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Chemo- and Enantioselective Intramolecular Silver-catalyzed Aziridinations

Minsoo Ju, Cale D. Weatherly, Ilia A. Guzei, and Jennifer M. Schomaker*

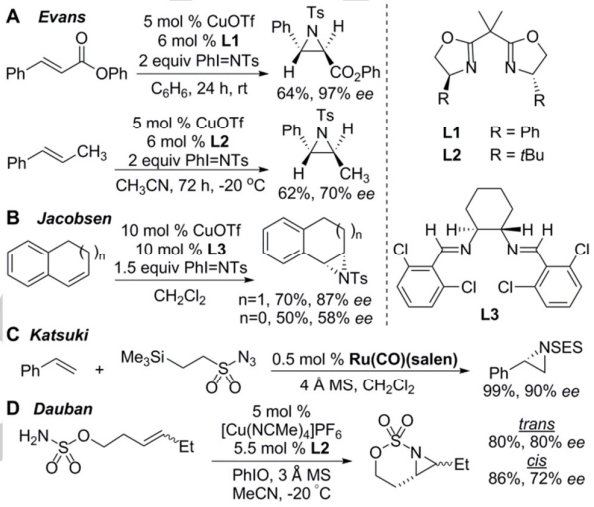
Abstract: Asymmetric nitrene transfer reactions are a powerful tool for the preparation of enantioenriched amine building blocks. Herein, we report chemo- and enantioselective silver-catalyzed aminations that transform di- and trisubstituted homoallylic carbamates into [4.1.0]-carbamate-tethered aziridines in good yields and *ee* up to 92%. The effects of the substrate, silver counteranion, ligand, solvent and temperature on both chemoselectivity and *ee* were explored to complement the scope of traditional metal-catalyzed nitrene transfer reactions. Stereochemical models were proposed to rationalize the observed absolute stereochemistry of the aziridines, which undergo nucleophilic ring-opening to yield enantioenriched amines with no erosion in stereochemical integrity.

Asymmetric, metal-catalyzed nitrogen-atom transfer reactions offer excellent opportunities to transform simple precursors into enantioenriched amines, key building blocks for pharmaceuticals, agrochemicals, natural products and ligands.[1,2] Additions of metal nitrenes to alkenes are particularly useful, as the strain in the resulting aziridines enables facile nucleophilic ring cleavage to furnish enantioenriched amines, amino acids, aminoalcohols and *β*-lactams.[3] Compared to asymmetric epoxidations, the corresponding aziridinations are underexplored and display narrower substrate scope. In this communication, we report an intramolecular chemo- and enantioselective silver-catalyzed nitrene transfer that furnishes di- and trisubstituted aziridines in good yields and *ee*. Ring-opening with diverse nucleophiles occurs at the distal aziridine carbon to yield amines with excellent retention of stereochemical information.

Early investigations of asymmetric metal-catalyzed nitrene transfer were pioneered by Evans and Jacobsen (Scheme 1A-B).[4,5] Cu supported by bis(oxazoline) (BOX) and diimine ligands were employed with imidoiodinanes as nitrogen sources. The biggest drawback of Cu-based catalysis is the limited scope, which is largely restricted to styrenes, terminal olefins and conjugate acceptors.[6] Chiral Ru catalysts supported by salen ligands (Scheme 1C)[7] use sulfonyl azides as nitrene precursors to furnish aziridines in up to 99% *ee*; however, the reaction works best with styrenes and terminal alkyl olefins. Dinuclear Rh catalysts and Zhang's porphyrin-Co complexes have also enjoyed success with certain classes of substrates.[1a,8]

Surprisingly, few examples of metal-catalyzed intramolecular asymmetric aziridinations have been reported, despite their potential for synthesizing valuable synthetic building blocks. A chiral Rh catalyst, $[Rh_2(4S\text{-MEOX})_4]$, gave aziridination of styrenes in up to 76% *ee* in moderate yields.[9] Aziridination of homoallylic sulfamates using $[Cu(MeCN)_4]PF_6$ supported by a BOX ligand has also been described (Scheme 1D).[10] Styrenes gave *ee* up to 84%, but replacing Ph with alkyl groups lowers the *ee*; to our knowledge, no successful examples of asymmetric aziridinations of trisubstituted alkenes have been reported.

Scheme 1. Approaches to metal-catalyzed chemoselective nitrene transfers.



