Chemo- and Enantioselective Intramolecular Silver-Catalyzed Aziridinations of Carbamimidates

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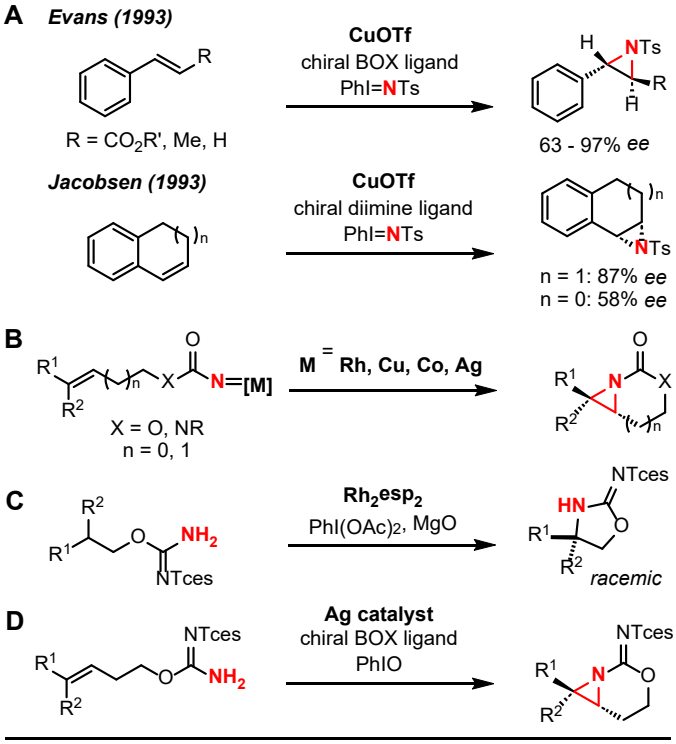
Abstract: Transition metal-catalyzed asymmetric nitrene transfer is a powerful method for the generation of enantioenriched amines frequently found in natural products and bioactive molecules. We report herein a highly chemo- and enantioselective intramolecular silver-catalysed aziridination that uses 2,2,2-trichloroethoxysulfonyl (Tces)-protected carbamimidates as an underexplored class of nitrene precursors. Several homoallylic carbamimidates containing di- and trisubstituted olefins were converted into [4.1.0]-bicyclic aziridines in good-to-excellent yields (up to 98%) and enantioselectivities (up to 99% *ee*). Computational insights shed insight into the reasons carbamimidates prove superior to the sulfamate and carbamate nitrene precursors that are traditionally used in this chemistry. Post-synthetic modifications afford difunctionalized amines bearing two contiguous, enantioenriched chiral centres.

Introduction

The presence of nitrogen functional groups in pharmaceuticals, agrochemicals, and natural products is essential to their beneficial physiochemical and biological properties.[1,2] This importance of the carbon-nitrogen bond has long inspired organic chemists to devise new methods for expedited and precise installation of nitrogen into compounds, advancements with significant potential to contribute to the identification and expansion of new chemical space. Toward this goal, transition metal-catalyzed nitrene transfer (NT) has emerged as an elegant strategy that directly transforms ubiquitous structural moieties, including 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 for their frequent occurrence in natural products and bioactive molecules, as well as their synthetic utility.[3,4] The reactivity of these smallest *N*-heterocycles is mainly attributed to their strained nature that leads to a high propensity to undergo ring-opening and ring-expansion processes, often with excellent regiocontrol and stereochemical integrity of the newly created stereogenic center(s).[3–7] Therefore, aziridines are exceptionally versatile and efficient intermediates for olefin difunctionalization, as well as the construction of higher- order heterocyclic scaffolds that feature prominently among medicinal chemists' most desirable synthetic targets.[8–19]

