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Probing the capabilities of copper complexes with nitrogen and sulfur containing macrocyclic ligands as aziridination catalysts

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Probing the Capabilities of Copper Complexes with Nitrogen and Sulfur Containing Macrocyclic Ligands as Aziridination Catalysts

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Chemistry Department
Colby College
Waterville, Maine
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Abstract

Aziridines are three-membered rings containing one nitrogen atom. They are useful as synthetic intermediates in many organic reactions. Much work has been devoted to synthesizing their analogs, cyclopropanes and epoxides, but little work has been done on the aziridination reaction. This study endeavored to probe the efficiencies of novel copper aziridination catalysts with N$_3$ and S$_3$ macrocyclic ligands compared to an N$_5$S$_2$ analog for the reaction with the nitrene precursor (N-(para-tosylsulfonyl)imino)phenyliodinane, PhINTs, and the olefin styrene. The nitrogen containing catalyst complex gave higher yields than the sulfur containing catalyst complex. Both ligands were found to decrease the yield of the aziridination reaction relative to the catalyst complex Cu(acac)$_2$. However, for the N$_3$ ligand system, only a slight decrease occurred and the possibility remains that the system could be adjusted to obtain higher yields. Preliminary studies using an N$_5$S$_2$ macrocyclic ligand in the copper catalyst complex showed it to have slightly higher yields than the N$_3$ and S$_3$ systems.
Acknowledgements

I would like to thank Professor Rebecca Conry for taking me on as her first research student at Colby College. The opportunity to work in a newly renovated and well-equipped laboratory under Professor Conry's guidance has been invaluable. Much of this thesis has been adapted from an unpublished account written by Professor Conry on work started with her coworkers at the University of Nevada at Reno.

I would also like to thank Professor Whitney King for his advice over the past four years. Professor Bradford Mundy was very helpful in getting me acquainted with a research laboratory in the Spring of 2000. The effort Professor Dasan Thamattoor has given in reading this thesis is greatly appreciated. Professor Steven Dunham has been a great help with the use of the new NMR spectrometer system.

Finally, the support and advice of my parents throughout my education has been indispensable. They made it possible for me to come to Colby and have always encouraged me to be the best I can at whatever I choose. Thanks again Mom and Dad.
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Introduction

Much work has been devoted to the development of reactions that effect catalytic atom or group transfers to olefins. Possible routes for these transfers are through epoxidation, cyclopropanation, and aziridination. Epoxidation involves the net addition of an oxygen atom across a double bond. In the epoxidation process, a three-membered ring containing one oxygen atom is formed (eq 1). Cyclopropanation is a similar reaction in which a ring with three carbon atoms is formed (eq 2).

\[
\text{Reaction 1: } \text{Epoxidation} \\
\text{Reaction 2: } \text{Cyclopropanation}
\]

For both epoxidation and cyclopropanation, the reactions have been extensively refined. However, for the aziridination reaction, the formation of a three-membered ring containing one nitrogen atom, much work remains to be done. This ring can have up to five different substituents, represented as R₁₋₅ in Figure 1. The first synthesis of an aziridine occurred in 1888 when Gabriel accidentally synthesized the parent member, C₂H₅N.
Figure 1. A representation of a general aziridine in which each R can be the same or different substituents.

Aziridines have been found to be key structural components of biologically active molecules and are frequently used as synthetic building blocks of natural products. Several naturally occurring antibiotics and antitumor drugs contain aziridine groups. An aziridine is naturally highly strained and susceptible to ring-opening reactions. The utility of aziridines as an intermediate in a multi-step synthetic reaction also makes them of interest.