Our group has reported tunable, chemo- and site-selective nitrene transfers catalyzed by Ag(I) complexes supported by diverse N-chelating ligands.[11-16] We wondered if the flexibility exhibited by these catalysts might improve both the scope and the *ee* of intramolecular alkene and allene aziridinations. Such studies would provide corroboration of our hypothesis that lower-coordination Ag(I) complexes favour aziridination, while higher coordination at the metal prefers C-H bond amination instead.[11]

In light of the need to favor low-coordinate Ag(I) complexes, preliminary studies focused on bidentate asymmetric ligands using $AgClO_4$ as the metal salt (see Supporting Information for full details). Chiral BOX ligands gave the best balance between chemoselectivity for aziridination and *ee*. Optimizations using homoallylic carbamates **1-(*Z*)** and **2-(*E*)** were carried out with various Ag salts and BOX ligands (Table 1, full details in the SI). **L2** and **L5** gave good chemoselectivity and *ee* with $AgClO_4$ (entries 1, 5), while other ligands displayed either poor yield or *ee* (entries 2-4). Various Ag salts with **L2** and **L5** (entries 6-13) showed that coordinating anions, such as ^-OAc (entry 6), were not effective. AgOTf (entries 7-8) was superior using **L5** *vs.* **L2**, while $AgBF_4$ and $AgPF_6$ (entries 9-12) behaved similarity, but gave lower *ee* compared to $AgClO_4$. The *ee* with $AgSbF_6$ (entry 13) was on par with $AgClO_4$, but due to lower cost, $AgClO_4$ was chosen for further study. Similar *ee* was seen using other non-coordinating anions with **2-(*E*)** (entries 14-18) and **L2**/**L5**.

Further optimization used **L2** and **L5** with $AgClO_4$ (Table S3 in the SI for details). CH_2Cl_2 was the optimal solvent, in contrast to Cu-catalyzed aziridination, where CH_3CN was preferred.[10] Interestingly, addition of an extra 10 mol % of $AgClO_4$ delivered high yields at -20 °C and increased *ee* to >90%. This likely results

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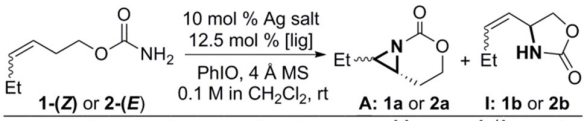
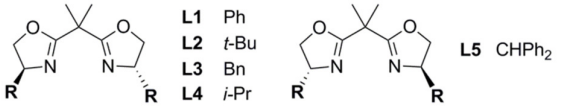
Table 1. Initial optimization of the asymmetric aziridination.



entry	substrate	Ag salt	ligand	yield **A**[a]	yield **I**[a,b]	*ee* **A**
1	**1-(*Z*)**	$AgClO_4$	**L1**	46%	7%	16%
2	**1-(*Z*)**	$AgClO_4$	**L2**	89%	10%	82%
3	**1-(*Z*)**	$AgClO_4$	**L3**	77%	6%	45%
4	**1-(*Z*)**	$AgClO_4$	**L4**	81%	11%	23%
5	**1-(*Z*)**	$AgClO_4$	**L5**	91%	9%	(-)80%
6	**1-(*Z*)**	AgOAc	**L2**	29%	16%	6%
7	**1-(*Z*)**	AgOTf	**L2**	63%	10%	67%
8	**1-(*Z*)**	AgOTf	**L5**	86%	6%	(-)81%
9	**1-(*Z*)**	$AgBF_4$	**L2**	92%	8%	71%
10	**1-(*Z*)**	$AgBF_4$[c]	**L2**	55%	5%	76%
11	**1-(*Z*)**	$AgBF_4$	**L5**	74%	10%	(-)67%
12	**1-(*Z*)**	$AgPF_6$	**L2**	69%	6%	71%
13	**1-(*Z*)**	$AgSbF_6$	**L2**	83%	5%	79%
14	**2-(*E*)**	$AgBF_4$	**L2**	73%	11%	83%
15	**2-(*E*)**	$AgPF_6$	**L2**	73%	13%	79%
16	**2-(*E*)**	$AgSbF_6$	**L2**	79%	8%	83%
17	**2-(*E*)**	$AgClO_4$	**L2**	79%	17%	85%
18	**2-(*E*)**	$AgClO_4$	**L5**	90%	10%	(-)84%

[a] NMR yield using mesitylene as internal standard. [b] **I:** C-H insertion byproduct. [c] NaBARF (BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl] borate) was employed as an additive.

