme 8. Proposed radical mechanism for the formation of thiazolyl aryl ketones

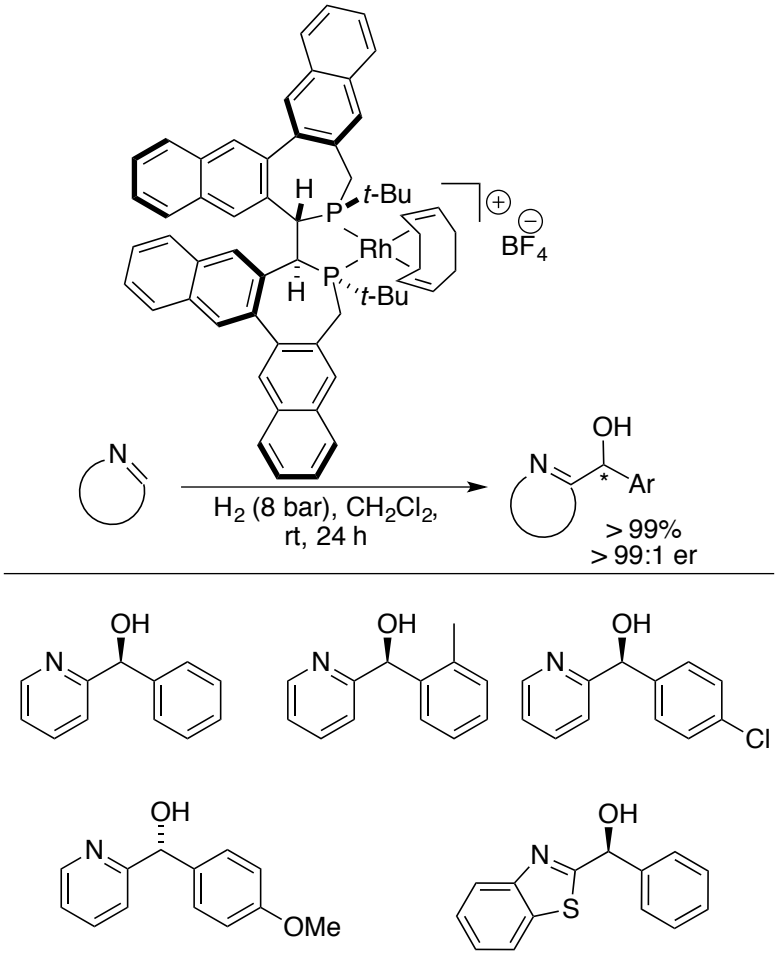
Asymmetric alcohols bearing azoles are enticing targets in the pharmaceutical community. A simple route to these desirable targets is the asymmetric reduction of the prochiral azolyl aryl ketones described above. Chen et al. used 1 mol% loading of a commercially available ruthenium BINAP DAIPEN catalyst to effectively hydrogenate a variety of 5-benzoylthiazoles with good selectivities (**Scheme 9**).[7] When applied to a 2-substituted thiazolyl aryl ketone, the system gave only a modest er. The procedure did perform better for a variety of

2-substituted pyridinyl aryl ketones. The best selectivities were achieved when an obvious steric difference between the two ketone substituents existed.



Scheme 9. Asymmetric hydrogenation of azolyl aryl ketones by Chen et al.

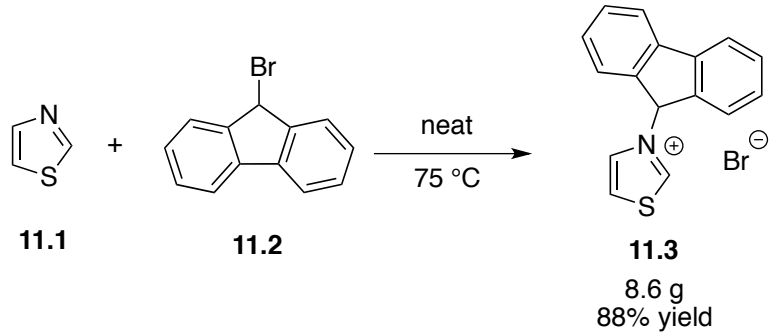
Recently, Zhang and Lv et al. more deeply explored the asymmetric hydrogenation of 2-ketoazoles.[8] By using a rhodium BINAPINE catalyst at 1 mol% loading, every example of diaryl ketone tested was reduced with complete conversion to the desired chiral alcohol with very high selectivities (**Scheme 10**). No effects of substituent placement, electronics, or steric bulk were noted in the 2-pyridinyl examples. A 2-benzothiazolyl ketone was also reduced with a high er by the system.



