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Ag(I)-Catalyzed Regioselective Ring-Opening of *N*-Tosylaziridine and *N*-Tosylazetidine with *S*-, *O*-, and *N*-Nucleophiles and Tethered Dinucleophiles

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$[Ag(COD)_2]PF_6$ catalyzes the ring-opening of *N*-tosylaziridines and -azetidines with alcohols, amines, thiols, and related tethered 1,2-ethane dinucleophiles. Initial rate studies and DFT-based evaluation of stepwise energetics suggest an inverse relationship between the nucleophilic reactivity of a heteroatom donor and its binding affinity to cationic Ag(I).

The strained *N*-heterocycles aziridines and azetidines are widely utilized as synthetic intermediates in organic synthesis, more importantly in the design of nitrogen-containing natural products and biologically active compounds.[1,2] A diverse range of organic architecture can be generated by the regioselective ring-opening of aziridines and azetidines with various nucleophiles.[3−6] In particular, for ring-opening using heteroatom centered *O*-, *N*-, and *S*-nucleophiles, chiefly alcohol, amine, and thiol, various catalytic routes have been devised employing an array of homogeneous and heterogeneous catalysts with varying degrees of efficiency and functional group selectivity. Compounds containing 1,2-diamine, amino ether, and amino thioether functionality find many synthetic uses.[7] Vicinal amino thioethers have also found utility as medicinal agents and bioactive compounds. Compounds containing the 1,2-diamino moiety have been used in cancer chemotherapy as oxaliplatin, NDDP, and NK121 drugs. Amino ethers

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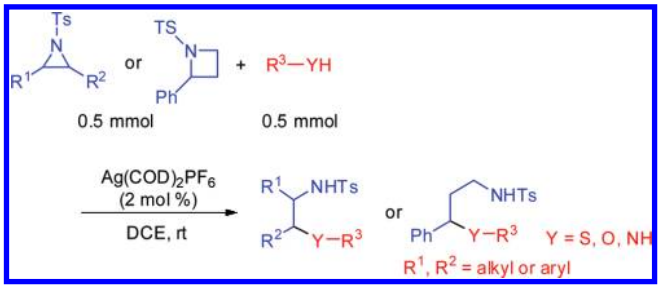
SCHEME 1. Ring-Opening of *N*-Tosylaziridine and *N*-Tosylazetidine with *N*-, *O*-, and *S*-Nucleophiles



and ether-containing peptide surrogates are popular as antibiotics for the treatment of anxiety and depression. Enantiomerically pure chiral vicinal compounds are also used in asymmetric catalysis as ligands and auxiliaries.

Within the ambit of our ongoing program on Tm catalysis for fine chemicals,[8] we have recently reported Ag(I)-catalyzed ring-opening of *N*-tosylaziridines and azetidines by a *C*-nucleophile.[9] By using propargyl alcohol as a *O*-nucleophile, we could also execute tandem ring-opening and ring-closing resulting in the formation of *N*,*O*-heterocycles, namely oxazines, oxazepines, and oxazocines.[10] In this paper, we report Ag(I)-catalyzed ring-opening of *N*-tosyl aziridines and azetidines with alcohols, amines, thiols, and tethered dinucleophiles, relative rate studies, and DFT-based evaluation of the binding ability of the tethered nucleophiles to cationic Ag(I).

The air-stable but light-sensitive complex $[Ag(COD)_2]PF_6$ was easily synthesized from $AgPF_6$ and 1,5-cyclooctadiene in methanol.[10] Control studies on ring-opening were performed at ambient temperature using *N*-tosyl-2-phenylaziridine as the representative aziridine and diphenylmethanol, *p*-toluidine, and *tert*-butylthiol as the representative *O*-, *N*-, and *S*-nucleophile, respectively (Supporting Information). Among the catalysts screened, $AgNO_3$, Ag_3PO_4, and AgOAc showed negligible activity. On the other hand, $Ag(COD)_2PF_6$, $AgPF_6$, $AgBF_4$, and $Ag[(COD)_2]BF_4$ showed good to excellent catalytic efficiency in dichloroethane as solvent and at an optimum loading of 2 mol %. Using $Ag(COD)_2PF_6$ as catalyst, the ring-opening of substituted aziridines and *N*-tosylazetidine with alcohols, phenols, aliphatic, and aromatic amines and thiols have been accomplished giving rise to corresponding 1,2-amino ethers, diamines, amino thioethers, and 1,3-amino ethers in good yields (Scheme 1, please see later for substrate scope).