There are three common synthetic routes to form aziridines. A carbene moiety can be catalytically added to an imine (eq 3), but low yields are often encountered so this is not the reaction of choice. As carbenes are not available by themselves, metals are often used as catalysts for the reaction and are thought to form metal-carbenes intermediates.
Nitrene reaction with olefins is another possible route, but thermally and photochemically produced nitrenes are very reactive and frequently form many side products. Metal-catalyzed reactions of nitrenes with olefins seem to be the most efficient processes and were used in this study (eq 4).

\[
\begin{align*}
\text{N} & \quad \text{Olefin} \quad \text{Metal-catalyst} \quad \text{Aziridine} \\
\text{M} & \quad \text{N} \\
\end{align*}
\]

Several catalysts have been found to mediate the aziridination reaction. These include manganese(V), iron(III), palladium(II), and copper(I) systems. However, the capabilities of both Cu(I) and Cu(II) complexes as aziridination catalysts are relatively recent discoveries and are, thus, underdeveloped. The first metal-catalyzed aziridination was reported by Kwart and Kahn in 1967. They found the copper-catalyzed decomposition of benzenesulfonyl azide yielded products consistent with the nitrene-transfer mechanism in the presence of cyclohexene (eq 5). In this transfer process, the nitrogen atom is incorporated into the three-membered ring and the group attached to the nitrogen atom becomes a substituent of the ring at the nitrogen atom. However, such low yields of aziridine were found that this type of aziridination was not explored further for almost twenty years.
Work continues to be done to improve the catalytic capabilities of copper catalysts. There is considerable public interest for the development of new catalysts in the commercial market. It is desirable to find catalysts that can be used in the larger scale applications of the pharmaceutical and agrochemical industries. Large-scale applications require catalysts that can be used in minimal quantities with high yields and the ability to recover the catalyst at the end of the process.

Evans has reported that Cu(I) and Cu(II) triflate and perchlorate salts are competent aziridination catalysts. Several observations have been made indicating that both forms of the metal, Cu(I) and Cu(II), reach a common oxidation state in the course of the reaction. Brandt studied the aziridination reaction mechanism for both Cu(I) and Cu(II) starting materials and suggested that a Cu(I) complex is the active species. Brandt found strong indications that the Cu(II) complex enters a Cu(I)/Cu(III) complex cycle through reaction with (N-(para-tosylsulfonyl)imino)phenylidinane (PhINTs), a nitrene precursor for the aziridination reaction. The Cu(III) complex is a reactive intermediate. This finding is similar to an earlier suggestion made by Jacobsen. It has also been suggested by Pérez and coworkers that a Cu(II) complex was the active species. A 1994 report by Evans and coworkers concluded that for the reaction conditions they employed, Cu(II) was the active oxidation state. These conflicting reports suggest further mechanistic studies would be important to establish what the oxidation state of the catalyst is or whether the copper oxidation state is system dependent.

Evans and coworkers compared the yields of aziridine from the reaction of PhINTs with two different olefins. The reactions were performed in the presence of a
variety of catalyst precursors, most of them monodentate bearing ligands (Table 1). The yields are determined relative to the limiting starting reagent PhINTs. There should be one equivalent of product for every equivalent of PhINTs used in the reaction. Comparison of these two quantities determines the percentage yield.

In 1993, Jacobsen and coworkers reported that in order for an aziridination reaction to occur, one or more open coordination sites at the copper ion were essential. They found that no aziridine product resulted from tetradentate-ligated complexes while similar complexes with bidentate ligands had significant catalytic capabilities. Thus, the availability of one or more coordination sites at the copper ion is a key component to the effectiveness of the complexes as aziridine catalysts. Stockheim et al. have studied the coordination chemistry of 1,4,7-triazacyclononane (1) and its N-methylated derivative (2) with Ag(I) and Hg(II). Many other studies have also been reported on the coordination chemistry of 1 and 2. The coordination chemistry of Ag(I) with 1,4,7-trithiaclononane (3) and a macrocyclic ligand [9]ane-NS$_2$ (4) had been reported by Parker and coworkers. The design of catalytically active metal complexes often incorporates the protecting or blocking of certain coordination sites while also incorporating specific, coordinately labile positions at the metal center. This blocking or protecting of coordination sites allows for the site to later be opened when the catalytic activity is desired.

