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Chemo- and Enantioselective Intramolecular Silver-Catalyzed Aziridinations of Carbamimidates

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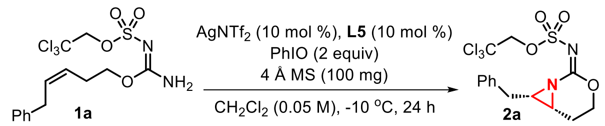
Transition metal-catalyzed asymmetric nitrene transfer is a powerful method to generate enantioenriched amines found in natural products and bioactive molecules. A highly chemo- and enantioselective intramolecular silver-catalysed aziridination of 2,2,2-trichloroethoxysulfonyl (Tces)-protected carbamimidates gives [4.1.0]-bicyclic aziridines in good yields and up to 99% *ee*.

Nitrogen functional groups in pharmaceuticals, agrochemicals, and natural products are key to their beneficial physiochemical and biological properties.[1,2] Transition metal-catalyzed nitrene transfer (NT) has emerged as an elegant strategy to directly transform olefins and C–H bonds into valuable nitrogen-containing building blocks. Chief among these are aziridines, resulting from nitrene insertions into alkenes, which are well-known[3-7] as versatile and efficient intermediates for olefin difunctionalization, as well as the construction of higher- order heterocyclic scaffolds.[8–10]

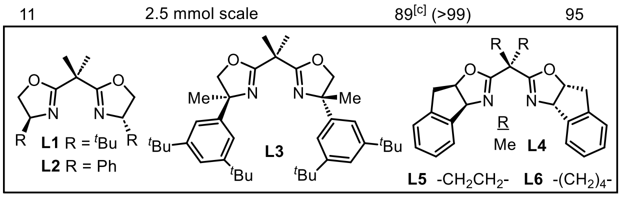
The majority of asymmetric aziridinations via NT involve intermolecular reactions of terminal, styrenyl and conjugated olefins, while intramolecular aziridinations via NT have received much less attention.[3,4,11,12] Given the scarcity of such methods, we wanted to expand the scope, *ee* and utility of silver-catalyzed aziridination[13-15] by exploring carbamimidates, which have not been used as nitrene precursors in asymmetric NT. We hypothesized that the additional valency on the imidate nitrogen, as compared to carbamates or sulfamates, would enable tuning of catalyst/substrate interactions in the NT transition state to improve chemo-, site- and enantioselectivity. The 5-member dihydrooxazol-2-amine and 6-member 1,3-oxazin-2-amine products using carbamimidates in asymmetric aziridination and ring-opening are found in several compounds with useful bioactivities.[16-19]

There is only one example of a NT using a carbamimidate, where Dauban reported Rh-catalyzed intramolecular C–H aminations to give racemic amines.[20] Prompted by promising bioactivities of cyclic carbamimidates, we aimed to develop an asymmetric silver-catalyzed aziridination of homoallylic carbamimidates, where matching the steric bulk from the imine *N*-protecting group with the chiral ligand would furnish high chemo- and enantioselectivity.[21,22] A 2,2,2-trichloro-ethoxysulfonyl (Tces) moiety in **1a** gave promising results using $AgNTf_2$ as the silver salt. A small set of commercially available and custom-synthesized BOX ligands were screened (Table 1, entries 1-6). Ligands **L1**-**L6** all gave **2a** in good yields and chemoselectivity (only a trace amount of allylic C–H amination was observed), but the differences in *ee* were remarkable. **L1** gave **2a** in only 35% *ee* while enantioinduction with **L2** and **L3** were marginal. We proposed the bulky Tces group could be better accommodated by allowing extra space near the metal center. Indeed, the *ee* of **2a** dramatically increased when

Table 1. Optimization of reaction conditions.



entry	variation from standard conditions	yield (conversion, %)[a]	*ee* (%)[b]
1	none	92 (98)	97
2	**L1** instead of **L5**	75 (89)	35
3	**L2** instead of **L5**	63 (77)	9
4	**L3** instead of **L5**	71 (85)	12
5	**L4** instead of **L5**	86 (96)	91
6	**L6** instead of **L5**	78 (89)	93
7	$AgClO_4$ instead of $AgNTf_2$	74 (92)	93
8	AgOTf instead of $AgNTf_2$	73 (90)	76
9	-20 °C, 24 h	26 (32)	96
10	$AgNTf_2$ (5 mol%), **L5** (5 mol%)	73 (92)	93
11	2.5 mmol scale	89[c] (>99)	95



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Electronic Supplementary Information (ESI): Experimental procedures, characterization data, computational details. See DOI: 10.1039/x0xx00000x indane-based BOX ligands **L4**-**L6** were used, with **L5** (entry 1) giving 97% *ee* and 92% yield.