Due to the potential of alkene aziridination to introduce structural and stereochemical complexity from feedstock starting materials, the development of enantioselective aziridination strategies via NT is of key importance in organic synthesis. Early work by Evans and Jacobsen reported asymmetric intermolecular aziridinations with copper salts supported by chiral bis(oxazoline) (BOX)[20] and chiral diamine-based ligands[21], respectively (Scheme 1A). Although satisfactory yields and *ee* were observed with only a few select substrates, these results stimulated the discovery of several catalytic systems for both asymmetric inter- and intramolecular aziridinations that employ a variety of other metals, ligand scaffolds, and nitrene precursors.[7,22–24] Despite remarkable advances in both generality and efficiency, most of these methods, especially for intermolecular reactions, give the best results for terminal, styrene-based, and other conjugated olefins. In contrast, intramolecular aziridinations via NT exhibit superior reactivity and stereoselectivity with internal and unactivated olefins, yet have received much less attention (Scheme 1B). In 2003, Che developed a chiral dirhodium complex to catalyze intramolecular aziridination of alkenes with sulfonamides and carbamates in up to 76% *ee*.[25] Dauban later used a copper-BOX complex to afford the intramolecular aziridination of sulfamates in up to 84% *ee*, although substrates bearing unconjugated or terminal olefins gave less satisfactory results.[26] In 2017, Zhang used an alternative strategy to iminoiodinane-based nitrene formation, reporting enantioselective aziridinations with allyl azidoformates via a radical pathway catalyzed by a cobalt-porphyrin complex.[27] This catalyst gave excellent enantioselectivity when substrates containing (*E*)-olefins



Scheme 1. A) Early enantioselective intermolecular aziridinations via NT. B) Enantioselective intramolecular aziridinations via NT. C) Intramolecular C–H amination with carbamimidate nitrene precursors. D) This work: Silver-catalyzed enantioselective aziridination of carbamimidate nitrene precursors.

were used (up to 99% *ee*), albeit with a significant decline in *ee* employing (*Z*)-olefins. Later that year, our group reported asymmetric silver-catalyzed NT of homoallylic carbamates bearing unconjugated, *Z/E* di-/trisubstituted olefins to give aziridines in a range of *ee* values depending on substrate.[28]

Given the scarcity of asymmetric intramolecular aziridination methods, we were interested in opportunities to further improve the scope and utility of silver-catalyzed asymmetric aziridination via NT.[28,29] Carbamimidates are an underexplored class of nitrene precursors, where the additional valency on the imidate nitrogen, as compared to carbamates or sulfamates, offers an opportunity to tune catalyst/substrate interactions in the NT transition state to improve chemo-, site- and enantioselectivity. In addition, the 5-member dihydrooxazol-2-amine and 6-member 1,3-oxazin-2-amine products from asymmetric aziridination and ring-opening sequences employing carbamimidate precursors are found in several compounds with useful bioactivities (Figure 1).[30-33]

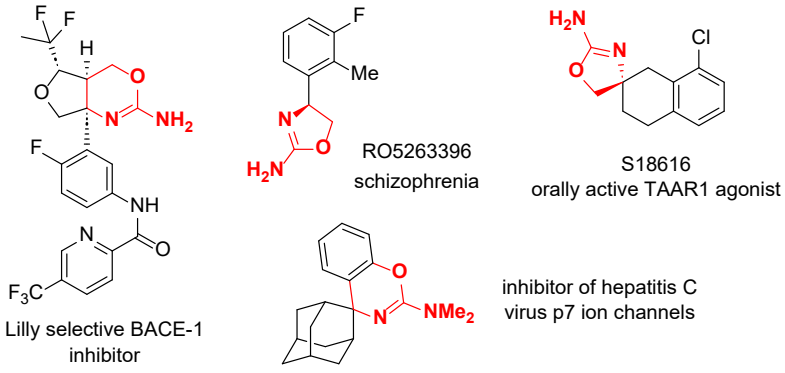


Figure 1. Bioactive 1,3-oxazin-2-amines and dihydrooxazol-2-amines.

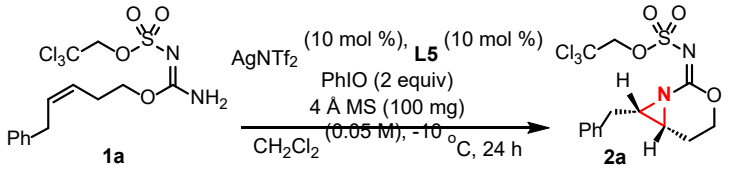
Despite their structural resemblance to carbamates, thus far only one example of the use of carbamimidates has been reported. The Dauban group employed Rh-catalyzed intramolecular C–H aminations of carbamimidates (Scheme 1C) to give racemic products.[34] Prompted by this example and reports on promising applications of cyclic

carbamimidates in medicinal chemistry,[35] we herein disclose a method for asymmetric intramolecular aziridinations of homoallylic carbamimidates mediated by a chiral silver-BOX complex (Scheme 1D). We envisioned that the extra bulk from the imine *N*-protecting group in carbamimidates, as compared to carbamates, would have a substantial impact on catalyst-substrate steric interactions that could lead to increased levels of chemo- and enantioselectivity with suitable catalysts.