Most of the catalyst precursors reported in Table 1 were bound to monodentate ligands. Little work has been reported on the influence of ligand and chelate ring size and identity of ligand coordinating atoms on the capabilities of copper complexes as aziridination catalysts. Several bi- and tridentate ligated copper complexes have been
Table 1: Yields from the Aziridine Reaction Using Different Metal Catalyst Precursor Complexes


<table>
<thead>
<tr>
<th>Catalyst Complex(^a)</th>
<th>Styrene(^b)</th>
<th>Cyclohexene(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Cu(CH(_3)CN)(_4)]ClO(_4)</td>
<td>90</td>
<td>54</td>
</tr>
<tr>
<td>(CuOTf(_2))C(_6)H(_6) (^c)</td>
<td>92</td>
<td>50</td>
</tr>
<tr>
<td>CuCl</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>CuBr</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Cu(acac)(_2) (^d)</td>
<td>95</td>
<td>30</td>
</tr>
<tr>
<td>Cu(OTf)(_2) (^e)</td>
<td>92</td>
<td>60</td>
</tr>
<tr>
<td>Mn(TPP)Cl(^f)</td>
<td>71</td>
<td>0</td>
</tr>
<tr>
<td>Mn(OTf)(_2) (^c)</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>Fe(TPP)Cl(^f)</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Fe(OTf)(_2) (^f)</td>
<td>63</td>
<td>21</td>
</tr>
<tr>
<td>Co(OTf)(_2) (^c)</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Rh(_2)(OAc)(_2) (^f)</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>Rh(PPh(_3))Cl</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Ni(acac)(_2) (^d)</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Ni(OTf)(_2) (^c)</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Pd(acac)(_2) (^f)</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) All reactions were performed using 5 mol % catalyst. \(^b\) 5 equivalents of olefin were used. \(^c\) OTf = triflate
\(^d\) acac = acetoacetonate ligand \(^e\) TPP = tetraphenylporphyrin \(^f\) OAc = acetate
reported as aziridination catalysts, but a systematic study has not been conducted. Figure 2 shows five different ligands (some bound to copper) that have been used repeatedly, when bound to copper, as aziridination catalysts. Evans\textsuperscript{25} developed 5 that, when bound to a metal, is nitrogen ligated. The ligand, and thus chelate ring size, can be varied, but little exploration has been done in this area. Jacobsen\textsuperscript{19} reported 6 in 1993. When complexed with a metal center, 6 would generate a complex with a chelate ring size of five. Templeton\textsuperscript{26} reported that 7 is an aziridination catalyst precursor in 1993. Notice 7 has chelate ring sizes of six and nitrogen ligation. More recently, Halfen reported that 8 is an efficient copper aziridination catalyst giving reaction yields of up to 99%. Catalyst quantities of around 0.50\% of 8, a full order of magnitude lower than the amount traditionally used by most aziridination catalysts, proved sufficient. No other studies
have probed the use of such low catalyst quantities. Although not probed in the other systems, 8 has a ligand similar to 1, both generate a chelate ring size of five on a metal center. Finally, in 1997, Conry and coworkers developed 9, a copper catalyst active in the aziridination reaction. At the time, there were no other complexes with macrocyclic ligands reported to be catalytically active. The synthesis and characterization of 9 has been reported. A naphthyl group is appended to 9, a [10]-aneNS$_2$ macrocyclic ligand. Conry and coworkers have found 9 to be a competent catalyst for the aziridination of styrene as well as several other olefins. The nomenclature, [10]-aneNS$_2$, is intended to give a simpler notation of what the compound contains. The ten in [10]-aneNS$_2$ indicates that it is a ten-membered ring. The -ane portion reveals that there are no double bonds present in the ring. The final NS$_2$ is to represent the presence of the one nitrogen and two sulfur heteroatoms.