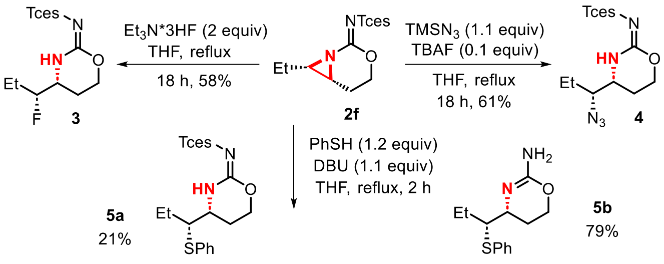
In contrast to previous silver-catalysed NT of carbamates and sulfamates, the counteranion was important, as $AgClO_4$ (entry 7) and AgOTf (entry 8) gave inferior results. This is attributed to the higher binding affinity of the corresponding anions of these salts as compared to $AgNTf_2$, and their increased steric interactions with the carbamimidate. Lowering the temperature from -10 °C to -20 °C (entry 9) decreased the conversion with no improvement in the *ee*, as did reducing the catalyst loading from 10 mol % to 5 mol % (entry 10). The reaction was amenable to scale-up (entry 11), as a gram-scale (2.5 mmol) reaction afforded **2a** in yields (89%) and *ee* (95%) comparable to the reaction conducted on a 0.1 mmol scale. The absolute stereochemistry of **2a** was (6*R*,7*S*) (see SI for details).

Scope studies (Table 2) showed that most carbamimidates of disubstituted alkenes give excellent yields (up to 91%) and *ee* (up to 99%). Aziridine **2b** was obtained from the corresponding (*E*)-alkene in 97% *ee*, suggesting a stereoretentive mechanism. Extending the alkyl chain length by one carbon (**2c**) gave better *ee* (99% *ee*), but further extension (**2d**) lowered *ee* (78% yield, 75% *ee*). A styrene **1e** provided **2e** in only 37% yield and 62% *ee*. Aziridines with linear alkyl groups (**2f-g**), protected alcohols (**2h**) and heteroarenes (**2i**) were all tolerated. Increasing steric bulk proximal to the alkene by installing isopropyl (**2j**), cyclohexyl (**2k**), *tert*-butyl (**2l**), or adamantyl (**2m**) groups did not negatively impact yield or *ee*. Applicability to complex molecules was highlighted by lithocholic acid-derived **2n**, obtained as a single diastereomer. A racemic stereocenter in **1o** afforded **2o** in a moderate 6.4:1 *dr*, with a 71% *ee* of the major isomer. Asymmetric desymmetrization gave high *dr* and *ee* for **2p** (> 20:1 *dr*, 94% *ee*). The stereochemistries of **2o** and **2p** were determined by NOESY (see the SI for details).

A series of 1,1',2-trisubstituted olefins also provided bicyclic aziridines **2q-s** in excellent *ee*, despite minimal competing C–H amination. This approach is attractive for securing quaternary amine-bearing stereocenters, even when the sterics of the two carbon substituents do not vary greatly (e.g. Me vs. Et in **2r**).

The 1,2,2'-trisubstituted olefins are challenging substrates for asymmetric aziridination. Cyclic olefin **1t** gave **2t** in 83% yield and a better 42% *ee* compared to a carbamate.[14] (1*R*)-(-)-nopol-derived **1u** gave a single diastereomer of **2u** in 99% yield. In addition to [4.1.0] bicyclic aziridines, other azabicyclic patterns were explored. Disubstituted alkene **1v** afforded **2v** in 79% *ee* after ring-opening of the corresponding aziridine (see Table 2 footnote for details). Moderate yields and *ee* of 5-membered rings were obtained from trisubstituted alkenes **1w** and **1x**. Computations (Figure 1, *vide infra*) were conducted to understand why lower *ee* is observed with shorter tethers. Alkene migration was also seen during fast ring-opening of [3.1.0] bicyclic aziridines. A longer tether did not give the 7-membered ring (**2y**, see the SI)- only allylic C–H insertion.