Scheme 10. Asymmetric hydrogenation of 2-azolyl aryl ketones by Zhang and Lv et al.

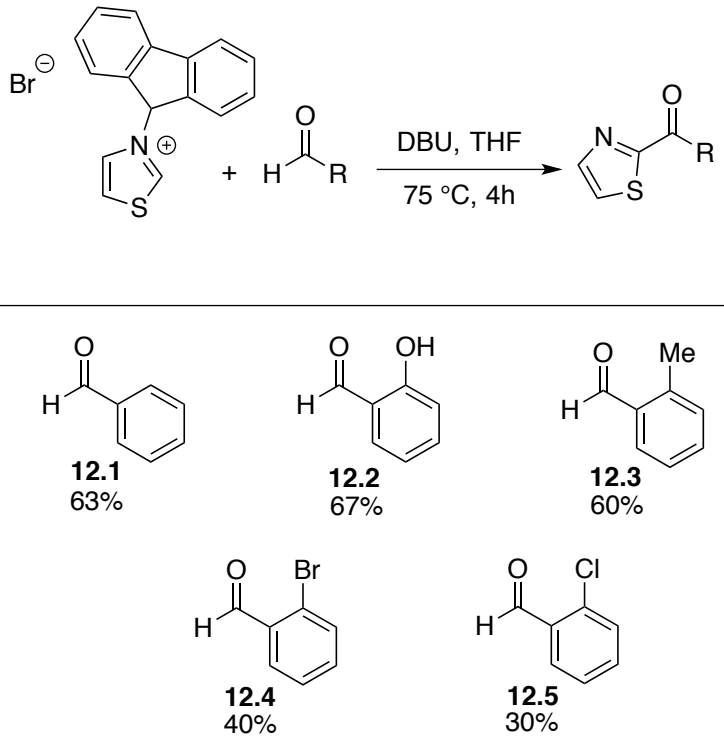
C. Results and Discussion

We desired to try CuIPhEt in the asymmetric hydrogenation of these 2-ketoazoles. In order to synthesize the targets, we followed the two-step McIntosh procedure (**Scheme 11**). The *N*-fluorenyl thiazolium bromide **11.3** was easily prepared by simply mixing the thiazole **11.1** and 9-bromofluorene **11.2** in a pressure tube and heating at 75 °C. The bromofluorene melts to give a homogenous reaction mixture, which solidifies upon formation of **11.3**. Simple trituration with diethyl ether gives the pure salt in good yields. The reaction is easily scalable as well. In only two hours, 8.6 g of product were obtained in 88% yield.



Scheme 11. Large-scale formation of *N*-fluorenyl thiazolium bromide

With the salt in hand, a variety of azolyl ketones were made on a larger scale than the initial McIntosh screenings (**Scheme 12**). One equivalent of the *N*-fluorenyl salt was mixed with a slight excess of the aryl aldehyde in THF. Upon reaching 75 °C, 1.2 eq of base was added to eventually afford the ketone in low to moderate yields. Benzaldehyde **12.1** was the aldehyde of choice for optimizing this large-scale reaction due to its simplicity. The only modification needed was changing the solvent to THF, which provides a much cleaner reaction TLC and ensuing column—possibly due to the precipitation of the protonated DBU. A variety of *ortho*-substituted aryl aldehydes were used to create the eventual substrate scope for the CuIPhEt hydrosilylations. Salicylaldehyde **12.2**, despite a potentially reactive unprotected hydroxyl group, was well tolerated in the acylation reaction. In case the free hydroxyl group did not work in the forthcoming hydrosilylation system, the sterically similar o-tolylaldehyde **12.3** was utilized. Electron withdrawing *o*-bromo **12.4** and *o*-chloro **12.5** benzaldehydes gave the desired ketones in lower yields.