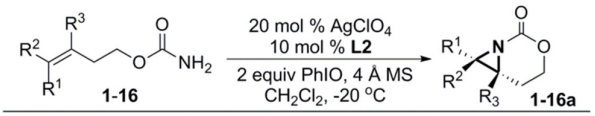


from the role the Ag salt plays in breaking up polymeric PhIO, a process that suffers at low temperatures.[17] $Sc(OTf)_3$ could be substituted for additional $AgClO_4$, with **L5** also showing increased *ee* upon cooling to -20 °C (see Table S3).

With optimized conditions in hand, the scope was explored (Table 2). Dialkylsubstituted alkenes **1-(*Z*)** and **2-(*E*)** (entries 1-2) gave excellent yields and >90% *ee*. The remainder of the mass balance in Table 2 was C-H insertion product, easily separated from the aziridine by column chromatography or recrystallization. Changing the length or steric bulk of the alkyl side chain (entries 3-4) furnished products in high *ee*. Benzyl and ether-containing alkyl groups were well-tolerated (entries 5-6); the *ee* of **5a** increased to >99% after one recrystallization. In contrast to Cu-catalyzed enantioselective aziridination, styrene **7-(*E*)** initially gave racemic aziridine **7a**. Interestingly, changing the solvent to C_6H_6, improved the *ee* to 70%; decreased *ee* was observed in toluene and xylene. Other substrates did not show this effect, suggesting that Ag-π interactions may be responsible for the increased *ee*.[10,18]

Gratifyingly, 1,1',2-trisubstituted alkenes **8-(*E*)**-**12-(*E*)** gave good chemoselectivity and *ee* for **8a**-**12a** (entries 8-12). A 1,2,2'-substitution pattern in **13-(*E*)** (entry 13) lowered *ee* to 22%, although the yield and chemoselectivity remained high. Steric bulk in the tether between the alkene and carbamate of **14-(*Z*)** (entry 14) resulted in lower yield, but good *ee* after one recrystallization. However, moving the bulk closer to the alkene in **15-(*Z*)** (entry 15) had a detrimental effect on the *ee*. Asymmetric aziridination of allene **16** to methyleneaziridine **16a** (entry 14) gave a promising 62% *ee*; further optimization studies

Table 2. Scope of the asymmetric aziridination.



entry	substrate	product	entry	substrate	product
1	**1-(*Z*)**	83% **1a** 91% *ee*[a]	9	**9-(*E*)**	81% **9a** 92% *ee*[a]
2	**2-(*E*)**	87% **2a** 92% *ee*[a]	10	**10-(*E*)**	84% **10a** 90% *ee*
3	**3-(*E*)**	85% **3a** 91% *ee*[a]	11	**11-(*E*)**	81% **11a** 87% *ee*
4	**4-(*E*)**	63% **4a** 92% *ee*[a]	12	**12-(*E*)**	84% **12a** 89% *ee*
5	**5-(*E*)**	80% **5a** 91% *ee* >99% *ee*[b]	13	**13-(*E*)**	89% **13a** 22% *ee*[a]
6	**6-(*E*)**	87% **6a** 92% *ee*[a]	14	**14-(*Z*)**	55% **14a** 88% *ee*[b]
7[c]	**7-(*E*)**	52% **7a** 70% *ee*	15	**15-(*Z*)**	94% **15a** 48% *ee*[a]
8	**8-(*E*)**	84% **8a** 87% *ee*	16	**16** *allene*	57% **16a** 62% *ee*

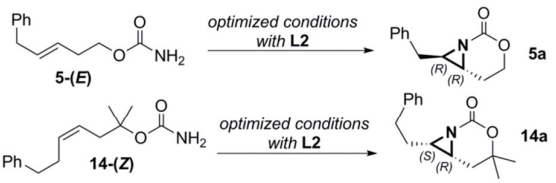
[a] *ee* was determined after ring-opening of aziridine with NaI. [b] *ee* after one recrystallization. [c] Reaction was run in C_6H_6 at room temperature.

are underway.[19] Although allylic carbamate substrates precludes issues of chemoselectivity, no *ee* was noted.