To demonstrate the post-synthetic utility of carbamimidate-derived bicyclic aziridines, **2f** was treated with fluoride (**3**), azide (**4**), and thiol (**5** and **5'**) nucleophiles to give the corresponding cyclic carbamimidates with no erosion of *dr* or *ee* (Scheme 1). The Tces group was not removed directly from **2f** due to lability



Scheme 1. Post-synthetic modifications of **2f** (0.1 mmol).

of the aziridine, but is cleaved with mild reductive conditions.[23]

The carbamimidate is key to the high *ee* of this system compared to conventional sulfamates and carbamates. Density functional theory (DFT) calculations were conducted to investigate the origin of *ee* and the effects of ligand (Figure 2). In particular, we examined the difference between the modes of enantioinduction with **L5**, the best ligand with the carbamimidate, and **L1**, the optimal ligand in asymmetric aziridinations of carbamates but gave low *ee* with *N*-Tces carbamimidates. Computations show **L5**, with indane arms and a cyclopropyl backbone, is substantially more rigid than **L1**. In the **L5**-supported Ag–carbamimidate nitrene complex (**3a**), **L5** adopts a completely planar conformation, whereas the corresponding **L1**-supported complex has two conformers—a C2-symmetric **4a**, where the oxazolines adopt an envelope conformation with a twisted, but planar, six-membered metallacycle, and a non-C2-symmetric conformer (**4b**) with a non-planar boat conformation of the metallacycle. The boat shows decreased steric repulsion between the ligand and the bulky Tces group in the non-planar geometry. On the other hand, with the more rigid **L5**-supported Ag–nitrene complex, the non-C2-symmetric boat conformer (**3b**) cannot be located. Constrained geometry optimization forcing the six- membered metallacycle into a boat suggests the **L5**-supported **3b** is ~11.9 kcal/mol less stable than the planar geometry **3a**.

Ligand rigidity impacts the mode and effectiveness of enantioinduction in the stereoselectivity-determining transition state (TS) (Figure 1, see Figure S4 in the SI for less favorable TS conformers).[24,25] In the **L5**-supported TSs, the rigid ligand **L5** maintains the C2-symmetric geometry with a planar six-membered metallacycle. In the most favorable TS **TS1** that leads to the observed major enantiomer (*R*)-**2f**, the Et-substituted alkenyl carbon is placed in a quadrant not occupied by the C2-symmetric **L5** ligand. In contrast, in **TS2**, the TS leading to the opposite enantiomer (*S*)-**2f**, the Et-substituted alkenyl carbon is placed in an occupied quadrant, leading to greater ligand–substrate repulsion. The repulsion in **TS2** is evidenced by the relatively short C···H distance (2.78 Å) between an indane arm of the ligand and the Et on the alkene. This repulsion also results in a distorted asynchronous TS geometry with a notably longer C–N distance (2.46 Å) with the Et-substituted alkenyl carbon than the other forming C–N bond (2.12 Å). **TS2** is 1.9 kcal/mol less stable than **TS1**, which is consistent with the experimentally observed 95% *ee*. By contrast, when the more flexible ligand **L1** was used, the computed *ee* ($\Delta\Delta G^{\ddagger}$) decreased to 1.4 kcal/mol.