The coordination chemistry and characterization of 5-9 have been studied but, once again, little work has been done on determining which characteristics affect the catalytic capabilities for the aziridination reaction. The current study was designed to probe what characteristics of ligands affect the aziridination capabilities of the copper complexes bearing those ligands. Novel copper(I) aziridination catalysts were employed using 1 and 3 as ligands to form aziridination catalysts which were tested for efficiencies. Comparison was drawn with 9, the complex developed by Conry and coworkers.

In this investigation the ligand ring size was changed from ten atoms (10-ane) to nine atoms (9-ane). Both 1 and 3 are commercially available, making them logical choices for exploration. The three ring heteroatoms were also changed, from NS$_2$ to S$_3$ and N$_3$. The ligands in the two catalysts 10 and 11 can be represented as [9]-aneS$_3$ and
Figure 2. Five different complexes or ligands used to form copper complexes with capabilities as aziridination catalysts. The bridge in 5 can be any number of carbon bonds, but usually is two.
[9]-aneN₃, respectively. If this two-fold change shows encouraging results, further studies can determine which part, or if both parts, of the variations caused the change in yield.

The work reported here involves the aziridination of the olefin styrene using the nitrene precursor PhINTs in the presence of either 10 or 11 to yield 12 (eq 6).

\[
\text{5} + \text{PhINTs} \xrightarrow{\text{10 mol} \% \text{10 or 11}} \text{12} \quad \text{eq 6}
\]
Results and Discussion

As previously stated, olefins are generally used as the starting material for aziridination reactions. However, there have been some problems with low or no yields with some olefin substrates due to competing reactions. These reactions include hydrogen abstraction and insertion. Styrene has been found to give high yields (56-95%) with a wide variety of catalysts and solvents.

Evans and coworkers have examined four different nitrene sources 13-16 for the aziridination reaction with the best being 15, (N-(para-tosylsulfonyl)imino)-phenyliodonane, PhINTs. The condition used in this Evans study included the use of excess styrene, as the olefin, with 5 mol % CuOTf as the catalyst at room temperature. No reaction occurred without the presence of catalyst.

\[
\begin{align*}
\text{PhMeSNTs} & \quad 13 \\
N^+ \quad \text{TsN} & \quad 14 \\
\text{PhINTs} & \quad 15 \\
\text{TsN=NTs} & \quad 16
\end{align*}
\]

More recently two new nitrene sources for the aziridination reaction have been developed. Chloramine-T\textsuperscript{30} (TsNNaCl) and Bromamine-T\textsuperscript{8,31} (TsNNaBr) have both proven to be competent nitrene sources. Chloramine-T (17, N-chloro-N-sodio-p-toluenesulfonamide) has found several other synthetic uses,\textsuperscript{32} but Bromamine-T (18, N-bromo-N-sodio-p-toluenesulfonamide) appears to be a superior nitrene source for the aziridination of olefins.
The yields from the aziridination of olefins with 17 and 18 as the nitrene sources are still somewhat low and the process is developing. Research has been published on the iodine$^{24}$ and copper$^{33}$ catalyzed aziridination of olefins with 17 as the nitrene source.

At this time, PhINTs remains the most efficient and widely used nitrene precursor for the aziridination reaction. PhINTs was synthesized in the laboratory (eq 7) and is characterized by $^1$H NMR spectroscopy using DMSO-$d_6$ as the solvent. Figure 3 shows the $^1$H NMR spectrum of PhINTs in DMSO-$d_6$. The exact solid-state structure of PhINTs is not known as no crystallographic study has been reported. In concurrence with the literature values given by Yamada,$^{34}$ there was a chemical shift in the region of 2.30 ppm due to the three methyl hydrogens on the tosyl group. The aromatic protons produced several peaks in the region between 7 to 7.80 ppm, also agreeing with the literature values.
Figure 3. $^1$H NMR spectrum of PhINTs in DMSO-$d_6$. 
Dimethyl sulfoxide-\textit{d}_6 is very hygroscopic, thus, it contains a peak at 3.4 ppm resulting from water in addition to a resonance at 2.5 ppm due to the incomplete deuteration of the solvent. A spectrum just containing the solvent was taken to confirm that these peaks came from the solvent and not the reaction products.