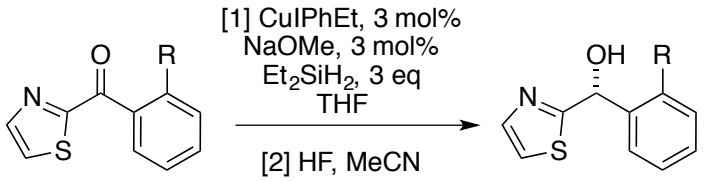


Scheme 12. Product scope for the large-scale formation of thiazolyl aryl ketones

The CuIPhEt hydrosilylation of azolyl ketones was optimized on the benzyl thiazolyl ketone. It was found that 3 mol% of catalyst and base were necessary to achieve conversion to the reduction product in under an hour without heating. In order to separate the racemate formed from a simple $NaBH_4$ reduction on a chiral GC, the silane was cleaved to the alcohol in work-up with 5% HF in MeCN. A Kugelrohr distillation of the crude reaction mixture gave the desired alcohols in low to excellent yields.

Unfortunately, CuIPhEt did not provide good selectivities in the reduction of azolyl aryl ketones (**Table 1**). In the case of the thiazolyl benzyl ketone (entries 1-3), the selectivity did increase as the reaction temperature was lowered, but at best, only moderate selectivities similar to those found by Chen et al. above were observed. Hoping a more sterically demanding substituent could influence the selectivity, we tried the thiazolyl salicyl ketone (entries 4-5). Neither cryogenic nor room temperatures afforded any isolable product. The *o*-tolyl thiazolyl

ketone did provide the desired alcohol in good yields, but again, only a low er was observed (entry 6). Reducing the reaction temperature in this instance gave no conversion to product (entry 7). Electron withdrawing substituents gave both extremely low yields and selectivities (entries 8-9).



Entry	R	Temperature (°C)	% Yield	er (R:S)	%ee
1	H	23	90	54:46	8
2	H	0	92	58:42	16
3	H	-78	53	65:35	30
4	OH	-78	0	-	-
5	OH	23	0	-	-
6	Me	23	90	56:44	12
7	Me	-78	0	-	-
8	Br	23	10	51:49	2
9	Cl	23	12	54:46	8

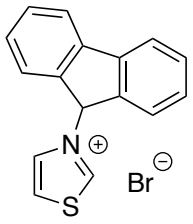
Table 1. Attempts toward the asymmetric hydrosilylation of thiazolyl aryl ketones with CuIPhEt

D. Conclusion

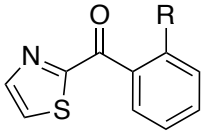
Thiazolyl aryl ketones and alcohols are useful and desired synthetic targets. The McIntosh lab designed a new, efficient radical pathway to access these ketoazoles through modifications to their Claisen chemistry. The two-step synthesis consists of a formation of an *N*-fluorenyl salt followed by a reaction with an aryl aldehyde to give the ketone. These ketones

were made on 2 g scale and reduced by CuIPhEt. The best selectivity was achieved on the benzyl thiazolyl ketone at -78 °C but with only a modest 65:35 er.

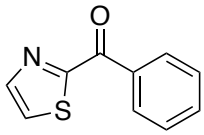
E. Experimental



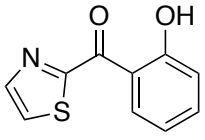
N-Fluorenyl thiazolium bromide: Thiazole (29.7 mmol, 2.1 mL) was mixed neat with a 1.1 eq of 9-bromofluorene (32.6 mmol, 8 g) and the mixture heated to 75 °C until the reaction mixture solidified (2 hours). The resulting solid was then washed three times with diethyl ether. The solvent was decanted and the solid dried under nitrogen to yield the pure salt (8.6 g) in 88% yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.21 (s, 1H), 7.42 (td, J = 7.5, 1.1 Hz, 2H), 7.60 (m, 4H), 8.04 (m, 3H), 8.28 (dd, J = 3.8, 2.4 Hz, 1H), 10.53 (s, 1H). 13C NMR (101 MHz, DMSO) δ 161.1, 140.9, 140.1, 135.2, 131.1, 129.1, 128.8, 126.1, 121.7, 67.7.