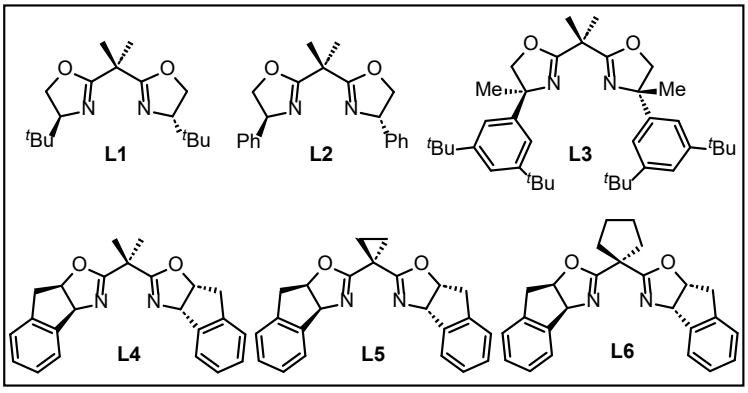
Results and Discussion

The identity of the *N*-protecting group is key to successful reactivity when using uncommon nitrene precursors, such as carbamimidates,[34] ureas, and guanidines.[36,37] We found that a 2,2,2-trichloroethoxysulfonyl (Tces) moiety in model substrate **1a** serves as a convenient imine protecting group. After optimization of $AgNTf_2$ as the silver salt, a small set of commercially available and custom-synthesized BOX ligands were screened (Table 1, entries 1-6). While ligands **L1**-**L6** all provided **2a** in good-to-excellent yields with exceptional chemoselectivity (only a trace amount of the allylic C–H amination product was observed in the crude mixtures by NMR), the differences in *ee* were remarkable. **L1**, which was the optimal ligand in asymmetric aziridinations of carbamates, gave **2a** in only 35% *ee*, while the levels of enantioinduction with **L2** and **L3** were marginal. We hypothesized that the bulky Tces group could be better accommodated by allowing extra space near the metal center by modifying the BOX ligand scaffold. Indeed, the *ee* of **2a** dramatically increased when indane-based BOX ligands **L4**-**L6** were used, with **L5** (entry 1) resulting in optimal enantioselectivity (97% *ee*) and yield (92%).

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



[a] Reactions were carried out on a 0.1 mmol scale unless indicated otherwise. Yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] The *ee* was determined by chiral HPLC after purification. [c] Isolated yield.