Different solvents for the aziridination reaction have been used by different researchers with evidence showing that solvent polarity does not have a significant impact on the aziridination reaction involving styrene. Evans found that benzene was the best solvent for the copper-catalyzed aziridination of styrene as the reaction yielded 99\% of the expected aziridine using a variety of copper catalysts\textsuperscript{1}. However, it was noted that for other olefins this observation no longer held. Reaction rates and efficiencies for less reactive substrates were enhanced by increased solvent polarity. Such polar solvents include MeCN and MeNO\textsubscript{2}. The best solvent for the aziridination of a wide variety of olefins with PhINTs was found to be acetonitrile\textsuperscript{1}. The Conry group has consistently used nitromethane as the solvent after their own careful screening of various possibilities\textsuperscript{23}. They found that the polar solvents were best, similar to what Evans found, but MeNO\textsubscript{2} consistently gave the best aziridine yields. In this way, reactions could be carried out using a variety of substrates and could be directly compared instead of optimizing the polarity of the solvent for each substrate.

Different methods of removing the solvent once the reaction has gone to completion were evaluated. The first method employed a rotary evaporator to distill away the solvent. Unfortunately, it went slowly at room temperature due to the fairly high boiling points of MeNO\textsubscript{2} and excess styrene. The addition of heat contributes to the degradation of the product due to its natural instability. To overcome this problem, the
solvent removal was done by vacuum distillation using Schlenk techniques. No heat was added except in the form of a room temperature water bath to maintain the solution temperature as heat was lost to the environment.

An internal standard of triphenylmethane was used to determine the aziridine yield of the reaction. One equivalent of triphenylmethane was added compared to the limiting reagent, PhINTs. Triphenylmethane is unreactive with the other chemicals present; thus it contains a constant signal in the $^1$H NMR spectrum. The characteristic peak of interest occurs as a singlet at a chemical shift of about 5.5 ppm and results from proton H$_a$ attached to the central carbon in triphenylmethane 19. Since there is only one proton for the resonance of H$_b$ in the aziridine 20 as well as the resonance for proton H$_a$ in 19, the peak integrals can be directly compared because both resonances are for one hydrogen.

The aziridine proton H$_b$ gives a doublet of doublets with a chemical shift of about 3.7 ppm. Figure 4 is an enlargement of the desired area of the NMR spectrum with the inset showing the quartet more clearly. To determine the percentage yield the two signals are integrated and the area underneath each compared. One equivalent of aziridine should be produced. Comparison of the ratios of the two peaks will give a percentage of
Figure 4. Enlargement of $^1$HNMR spectrum in area used to determine yield
the aziridine actually formed.

Formation of the two catalysts 10 and 11 involved the synthesis of tetrakis(acetonitrile)copper(I) hexafluorophosphate (eq 8) as a copper ion source. The product, 22, was characterized by FT-IR spectroscopy in Nujol (Figure 5). The infrared spectrum showed peaks due to CH$_3$CN at 2274 (m) and 2301 (m) cm$^{-1}$ compared with literature values$^{35}$ of 2277 (m) and 2305 (m) cm$^{-1}$. There are also peaks due to [PF$_6$]$^-\,$ at 839 (vs) and 557 (s) cm$^{-1}$ that correlate with literature values of 850 (vs) and 557 (s) cm$^{-1}$. The two peaks at 1460 (s) and 1377 (s) cm$^{-1}$ result from Nujol and are marked with stars.

The next step involved reacting 22 separately with ligands 1 and 3 to generate the copper-acetonitrile complex, $in situ$. This synthesis involved the reaction of 22 with either 1 or 3 (illustrated with 3 in eq 9). This resulting complex was generated in solution.
Figure 5. FT-IR spectrum of tetrakis(acetonitrile)copper(I) hexafluorophosphate
and was then used to catalyze the subsequent aziridination reaction without further manipulation. The products were then analyzed by $^1$H NMR spectroscopy as described above. As an aziridine is highly reactive, it easily decomposes. It has been observed that these competing reactions occur continuously, lowering the yield of the desired aziridine over time after the reaction, thus necessitating immediate analysis. It was found that if immediate analysis was not possible, cold storage (-15 °C) of the aziridine reaction product minimized the degradation process. However, once dissolved in the deuterated chloroform solvent the aziridine decomposed rapidly so spectra were taken as quickly as possible.