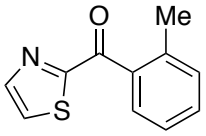
General procedure for the formation of the aryl azolyl ketones: To a mixture of N-fluorenylthiazolium bromide (1 eq, 6 mmol, 2g) and aldehyde (1.2 eq, 7.3 mmol) in THF (0.15M, 40 mL) at 75 °C was added DBU (1.2 eq, 7.3 mmol, 1.1 mL). The reaction was stirred for 4 hours or until aldehyde consumption ceased by TLC. The solvent was removed en vacuo and the residue was purified via column chromatography with 95:5 hexanes/EtOAc.



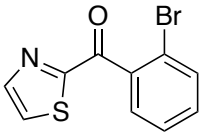
Phenylthiazolyl ketone: Red solid, 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (t, J = 7.5 Hz, 2H), 7.65 (m, 1H), 7.74 (d, J = 3.0 Hz, 1H), 8.11 (d, J = 3.1 Hz, 1 H), 8.47 (dd, J = 1.5, 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.3, 128.4, 131.1, 133.6, 135.2, 144.9, 167.9, 184.2.



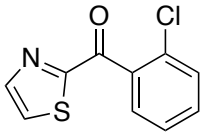
Salicylthiazolyl ketone: Orange solid, 67% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (m, 2H), 7.57 (td, J = 1.6, 9.9 Hz, 1H), 7.77 (d, J = 3.0 Hz, 1H), 8.15 (d, J = 3.1 Hz, 1H), 9.19 (dd, J = 1.7, 8.2 Hz, 1H) 12.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.0 (Ar C), 118.4 (Ar CH), 119.4 (Ar CH), 126.5 (Ar CH), 133.9 (Ar CH), 137.2 (Ar CH), 144.9 (Ar CH), 164.1 (Ar C), 167.9 (SC=N),186.5 (C=O). IR (CH2Cl2) υmax: 3086 (br), 2922, 1620, 1585, 1440, 1477, 1388.



o-Tolylthiazolyl ketone: Red solid, 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 7.34 (m, 2H), 7.44 (m, 2H), 7.74 (d, J = 3 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 8.08 (d, J = 3 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 125.3, 126.5, 130.7, 131.4, 131.7, 135.6, 138.5, 145.1, 168.3, 188.2

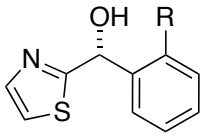


o-Bromophenylthiazolyl ketone: Orange solid, 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (td, J = 2, 9.6 Hz, 1H), 7.47 (td, J = 1.2, 8.8 Hz, 1H), 7.64 (dd, J = 2, 7.6 Hz, 1H), 7.70 (dd, J = 0.8, 8.0 Hz, 1H), 7.80 (d, J = 2.8 Hz, 1H), 8.08 (d, J = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.2, 127.0, 127.1, 130.2, 132.2, 133.6, 138.4, 145.5, 166.3, 187.0

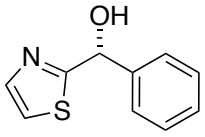


o-Chlorophenylthiazolyl ketone Orange solid, 30% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 1H), 7.48 (d, J =8.8 Hz, 1H), 7.64 (dd, J = 2, 7.6 Hz, 1H), 7.77 (m, 1H), 7.80

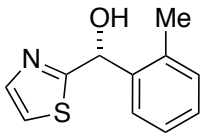
(d, J = 2.8 Hz, 1H), 8.08 (d, J = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.2, 125.1, 126.1, 129.2, 132.0, 132.6, 136.4, 141.5, 164.4, 185.0



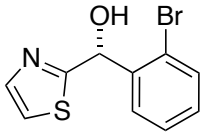
General procedure for the reduction of the aryl azolyl ketones: CuIPhEt (3 mol%, 12 μmol, 9 mg) was weighed into an oven dried flask with stir bar and septum. The flask was evacuated and flushed with N_2 three times. Dry THF (0.5 mL) was added and stirred until the CuIPhEt dissolved. NaOMe in MeOH (0.5 M, 3 mol%, 24 μL) was added and stirred for 5 min. Freshly distilled diethyl silane (3 eq, 1.2 mmol, 0.15 mL) was added and stirred for 5 min. Aryl azolyl ketone (1 eq, 0.4 mmol) was dissolved in THF (0.5 mL) and added to the reaction mixture. The reaction was stirred for 45 minutes before adding 5% HF/MeCN (1 mL). The solvent was removed en vacuo and the residue was purified via Kugelrohr distillation.