X-ray crystallography (SI for details) of **5a** resulting from reaction of **5-(*E*)** with **L2** (Scheme 2) contained (*R,R*) absolute stereochemistry. Reaction of **14** with **L2** gave (*S,R*)-**14a**, while **L5** furnished the antipodes. Interestingly, the observed absolute stereochemistry of *trans*-**5a** was opposite to that seen in Cu-catalyzed aziridination of homoallylic sulfamates.[10]

The results in Table 2 point to several alkene features important to obtaining high *ee* with Ag-catalyzed nitrene transfer. These include at least one substituent on the distal alkene carbon, monosubstitution only at the proximal alkene carbon, distal substituents that are not conjugated to the alkene and a two-

Scheme 2. Determination of the absolute stereochemistry.



Optimized conditions: 20 mol % $AgClO_4$, 10 mol % **L2**, 2.0 equiv. PhIO, 4 Å MS, 0.05 M in CH_2Cl_2, -20 °C.

carbon tether between the carbamate and the site of unsaturation. These observations, coupled with our knowledge of the absolute aziridine stereochemistry (Scheme 2), suggested the model for stereochemical induction proposed in Figure 1. High *ee* is observed when substitution is present at R^1, R^2, or at both R^1 and R^2. The poor *ee* observed when the proximal alkene carbon R^3 is substituted is rationalized by steric clashing between substrate and catalyst. Furthermore, the dramatic solvent effect observed with the styrene **7-(*E*)** suggests that potential π-cation interactions between the Ph group and the silver complex may erode the *ee* in non-aromatic solvents. Using

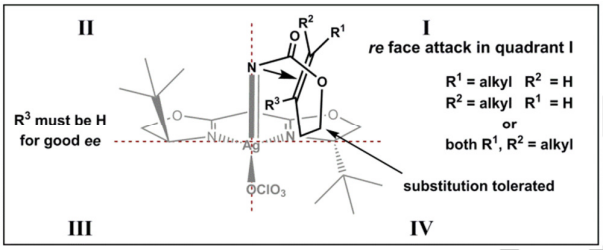
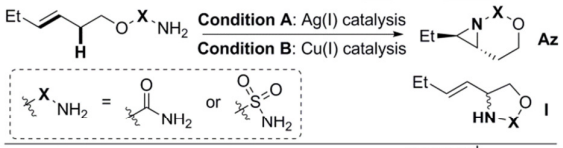


Figure 1. Stereochemical model for asymmetric aziridination.

C_6H_6 as solvent (Table 2, entry 7) may interfere with these substrate-catalyst interactions, restoring some *ee* to the reaction. Other aromatic solvents (C_6H_5F and $C_6H_5CF_3$) also restored some *ee*, but not as effectively as C_6H_6.

A comparison of Ag(I) *vs.* Cu(I) catalysts supported by **L2** using both carbamates and sulfamates was carried out to better understand the differences between these two systems (Table 3). Our Ag(I) catalysts required carbamates as precursors (entry 1); a sulfamate gave only trace aziridine (entry 3). This was surprising, as we have previously shown sulfamates to be effective in other Ag-catalyzed nitrene transfers.[12,13] Closer examination by ^{1}H NMR showed formation of an iminoiodinane intermediate, which eventually furnished the aziridine over a period of days (Figure S2 for details). We propose this arises from either increased Lewis acidity of Ag(I) compared to Cu(I), or more likely, the increased size of the Ag(I) cation (115-126 pm) vs. a Cu(I) ion (96 pm). The sulfamate oxygen and the Ph of the iminoiodinane may bind to Ag, slowing down the formation of the active silver nitrenoid species, even at rt (Figure S2). This is not an issue in Ag catalysts with fewer open coordination sites on the metal.[12,13] Attempts to utilize $[Cu(MeCN)_4]PF_6$ with carbamates gave no reaction (entry 2), while sulfamates were successful as previously reported (entry 4).[10] These results highlight the impact of differences in metal identity and nitrogen transfer reagent on reaction behavior and point to the importance of further studies to better understand such effects.

Table 3. Comparison of carbamates and sulfamates in Cu- and Ag-catalyzed asymmetric nitrene transfer.