The aziridination of styrene with PhINTs was first performed using a previously studied copper catalyst, Cu(acac)$_2$, so as to have a standard with which to compare yields. The reaction was analogous to equation 6 with a different catalyst. The aziridine product was analyzed by $^1$H NMR spectroscopy in CDCl$_3$ (Figure 6). The peaks resulting from various hydrogen atoms can be seen on the NMR spectrum. From 7 to 8 ppm, the signals from the hydrogen atoms on the two aromatic rings are seen. $H_a$ and $H_b$ resonances are found at 3.8 and 3.0 ppm, respectively. The singlet at 2.45 ppm results from the methyl group attached to the aromatic ring. The remaining peaks are from side products as confirmed by spectra of tosylamine and iodobenzene. There are no other peaks present indicating that only one aziridine isomer is formed from the aziridination of styrene.

Table 2 is a compilation of results from the many aziridination reactions performed. Two reactions with different catalysts were always run simultaneously as a method of comparison. The catalyst Cu(acac)$_2$ was always used as one of the two catalysts as the results from that system were well established.
Figure 6. $^1$H NMR spectrum of a typical aziridination reaction product in CDCl$_3$.
Table 2. Compilation of aziridine yields from aziridination reactions run in pairs of two catalysts.

<table>
<thead>
<tr>
<th>Catalyst A</th>
<th>% Yield</th>
<th>Catalyst B</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu(acac)$_2$</td>
<td>69</td>
<td>10</td>
<td>58</td>
</tr>
<tr>
<td>Cu(acac)$_2$</td>
<td>51</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Cu(acac)$_2$</td>
<td>56</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>Cu(acac)$_2$</td>
<td>50</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Cu(acac)$_2$</td>
<td>31</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Cu(acac)$_2$</td>
<td>46</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Cu(acac)$_2$</td>
<td>37</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Cu(acac)$_2$</td>
<td>46</td>
<td>11</td>
<td>40</td>
</tr>
</tbody>
</table>

The two columns on the left list the catalyst Cu(acac)$_2$ and its respective aziridine yields. This reaction was used as a standard, against which the results from the new catalysts were compared. The two columns on the right show the aziridine yields from aziridination reactions catalyzed by 10 or 11. The sensitivity of the aziridination reaction can be seen in the wide range of yields obtained. The reactions catalyzed by 10 or 11 proceeded very quickly, as seen by the fast dissolution of PhINTs. On the other hand, in the presence of Cu(acac)$_2$, reaction times were on the order of twenty minutes. In an effort to maintain consistency between the reactions, all reactions were allowed to proceed until the final one reached completion. It is thought that in this time degradation of the aziridine product began in the reactions using 10 or 11, thus, lowering the yields compared to Cu(acac)$_2$.

The average yields for reactions catalyzed by Cu(acac)$_2$, 10, and 11 were 48.2, 28.9, and 33.6%, respectively. The $N_3$ ligated system gave higher yields than the $S_3$ ligated system. In all cases that the reaction time was limited by Cu(acac)$_2$ and the yield in the presence of Cu(acac)$_2$ was higher. However, closer examination of the data for the reactions catalyzed by 11, reveals only a slight depression in yield from that of Cu(acac)$_2$, a difference of only 8% on average. Preliminary studies to compare the aziridine yields...
of reactions catalyzed by 11 (34.7%) with reactions catalyzed by a copper complex with the [10]ane-NS₂ ligand system (23, 40.8%) indicated slightly lower yields for reactions catalyzed by 11. For this study, all reactions were allowed to proceed for the approximately twenty minutes that the reaction catalyzed by Cu(acac)₂ requires. The identity of the heteroatoms on the ligand ring appears to have a small impact on aziridine yield. It is possible that a combination of sulfur and nitrogen heteroatoms gives the best aziridine yields. There is a 12% change in yield from the variations that were made between N₃, S₃, and NS₂ ligation.