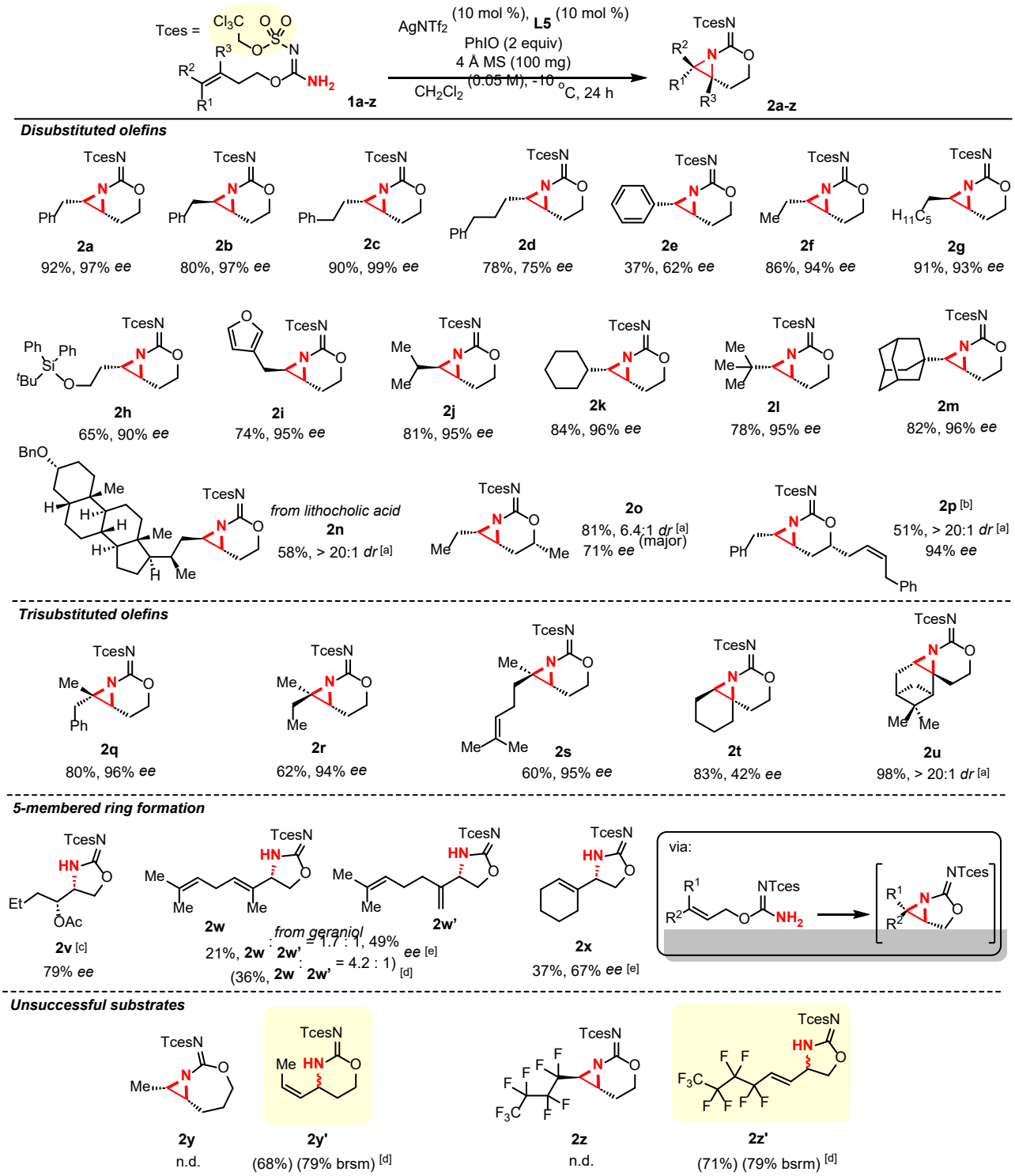


Figure 2. Substrate scope. Reactions were carried out on a 0.1 mmol scale; yields and *ee* values are reported for isolated products (chiral HPLC analysis). [a] Diastereomeric ratio (*dr*) values are reported based on ^{1}H NMR analysis of crude mixtures. [b] Incomplete conversion after 24 h; the crude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

Interestingly, and in contrast to previous observations in silver-catalyzed NT, the counteranion identity was also 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 $AgNTf_2$. When the temperature was lowered from -10 °C to -20 °C (entry 9), the conversion after 24 h dropped significantly with no improvement in the *ee*. An attempt to reduce the catalyst loading from 10 mol % to 5 mol % (entry 10) led to decreased yield and *ee*. Finally, the reaction was amenable to scale-up (entry 11), as a gram-scale (2.5 mmol) reaction afforded **2a** in yields (89%) and enantioselectivity (95% *ee*) comparable to reaction carried out on a 0.1 mmol scale. The absolute stereochemistry of **2a** was shown to be (6*R*,7*S*) by X-ray crystallography (Supporting Information for details).