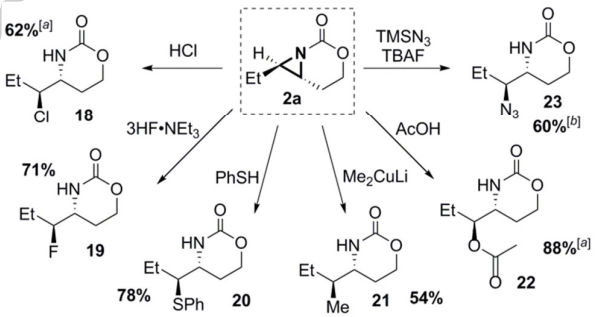


entry	substrate		conditions	yield **Az**	yield **I**	recovered substrate	*ee* of **Az**
1	**X** = CO	**2-(*E*)**	**A**	87%	10%[a]	n/d	92%
2	**X** = CO	**2-(*E*)**	**B**	15%[a]	5%[a]	44%[a]	n/a
3	**X** = SO_2	**17-(*E*)**	**A**	3%[a]	n/d	28%[a]	n/a
4[b]	**X** = SO_2	**17-(*E*)**	**B**	83%	n/a	n/a	80%

Condition A: 20 mol % $AgClO_4$, 10 mol % **L2**, PhIO, 4 Å MS, CH_2Cl_2, -20 °C. **Condition B:** 5 mol % $Cu(CH_3CN)_4PF_6$, 5.5 mol % **L2**, PhIO, 3 Å MS, CH_3CN, -20 °C. [a] NMR yield, mesitylene internal standard. [b] See ref. 10.

Nucleophilic ring-opening of aziridines introduces valuable functionality into the amine products.[3] To demonstrate that the stereochemical integrity of the aziridination is maintained during subsequent manipulations, **2a** was opened with diverse nucleophiles to give enantioenriched amines **18**-**23** (Scheme 3).[20,21] These ring-openings display reactivity complementary to that of the corresponding cyclic sulfamates, which open at the proximal aziridine carbon.[10] For example, **2a** undergoes ring-opening with halides, azides, carboxylic acids, sulfides and cuprates at the distal aziridine carbon. No erosion in either *dr* or *ee* of the amine products was noted. These aziridines could also be transformed into (2-aziridinyl)acetic acids by carbamate cleavage and oxidation of the primary alcohol.[22]

Scheme 3. Ring-openings of enantioenriched aziridines.



[a] See ref. 20. [b] See ref. 21.

In conclusion, we have described the first general examples of intramolecular, asymmetric aziridination proceeding *via* a silver-catalyzed nitrene transfer pathway. A BOX-supported $AgClO_4$ complex transforms di- and trisubstituted homoallylic carbamates to [4.1.0]-carbamate-tethered aziridines in good yields and *ee* ~90%. Nucleophilic ring-opening occurs smoothly at the distal aziridine carbon to furnish enantioenriched amines with no erosion of stereochemical information. Future efforts will explore ligands for asymmetric Ag-catalyzed C-H amination and expand the scope of asymmetric allene aziridination.

Experimental Section

A pre-dried reaction flask was charged with $AgClO_4$ (10.4 mg, 0.050 mmol, 20 mol %) and BOX ligand **L2** (7.4 mg, 0.025 mmol, 10 mol %). CH_2Cl_2 (5 mL) was added and the mixture stirred vigorously for 15 min. 4 Å molecular sieves (250 mg, 1 g of sieves/mmol of substrate) were added and the mixture stirred for 5 min. The carbamate (0.25 mmol, 1 equiv) was added, the mixture stirred for 2 min, cooled to -20 °C and PhIO (110 mg, 0.50 mmol, 2 equiv) added in one portion. The reaction mixture was stirred at -20 °C until ^{1}H NMR indicated complete alkene consumption (1-2 days). The mixture was filtered through Celite and the filtrate concentrated under reduced pressure. The crude aziridine was purified by silica gel chromatography using CH_2Cl_2/ethyl acetate.

Acknowledgements

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Keywords: nitrene • silver • aziridines • asymmetric • amines

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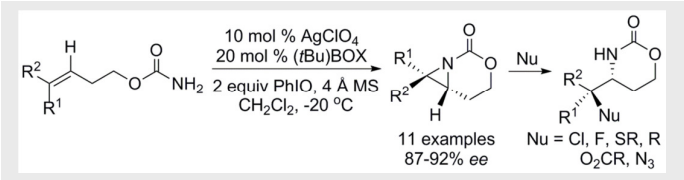

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Chemo- and Enantioselective Silver-catalyzed Aziridinations

Asymmetric nitrene transfer reactions are a powerful tool for preparing enantioenriched amines. We have developed chemo- and enantioselective silver-catalyzed aminations that transform di- and trisubstituted homoallylic carbamates into aziridines in good yields and *ee* of up to 92%. Stereochemical models are proposed to rationalize the observed absolute stereochemistry of the products, which undergo nucleophilic ring-opening to yield enantioenriched amines with no