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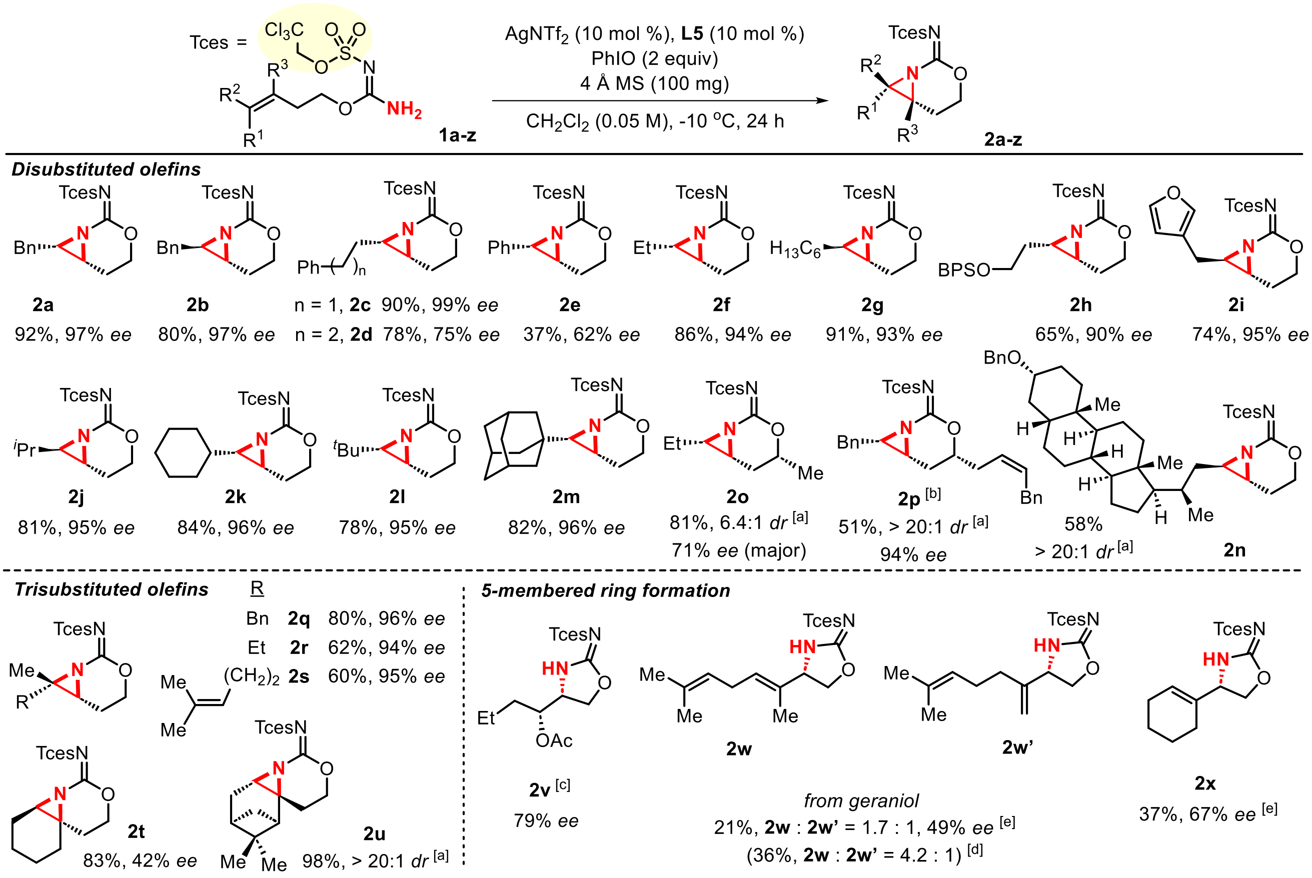
Table 2. Substrate scope.