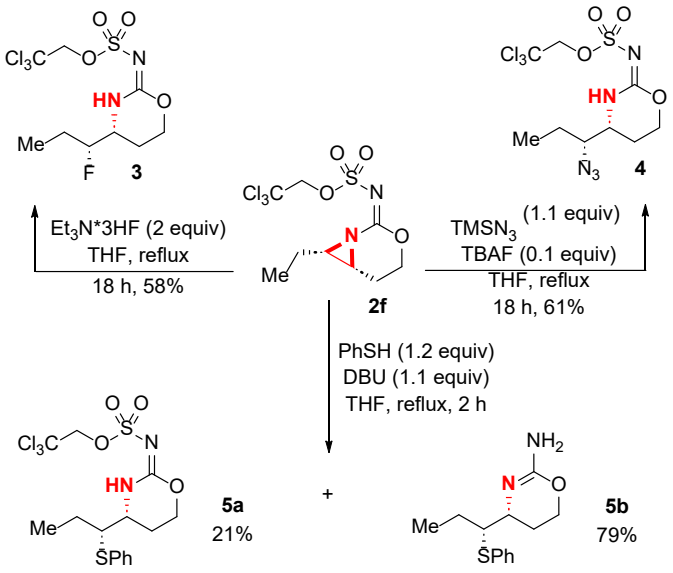
With optimized conditions in hand, the scope was investigated (Figure 2). In general, carbamimidates bearing disubstituted alkenes provided excellent yields (up to 91%) and enantioselectivity (up to 99% *ee*). Aziridine **2b**, which is the (*E*)-isomer of **2a**, was obtained from the corresponding (*E*)-alkene in 97% *ee*, suggesting a concerted, stereoretentive mechanism or alternatively, hydrogen atom abstraction followed by rapid radical rebound. Extending the alkyl chain length by one carbon (**2c**) gave better *ee* (99% *ee*), although further extension (**2d**) surprisingly lowered *ee* (78% yield, 75% *ee*). This method was complementary to methods for styrene aziridinations, as **1e** provided **2e** in only 37% yield and 62% *ee*. Aziridines containing linear alkyl substituents (**2f-g**) were obtained in excellent yields and *ee*. The reaction also tolerated a bulky silyl-protected alcohol moiety (**2h**) or a heteroarene (**2i**). Increasing the steric bulk proximal to the olefin moiety by installing isopropyl (**2j**), cyclohexyl (**2k**), *tert*-butyl (**2l**), or adamantyl (**2m**) groups did not negatively impact either yield or *ee*. Applicability to complex molecules was highlighted by a lithocholic acid-derived product (**2n**), obtained as a single diastereomer. The presence of a racemic stereocenter at the secondary alcohol used to form the carbamimidate **1o** afforded **2o** in a moderate 6.4:1 *dr*, with a 71% *ee* of the major stereoisomer. We were pleased to observe both high *dr* and *ee* for **2p** (> 20:1 *dr*, 94% *ee*), highlighting the capability of this method for desymmetrization. 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** with excellent *ee*, despite moderate decreases in yield due to small amounts of competing C–H amination. This approach is attractive for securing quaternary amine-bearing stereocenters, even when the two carbon substituents do not vary greatly in terms of their sterics (e.g. Me vs. Et in **2r**).

The 1,2,2'-trisubstituted olefins are challenging substrates for intramolecular asymmetric aziridination. A cyclic 1,2,2'-trisubstituted olefin **1t** gave **2t** in 83% yield and an improved 42% *ee* over our previous result with a carbamate substrate.[28] A cyclic 1,2,2'-trisubstituted olefin derived from (1*R*)-(-)-nopol gave a single diastereomer of the corresponding aziridine **2u** in near-quantitative yield (see the SI for assignments of relative stereochemistry using NOESY). In addition to the [4.1.0] bicyclic aziridine products, other azabicyclic patterns were also explored. A disubstituted allylic carbamimidate **1v** affords a five-membered ring product **2v** in good 79% *ee* after isolation, presumably due to ring-opening of the corresponding aziridine (see Figure 2 footnote for details). Moderate yields and *ee* of other five-membered ring products were obtained from trisubstituted allylic carbamimidates **1w** and **1x**. Alkene migration was also observed as a result of fast ring-opening of the [3.1.0] bicyclic aziridines. Seven-membered ring formation (**2y**) was not detected (only the allylic C–H insertion product **2y'** was obtained). Aziridination was also unsuccessful with a perfluoroalkyl-substituted olefin (**2z**), which underwent exclusive allylic C–H insertion (**2z'**), highlighting the continued need for catalysts that are able to override substrate control.