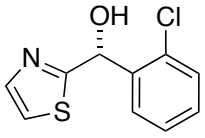
Phenylthiazolyl alcohol: White needles, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (d, J = 3.5 Hz, 1H), 6.06 (d, J = 3.2 Hz, 1H), 7.35 (m, 4H), 7.45 (d, J = 7.1 Hz, 2H), 7.70 (dd, J = 0.8, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.9, 119.6, 126.6, 128.5, 128.8, 141.5, 142.3, 174.4.



o-Tolylthiazolyl alcohol: Yellow solid, 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 4.19 (br s, 1H), 6.25 (s, 1H), 7.25 (m, 3H), 7.55 (m, 2H), 7.70 (d, J = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 73.9, 119.9, 125.6, 128.3, 128.9, 142.5, 143.3, 179.3.



o-Bromophenylthiazolyl alcohol: Yellow oil, 10% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (br s, 1H), 6.35 (s, 1H), 7.45 (m, 2H), 7.63 (m, 2H), 7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.2, 117.7, 120.6, 128.9, 133.5, 145.5, 162.7, 174.3.



o-Chlorophenylthiazolyl alcohol: Orange oil, 12% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (br s, 1H), 6.30 (s, 1H), 7.35 (m, 2H), 7.45 (m, 3H), 7.51 (d, J = 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.9, 118.7, 127.9, 128.1, 128.8, 140.5, 142.5, 175.3.

F. Works Cited

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(8) Yang, H.; Huo, N.; Yang, P.; Pei, H.; Lv, H.; Zhang, X. Rhodium Catalyzed Asymmetric Hydrogenation of 2-Pyridine Ketones. *Org. Lett.* **2015**, *17*, 4144–4147.

6. Conclusion

Aromatic N-heterocyclic carbenes (NHCs) are an important class of molecules in organic chemistry. Since the confirmation of their existence in 1968, the field has steadily grown. NHCs are employed today as ligands for metal catalysts, as organocatalysts, and as useful synthetic compounds. In this work, we have synthesized and applied CuIPhEt, an N-heterocyclic copper carbenoid, on large scales. In addition, we employed the use of NHC derived Breslow intermediates as key intermediates in the synthesis of azolyl ketones.

Our catalyst, CuIPhEt, was designed as a chiral analog to the well established achiral CuIPr. The original synthesis of CuIPhEt was completed on a 140 mg scale and involved a traditional resolution. In order to complete a scalable, asymmetric synthesis, a double asymmetric hydrogenation employing the chiral ligand DuanPhos was developed. Now, CuIPhEt is attainable as 5 g of a single enantiomer with 52% overall yield. This provides nearly 36 times more catalyst in quadruple the yields when compared to the original synthesis.

CuIPhEt was found to be an effective asymmetric hydrosilylation catalyst for a variety of alkyl aryl and dialkyl ketones; however, the procedure was not reproducible. An effort was undertaken in order to make the desired results more attainable. The solution to the reproducibility lay in exchanging to the less sterically hindered sodium methoxide base. The new procedure was used to asymmetrically reduce examples from the originally published substrate scope as well as new compounds. A *meso*-diketone used as a key intermediate toward the total synthesis of antascomicin B was reduced on a 10 g scale. Levulinic acid, a commodity chemical containing a ketone and carboxylic acid, was protected to the ethyl ester and reduced efficiently as well.

Azolyl ketones are important synthetic targets in the pharmaceutical and agrochemical fields. Several radical synthetic methods have been developed since Minisci's seminal work in the late 1960s. Efforts have been made to develop metal free and more functional group tolerant procedures. The McIntosh group developed a two-step synthesis to form these ketoazoles using only a weak base. The mechanism is thought to proceed through an NHC attacking an aldehyde to give the Breslow intermediate. Using this procedure, a variety of thiazolyl aryl ketones were synthesized on a 2 g scale—almost ten times more than the original screenings. These ketones were tested as possible substrates for the CuIPhEt hydrosilylations but gave only poor selectivities.