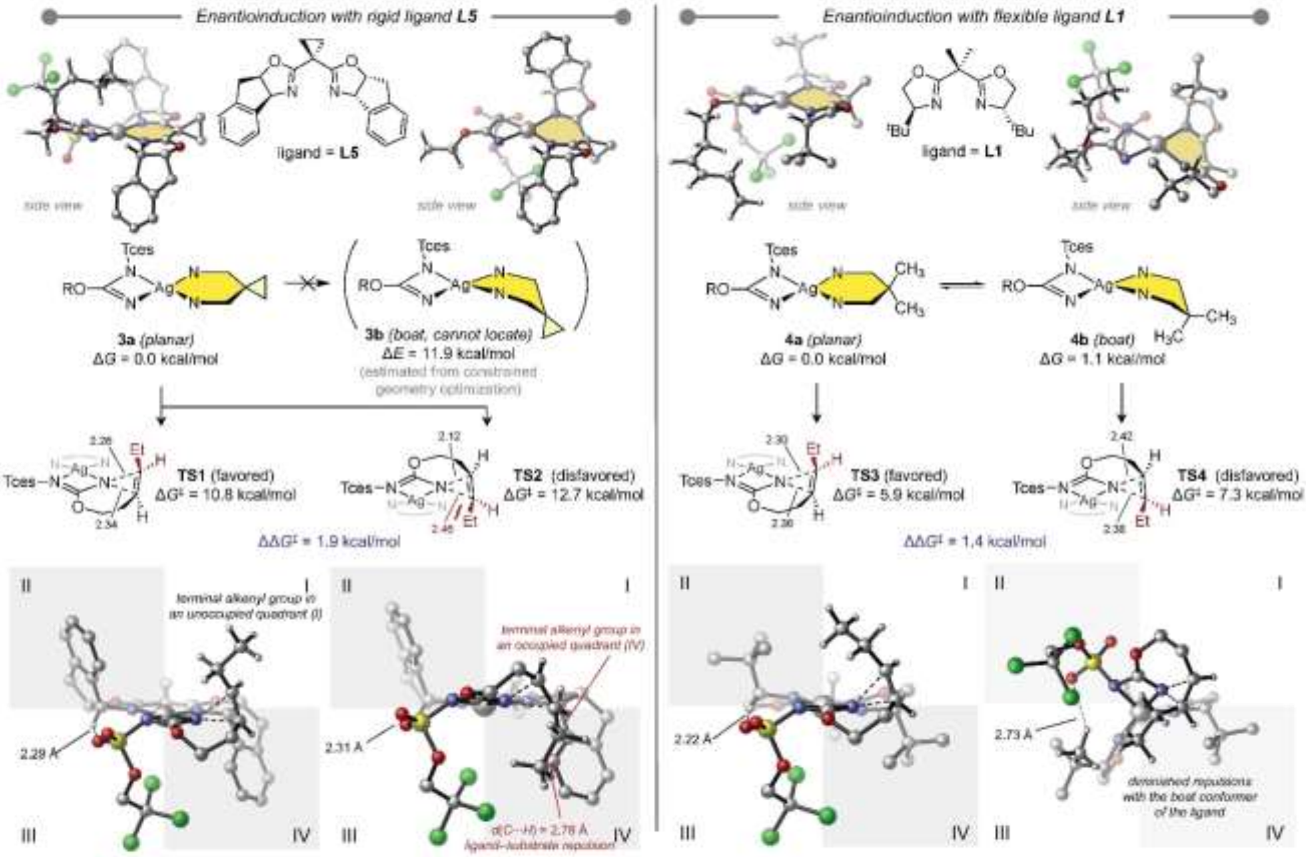


Reactions conducted on a 0.1 mmol scale; yields and *ee* reported for isolated products (chiral HPLC analysis). [a] Diastereomeric ratio (*dr*) values based on ^{1}H NMR analysis of crude mixtures. [b] Incomplete conversion after 24 h; crude mixture resubjected to standard conditions for 24 h. [c] The [3.1.0]-bicyclic aziridine seen by ^{1}H NMR analysis of crude but decomposed on purification. Minimal **2v** was isolated due to acetate ring-opening by trace amounts of $PhI(OAc)_2$. No ring-opening with [4.1.0]-bicyclic aziridines. [d] ^{1}H NMR yields in parentheses. [e] 20 mol% $AgNTf_2$ and 20 mol% **L5** were used.

The **L1** ligand in **TS3** leading to the major enantiomer has a C2-symmetric planar geometry where the Et-substituted alkenyl carbon is placed in the unoccupied quadrant. In contrast, **L1** in **TS4** leading to the disfavored enantiomer adopts a non-planar boat conformation. **TS4** is only 1.4 kcal/mol less stable than **TS3** as its non-planar geometry diminishes steric repulsions between ligand and the bulky *N*-Tces group, as well as the Et-substituted alkenyl carbon. The distance between the sulfonyl oxygen and the ligand (d(O···H)) is 2.73 Å in **TS4**, which is much longer than those in **TS1-TS3** (<2.31 Å) with the C2-symmetric planar ligand conformation. These DFT calculations highlight the importance of implementing a conformationally rigid BOX ligand (**L5**) to maintain the C2-symmetric steric environment. A more flexible ligand (**L1**) may distort to a non-C2-symmetric boat conformation to avoid steric repulsion with the bulky *N*-Tces group. This undesired conformational flexibility diminishes the stereochemical control in the aziridination TSs. This helps to rationalize why shortening the tether in the nitrene precursor leads to diminished *ee*, as the more sterically congested TS leads to a greater clashing between the substrate and ligand.

In conclusion, we have developed an enantioselective, silver-catalyzed aziridination employing unusual carbamimidate nitrene precursors to deliver products in excellent yields and stereoselectivities with good scope. The reaction tolerates diverse steric and electronic profiles and is amenable to large-scale synthesis. The enantioenriched bicyclic aziridines are versatile precursors for the regio- and stereocontrolled syntheses of 1,2-difunctionalized motifs. The ability to tune the steric and electronic nature of the carbamimidate to match the silver counteranion and ligand is currently being investigated for silver-catalyzed NT protocols with other novel classes of nitrene precursors and asymmetric intermolecular aziridinations.

Figure 1. Ligand effects on enantioselectivity of the aziridination of alkene **1f**. All energies were calculated at the ωB97X-D/def2-TZVPP/SMD(DCM)//ωB97X-D/def2-TZVPP(Ag)–def2-SVP level of theory.



Conflicts of interest

There are no conflicts to declare.

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