What is the relative reactivity of *N*-, *O*-, and *S*-nucleophiles in the ring-opening of *N*-tosylaziridine? To look for the answer, a kinetic study was attempted with 2-phenyl-*N*-tosylaziridine as the electrophile and phenol, aniline, and thiophenol as the representative nucleophile from each group. As shown in Figure 1, the pseudo-first-order rate data (vide ^1H NMR) indicate the reactivity order as $-SH > -OH > -NH_2$.

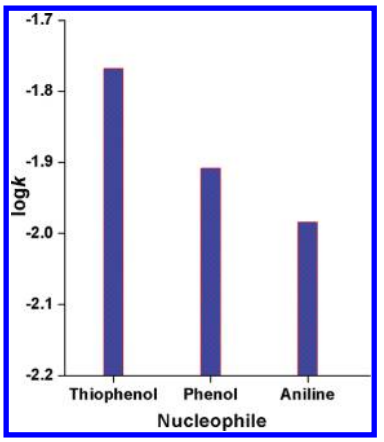
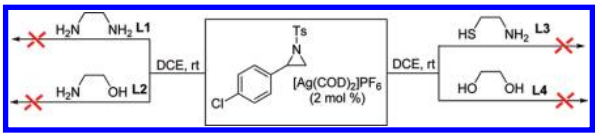


FIGURE 1. Pseudo-first-order rate constant (log *k*) in $[Ag(COD)_2]PF_6$-catalyzed ring-opening of *N*-tosylaziridine with *N*-, *O*-, and *S*-nucleophile.

SCHEME 2. Attempted Ring-Opening of 4-Chlorophenyl-*N*-tosylaziridine with Tethered Dinucleophiles (Donor = *N*/*S*, *N*/*N*, *N*/*O*, *O*/*O*)



To further augment the reactivity order, we conducted the reaction of 4-chlorophenyl aziridine and cyclohexylaziridine with tethered ethane 1,2-dinucleophiles bearing $-NH_2$, $-OH$, and $-SH$ groups (Schemes 2−4). The following results are particularly noteworthy: (1) Among the tethered homo dinucleophiles, only 1,2-ethanedithiol accomplished the ring-opening of 4-chlorophenylaziridine leading to **38** as the sole product. (2) Among the hetero-dinucleophiles, only 2-mercaptoethanol reacted with 4-chlorophenylaziridine giving rise to **39** (from *S*-attack) as the major and **40** (from *O*-attack) as the minor product. (3) 2-Mercaptoethanol also reacted with cyclohexylaziridine leading to **41** (from *S*-attack) as the exclusive product, while other hetero-dinucleophiles remained unreactive. (4) 4-Aminothiophenol reacted with 4-chlorophenylaziridine leading to **42** (from *S*-attack) as the sole product.

In an effort to understand the observed reactivity pattern of the tethered 1,2-ethane dinucleophiles, we looked into the simplest paradigm of *stability versus reactivity*. The *O*-, *N*-, and *S*-tethered dinucleophiles are ideally poised to bind to Ag(I) in 1:1 and 1:2 stoichiometry leading to the corresponding chelates. It is expected that the coordination strength of a donor atom could influence the nucleophilic reactivity in an inverse sense. To probe further, the energetics of the stepwise displacement of COD by dinucleophile L leading to the complexes $[Ag(COD)(L)]PF_6$ **C1**−**C6** (step 1) and $[AgL_2]PF_6$ **C7**−**C12** (step 2) have been evaluated at the B3LYP/SDD,