To demonstrate the post-synthetic utility of carbamimidate-derived bicyclic aziridines, **2f** was subjected to various nucleophilic ring-opening conditions to access diverse alkene difunctionalization patterns (Scheme 2). As expected, **2f** underwent facile reactions with fluoride (**3**), azide (**4**), and thiol (**5** and **5'**) nucleophiles to exclusively afford the corresponding six-membered cyclic carbamimidate products. In terms of stereochemical integrity, neither *dr* nor *ee* erosion was detected. Although we did not attempt to remove the Tces group directly from **2f** due to the aziridine's lability, it could be mildly deprotected under reductive conditions to provide an extra functionalization handle with the free amino group.[32] Other post-functionalization pathways, including ring expansions via aziridinium ylides,[8] are under investigation and will be reported in the future.

The carbamimidate nitrene precursor is key to the high *ee* exhibited in this system compared to more conventional sulfamates and carbamates. We performed density functional theory (DFT) calculations to investigate the origin of enantioselectivity and the effects of ligand (Figure 3). In particular, we examined the difference between the modes of enantioinduction with **L5**, the most effective ligand with the carbamimidate nitrene precursor, and **L1**, which was the optimal ligand in asymmetric aziridinations of carbamates but gave low *ee* with *N*-Tces carbamimidates. The computations show that **L5**, with two indane arms and a cyclopropyl backbone, is substantially more rigid than **L1**. In the **L5**-supported Ag–carbamimidate nitrene complex (**3a**) the **L5** ligand adopts a completely planar conformation, whereas the corresponding **L1**-supported complex has two conformers—a C2-symmetric conformer (**4a**) in which the oxazolines adopt an envelope conformation and the six-membered metallacycle is twisted but



Scheme 2. Post-synthetic modifications of the enantioenriched aziridine products on a 0.1 mmol scale.

nearly planar, and a non-C2-symmetric conformer (**4b**) featuring a non-planar boat conformation of the six-membered metallacycle. The boat conformer **4b** is only 1.1 kcal/mol less stable than **4a** because the steric repulsion between the ligand and the bucky Tces group on the carbamimidate is diminished 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 conformation suggests the **L5**-supported **3b** is about 11.9 kcal/mol less stable than the planar geometry **3a**.