\[
\begin{array}{c}
\text{CH}_3 \\
\text{C} \\
\text{N} \\
\text{Cu} \\
\text{S} \\
\text{N} \\
\text{CH}_3
\end{array}
\]

The reaction time has a major influence on the aziridine yield based on an initial study in which reactions catalyzed by 11 were allowed to proceed for ten and twenty minutes. The aziridine yield increased by more than two-fold, from 34.7 to 83.0%, for the reaction that was worked up after ten minutes. These findings indicate that immediate work-up after the reaction is completed is optimal to produce the highest aziridine yield. Another avenue to follow in this area would be to work-up all reactions when the first one goes to completion and compare the results at that point.
Conclusion

Indications are that the nitrogen ligated catalysts are more efficient than the catalyst containing sulfur heteroatoms. The results of the study indicate that the two new copper aziridination catalysts, 10 and 11, are not as efficient as some other more developed catalysts. In comparison to reactions catalyzed by 23 (NS₂), aziridine yields have also decreased for reactions catalyzed by 10 (S₃) and 11(N₃). A combination of heteroatoms as in 23 appears to give the best aziridine yields.

The reaction conditions could be further altered to help obtain optimal yields. Preliminary results suggest that side reactions and aziridine degradation occur rapidly in the reaction vessel. Indications are that reaction work-up immediately after completion gives higher aziridine yields. Lower temperatures could be also explored to slow down the side reactions. The influence of the age of the PhINTs was examined briefly to determine if it affects the aziridine yields but more work could be done in that area.
Materials. All chemicals were purchased from Acros or Aldrich. However, it is possible to synthesize 3 in the lab in yields of up to 60% using a template synthesis published by Sellman and Zapf.\textsuperscript{36} Ligand 1 also can be synthesized directly in the lab. It was first accomplished by Koyama\textsuperscript{37} and later refined by Atkins\textsuperscript{38} and Wieghardt.\textsuperscript{39}

Physical Measurement. $^1$H NMR spectra were recorded on a Bruker 400 MHz spectrometer in CDCl$_3$ unless otherwise specified. Infrared spectra were recorded on a Mattson Instruments 4020 Galaxy Series FT-IR spectrometer as a Nujol mull.

Preparation of (N-(para-tosylsulfonyl)imino)phenyliodinane (PhINTs). This procedure was adapted from a published protocol.\textsuperscript{34} The temperatures and time periods were adjusted slightly.

To methanol (80 mL) was added p-toluenesulfonamide (3.43 g, 20 mmol) and potassium hydroxide (2.81 g, 50 mmol). The solution was stirred and cooled in an ice bath. To this solution, iodobenzene diacetate (6.40 g, 20 mmol) was added. The resulting yellow solution was stirred for 3 hours at room temperature. Water (80 mL) was then added and the entire solution placed in the refrigerator overnight. By morning, a yellow solid had precipitated out of solution. The solid was then removed by filtration through a medium fritted funnel and washed with cold water. The solid was recrystallized from methanol to give 70.53\% PhINTs (4.81 g).
\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta 2.30\) (s, 3H, CH\(_3\)) and 7.00-7.80 ppm (m, 9H, aromatic protons).

**Preparation of Tetrakis(acetonitrile)copper(I) hexafluorophosphate.** The following synthesis was adapted from the original work done by Kubas.\(^3\) The crystallization temperatures and times were altered slightly.