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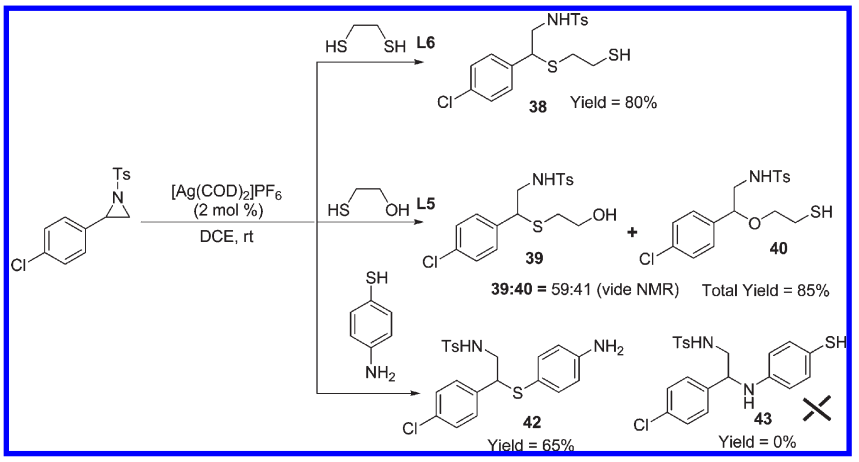
(11) (a) The structures of 12 complexes resulting from step 1 and step 2 were optimized at the B3LYP/SDD, 6-31G* level of theory. From the energy difference of product and reactant, complex formation energy was calculated without correction for zero-point energy differences. It was observed from the data that step 1 involving formation of complexes **C1**−**C6** is energetically more favorable than step 2 involving the formation of complex **C7**−**C12**. (b) For a perspective article on DFT-based studies of LA-catalyzed organic transformation, see: Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817.

SCHEME 3. Ring-Opening of 4-Chlorophenyl-*N*-tosylaziridine with Tethered dinucleophiles (donor = *S*/*S*, *S*/*O*, *S*/*N*)[a]



[a]Yield refers to isolated yield of product(s).

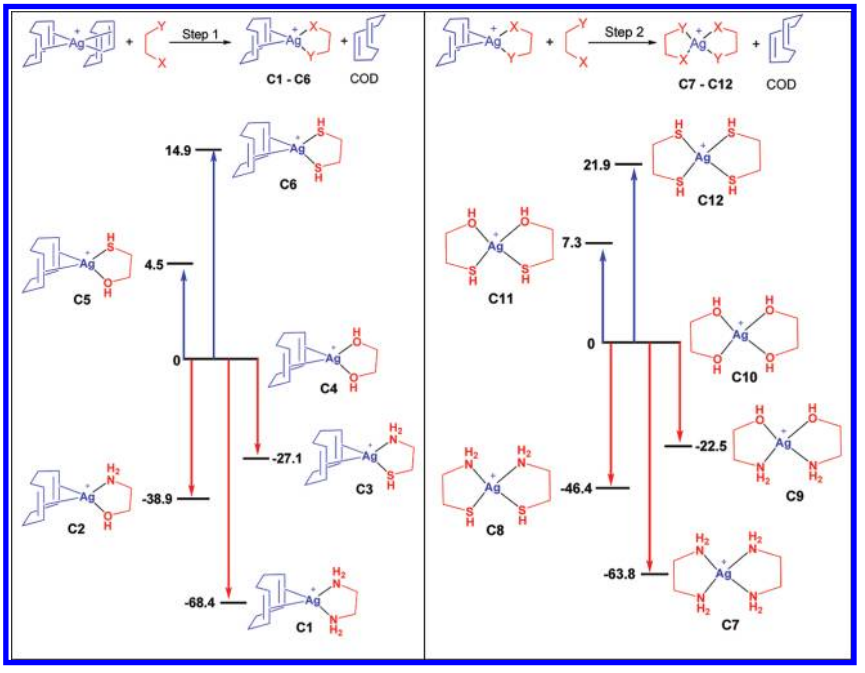
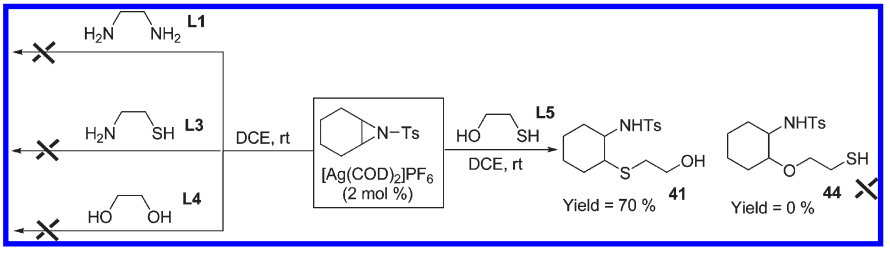