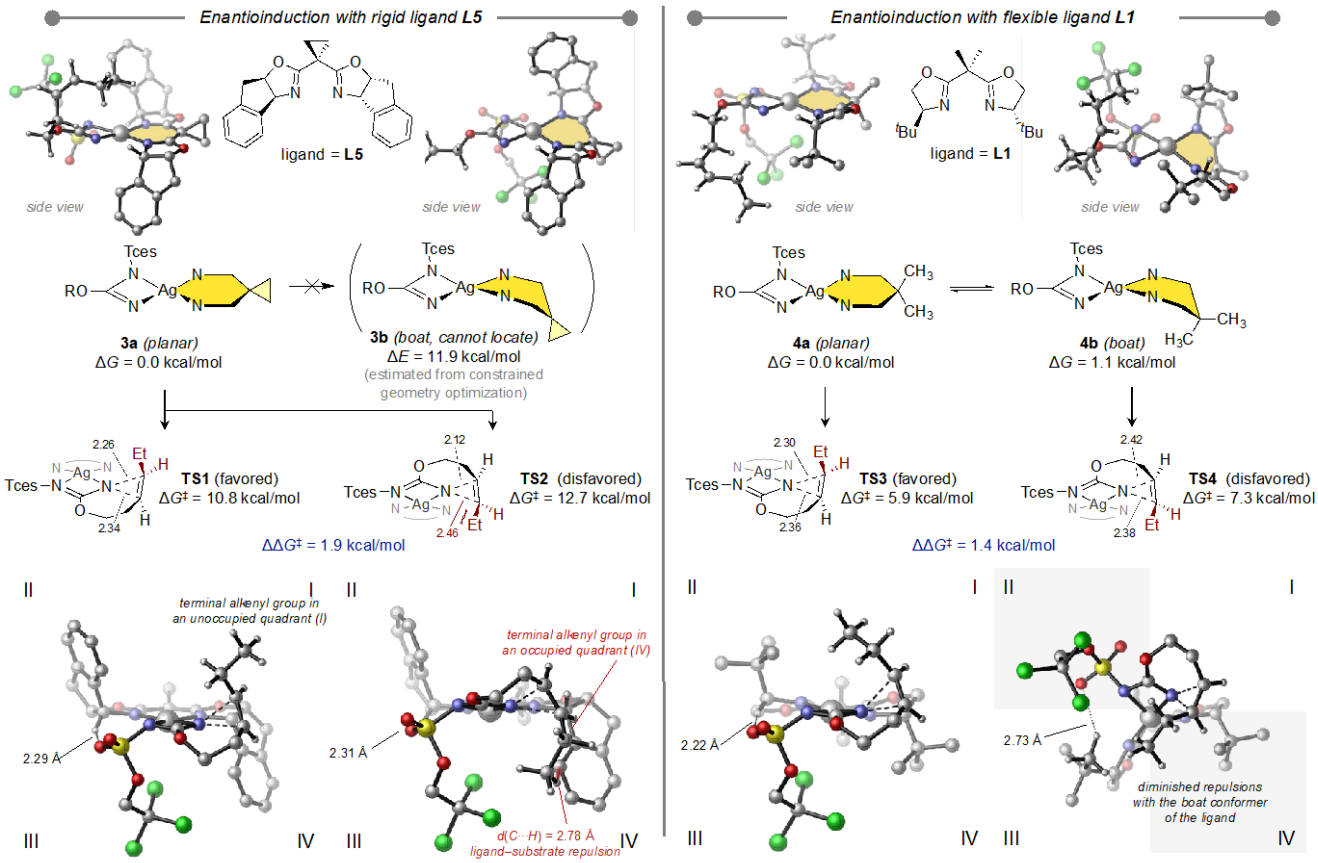


Figure 3. Ligand effects on enantioselectivity of the aziridination of alkene **1f**. All energies were calculated at the ωB97X-D/def2-TZVPP/SMD(DCM)//ωB97X-D/def2-TZVPP(Ag)–def2-SVP level of theory.

Ligand rigidity also impacts the mode and effectiveness of enantioinduction in the stereoselectivity-determining aziridination transition state (Figure 3, see Figure S4 in the SI for less favorable transition state conformers).[38] In the **L5**-supported transition states, the rigid ligand **L5** maintains the C2-symmetric geometry with a planar six-membered metallacycle. In the most favorable transition state **TS1** that leads to the observed major enantiomeric product (*R*)-**2f**, the Et-substituted alkenyl carbon is placed in a quadrant not occupied by the C2-symmetric **L5** ligand. By contrast, in **TS2**, the transition state 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 steric 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. Additionally, this repulsion results in a distorted asynchronous transition state 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 experimentally observed 95% *ee*. By contrast, when the more flexible ligand **L1** was used, the computed enantioselectivity ($\Delta\Delta G^{\ddagger}$) decreased to 1.4 kcal/mol. The **L1** ligand in **TS3** leading to the major enantiomeric product has a C2-symmetric planar geometry where the Et-substituted alkenyl carbon is placed in the unoccupied quadrant. By contrast, **L1** in **TS4** leading to the disfavored enantiomer adopts the non-planar boat conformation. **TS4** is only 1.4 kcal/mol less stable than **TS3** because its non-planar geometry diminishes the 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. Taken together, the DFT calculations highlighted 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 transition states.

Conclusion

In conclusion, we have developed an efficient and general method for enantioselective, silver-catalyzed intramolecular aziridination with carbamimidates that delivers excellent yields and stereoselectivities with broad scope. The reaction displays tolerance to diverse steric and electronic profiles as well as amenability to the large-scale synthesis. The enantioenriched bicyclic aziridines were versatile precursors for the regio- and stereocontrolled syntheses of various 1,2-difunctionalized motifs. Future directions will focus on investigating further synthetic applications of these carbamimidate-derived products, as well as developing asymmetric silver-catalyzed NT protocols with other novel classes of nitrene precursors.

Supporting Information

The authors have cited additional references within the Supporting Information,[42-64] experimental procedures and characterization for all new compounds, computational details and a summary of data for CDC Deposition Number 2279283.

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