To 80 mL acetonitrile was added copper(I) oxide (3.98 g, 27.8 mmol). To this stirred solution was added 10 mL (0.113 mol) of 60% hexafluorophosphoric acid in 2 mL aliquots. The temperature of the solution increased during this addition. The high temperature helped to keep the product dissolved. Stirring was continued for three minutes. The solution was subsequently filtered through a fritted funnel. Some crystallization occurred in the funnel. The filtrate was pale blue and the precipitate was off-white. A minimum amount of acetonitrile was used to redissolve the precipitate. Filtration was then continued. The filtrate was transferred to a closed flask and stored overnight at \(-15^\circ\)C. By morning, a white solid of [Cu(CH\(_3\)CN)\(_4\)] [PF\(_6\)] with a slight blue tint had crystallized. The precipitate was collected by vacuum filtration with a fritted funnel and washed with diethyl ether. The precipitate was then transferred to a beaker and immediately redissolved in 120 mL acetonitrile. Some remaining blue solid was removed by vacuum filtration through a medium fritted funnel. This blue solid was most likely a copper(II) impurity. Ethyl ether (100 mL) was added to the filtrate in an Erlenmeyer flask. This solution was stored at \(-20^\circ\)C for six hours.

The remaining portion of the synthesis was performed using standard Schlenk techniques. The filtrate from the recrystallization was filtered through a fritted funnel in
vacuo. It was then washed with deoxygenated ether and dried for 30 minutes. The solid was stored in an air-free funnel under an N₂ atmosphere to preserve the quality of the resulting white powder.

IR (Nujol mull): 2277 m, 2305 m, 850 vs, 557 s cm⁻¹.

**Typical Aziridination Reaction Conditions of Styrene with PhINTs and Cu(acac)₂.** To four to eight mL of nitromethane (CH₃NO₂) was added styrene (5.0 equivalents). The two liquids were stirred briefly followed by addition of one equivalent of PhINTs. The nitrene source, PhINTs, is essentially insoluble is nitromethane. The catalyst, Cu(acac)₂, (0.1 equivalent), was added and made a green slurry. The reaction progress can be followed by the dissolution of PhINTs, the limiting reagent. The solution was stirred until a homogeneous yellow solution was found (approximately 20 minutes). At this time, an internal standard (1.0 equivalent) of triphenylmethane was added. The solvent and excess styrene were then removed by distillation under high vacuum using Schlenk techniques. No heat was used as to preserve the integrity of the aziridine. The recovered aziridine was analyzed by ¹H NMR spectroscopy using deuterated chloroform as the solvent.

**Typical Aziridination Reaction Conditions for Styrene Using PhINTs and 10 or 11.** As some of the compounds for the reaction are air sensitive, the entire reaction was performed using air-sensitive techniques, though not strictly. First the solvent, four to eight mL of nitromethane, was combined with five equivalents of styrene and this solution deoxygenated. During this time, one equivalent of tetrakis(acetonitrile)copper(I)
hexafluorophosphate and one equivalent of 1 or 3 were combined. Tetrakis(acetonitrile)copper(I) hexafluorophosphate as well as 1 are slightly air sensitive, so every effort was made to minimize their contact time with the air. However, it was necessary to use a balance in open air. Once in the flask, the compound was flushed with nitrogen until the solvent was added. This solution was stirred for thirty minutes to make the catalyst in situ. At the same time, a solution containing Cu(acac)₂ as the catalyst was allowed to stir for comparison between the reactions.

One equivalent of PhINTs was added at this time and allowed to react with styrene. The PhINTs dissolved almost instantly in the flask containing 10 or 11, indicating a very fast reaction. The solution was allowed to stir for about twenty minutes as the PhINTs in the solution containing a catalyst of Cu(acac)₂ was allowed to react. The reaction progress could be followed by watching the dissolution of PhINTs. After both reactions went to completion, one equivalent of the internal standard triphenylmethane was added and the solvent removed under vacuum without heat. Immediate analysis by ¹H NMR spectroscopy was carried out whenever possible.
References


(2) For a review of the metal-catalyzed epoxidation reaction, see: Jorgensen, K. A. *Chem. Rev.* **1989**, *89*, 431.

(3) For a review of the metal-catalyzed cyclopropanation reaction, see: Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919.