FIGURE 2. Relative complex formation energy for the stepwise displacement of COD by dinucleophile. Diagram drawn with reference to the formation energy of (i) **C4** (-67.8 kJ mol^{-1}) as zero in step 1 (left) and (ii) **C10** (-8.8 kJmol^{-1}) as zero in step 2 (right). Details in the Supporting Information.

SCHEME 4. Attempted Reaction of Cyclohexyl-*N*-tosylaziridine and 1,2-Ethane Dinucleophiles (Donor = *N*/*S*, *N*/*N*, *N*/*O*, *O*/*O*)



6-31G* level of theory (Figure 2).[11] Figure 2 represents the relative complex formation energy data for both step 1 and step 2 by taking the complex formation energy of **C4** and **C10** as zero. One may note that in both the cases, the complex formation energy decreases in the order L1 > L2 > L3 > L4 > L5 > L6, suggesting higher binding affinity of cationic Ag(I) toward *N*-donor ligands than *O*- and *S*-donors.[12] We may therefore conclude that by virtue of their poor binding affinity to cationic Ag(I), the *S*-donor ligands L5 and L6 promote facile ring-opening of *N*-tosylaziridines; in contrast,

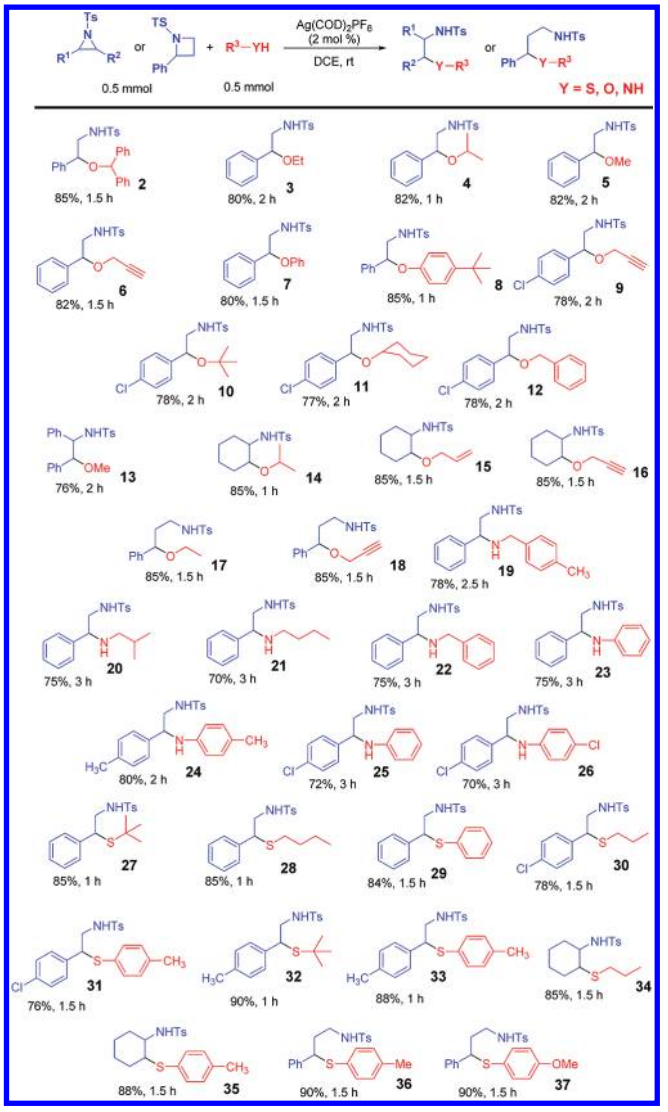


FIGURE 3. Substrate scope for Ag(I)-catalyzed regioselective ring-opening of *N*-tosylaziridine and *N*-tosylazetidine with *N*-, *O*-, and *S*-nucleophiles. Yield refers to isolated yields of pure products.

tethered dinucleophiles L1, L2, L3, and L4 show no reactivity. It will be interesting to explore whether similar correlation between binding affinity and nucleophilic reactivity exists in the case of other nucleophilic reactions involving heteroatoms which are catalyzed by cationic d^8/d^{10} metals.

(12) Selected examples of DFT-based calculations on cationic silver(I) complexes: (a) Shoeib, T.; Aribi, E. H.; Michael, S. W. K.; Hopkinson, C. A. *J. Phys. Chem. A* **2001**, *105*, 710. (b) Kim, K. C.; Kim, K. C.; Lee, S. B.; Won, J.; Kim, S. H.; Kang, S. Y. *J. Phys. Chem. A* **2001**, *105*, 9024. (c) Shoeib, T.; Hopkinson, C. A.; Michael, S. W. K. *J. Phys. Chem. B* **2001**, *105*, 12399.

As pointed out previously, we have successfully tested the substrate scope in the present $Ag(COD)_2PF_6$-catalyzed ring-opening of aziridines and *N*-tosylazetidine with *N*-, *O*-, and *S*-nucleophiles (Figure 3). In all cases, the products were isolated at good to excellent yields. In 2-arylaziridines, the nucleophiles always attacked the benzylic position. However, cyclohexyl-*N*-tosylaziridine did not react with aliphatic or aromatic amines even after increasing the catalyst loading and temperature. Attempted reaction of *N*-benzyl-2-phenylaziridine (as the electrophile) and ethanol (as the nucleophile) led to unidentified complex mixture, and the desired coupling product was not observed.

In summary, we have demonstrated in this note a facile $[Ag(COD)_2]PF_6$-catalyzed ring-opening of *N*-tosylaziridines and -azetidines with *N*-, *O*-, and *S*-nucleophiles including tethered 1,2-ethane dinucleophiles. Initial rate studies and DFT-based evaluation of stepwise energetics suggests that there exists an inverse relationship between the nucleophilic reactivity of a heteroatom donor and its binding affinity to cationic Ag(I). Further studies are warranted to arrive at the mechanistic description.

Experimental Section

All reactions were carried out under an argon atmosphere in flame-dried glassware using Schlenk techniques. Chromatographic purifications were done with either 60−120 or 100−200 mesh silica gel. For monitoring the reaction, precoated silica gel 60 F_{254} TLC sheets were used. Petroleum ether refers to the fraction boiling in the range 60−80 °C. Dichloroethane was dried and distilled prior to use.

Typical Procedure for the Ring-Opening of *N*-Tosylaziridine and Azetidine with *S*-, *O*-, and *N*-Nucleophile. A mixture *N*-tosylaziridine or azetidine (0.5 mmol), the nucleophile (0.5 mmol), and $[Ag(COD)_2]PF_6$ (2 mol %) in 3 mL of dry dichloroethane was stirred at room temperature. Following completion (via TLC), the reaction mixture was diluted with water (5 mL) and extracted with dichloromethane. The combined organic layer were dried over anhydrous sodium sulfate and concentrated in vacuum, and the resulting product was purified by column chromatography on silica gel (100−200 mesh, ethyl acetate−petroleum ether, gradient elution) to afford pure amino thioether, amino ether, or diamine derivatives.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for all new compounds; computational methodology, optimized structures with coordinates, and all the results in detail. This material is available free of charge via the Internet at http://pubs.acs.org.